GENEVA
LABORATORIES

FOR THE MEDICAL INDUSTRY WORLDWIDE

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

Global Health Solutions
Eye Care Candidate Formula
Lot No.: OV-02

Ocular Irritation Test
[ANSI/AAMI/ISO 10993-10:2010/(R)2014]
(Direct Application)
(GLP)

February 19, 2018

JN18A1623

JN18A1623

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SECTION 1

TEST PROTOCOL

GLP0002*

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GLP PROTOCOL

Ocular Irritation Test
[ANSI/AAMI/ISO 10993-10:2010/(R)2014]
(Direct Application)

SPONSOR: Global Health Solutions, LLC
5959 Topanga Canyon Blvd. #170
Woodland Hills, CA 91367

P.O. No.: PO000000025

TEST ARTICLE: Global Health Solutions
Eye Care Candidate Formula

LOT/ID: OV-02

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: 01-26-2018

Sandy Ott
Study Director/Toxicology
Geneva Laboratories, Inc.

SPONSOR: _____ DATE: 1/26/2018

Global Health Solutions, LLC

18-014

GENEVA LABORATORIES, INC.

PROTOCOL FOR OCULAR IRRITATION TEST (DIRECT APPLICATION) [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

Ocular Irritation Test (Direct Application)
[ANSI/AAMI/ISO 10993-10:2010/(R)2014]
Geneva Laboratories Proc. No. CL1003*

2). PURPOSE

To assess the potential of the material under test to produce ocular irritation.

3). IDENTIFICATION OF

	Name	CAS/Code (Lot No.)
Test Article:	Global Health Solutions Eye Care Candidate Formula	OV-02

4). SPONSOR NAME

Global Health Solutions, LLC
5959 Topanga Canyon Blvd. #170
Woodland Hills, CA 91367
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)
Weight Range:	2 kg to 3 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, numbered ear tag.

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

A. Ocular Irritation Test

1. Three (3) healthy, albino rabbits will be utilized.

2. Animals will be cared for in accordance with the Animal Welfare Act.

B. Preparation Test Article

1. Test article is to be applied undiluted from the final packaging as supplied by sponsor.

C. Procedure

1. Not more than twenty-four (24) hours before test application, the eyes of each rabbit are visually examined for evidence of ocular abnormality. If either eye shows any abnormality, the rabbit will be replaced with a rabbit with no ocular abnormalities.

2. The rabbits are housed in a clean, dust free, temperature controlled environment that excludes materials that might produce eye irritation.

3. One (1) animal shall be tested on initially. If a well defined response [see Table I (page 8), any positive response] is seen in one (1) animal, no further testing is necessary.

4. When no positive response is observed on initial testing, two (2) additional animals will be used.

5. Each rabbit is firmly, but gently, restrained until quiet.

6. In most cases, anesthetics will not be used. However, if the test material is likely to cause more than momentary pain, local anesthetics may be used prior to instillation. In such cases, anesthetics will be used only once. The eye used as control will also receive the same anesthetic.

7. The lower lid of the right eye is gently pulled away from the eyeball to form a cup and test article or its extract is instilled.

8. The lids are gently held together for about one (1) second.

9. The left eye serves as control and is left untreated.

D. Scoring

1. Using the criteria outlined in Table I (page 8), the cornea, iris and conjunctivae of both eyes are examined at one (1), twenty-four (24), forty-eight (48) and seventy-two (72) hours after application.

2. Examination may be facilitated by using a binocular scope, hand-held slit-lamp, optical instruments, fluorescein stain, UV light or flashlight.

3. Any animal exhibiting the following reactions at any time during the study will be withdrawn immediately.

   a. Very severe ocular damage.

   b. Blood stained or purulent discharge.

   c. Significant corneal ulceration.

   d. Absence of light reflex (iridial response grade 2) or corneal opacity (grade 4) without evidence of recovery within 24 ±2 hours.

   e. Maximum conjunctival inflammation (chemosis grade 4 along with redness grade 3) without evidence of recovery within 48 ±2 hours.

E. Results

1. If the treated eye in more than one animal shows a positive response at any observation [foot note grades in Table I (page 8)], then the test article is considered an eye irritant.

2. If only one (1) of three (3) eyes shows a mild or moderate reaction or reactions are equivocal, treat further animals.

3. When further animals are treated, the test article is considered to be an eye irritant if more than half of the eyes treated exhibit a positive reaction at any stage of the investigation.

4. A severe reaction in one (1) treated eye is sufficient to label the test article an eye irritant.

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

Diet: Teklad Global 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 -- Untreated

B. Test -- 0.1 mL of test article

11). METHOD AND FREQUENCY OF ADMINISTRATION

A single application of 0.1 mL of test article to the right eye.

12). TYPE AND FREQUENCY OF TEST MEASUREMENTS

The cornea, iris and conjunctiva are observed at one (1), twenty-four (24), forty-eight (48) and seventy-two (72) hours after application.

The twenty-four (24), forty-eight (48) and seventy-two (72) hour observations are used to determine the results.

13). RECORDS TO BE MAINTAINED

All raw data that is 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.

Table I
System for grading ocular lesions[1]

REACTION	NUMERICAL GRADING
1. Cornea	
Degree of opacity (most dense area)	
No opacity	0
Scattered or diffuse areas, details of iris clearly visible	1[a]
Easily discernible translucent areas, details of iris slightly obscured	2[a]
Opalescent areas, no details of iris visible, size of pupil barely discernible	3[a]
Opaque, details of iris not visible	4[a]
Area of cornea involved	
One-quarter (or less), not zero	0
Greater than one-quarter, but less than half	1
Greater than half, but less than three-quarters	2
Greater than three-quarters, up to whole area	3
2. Iris	
Normal	0
Folds above normal, congestion swelling, circumcorneal injection (any or all or combination of these), iris still reacting to light (sluggish reaction is positive)	1[a]
No reaction to light, haemorrhage, gross destruction (any or all of these)	2[a]
3. Conjunctivae	
Redness (refers to palpebral and bulbar conjuctiva excluding cornea and iris)	
Vessels normal	0
Vessels definitely injected above normal	1
More diffuse, deeper crimson red, individual vessels not easily discernible	2[a]
Diffuse beefy red	3[a]
Chemosis	
No swelling	0
Any swelling above normal (include nicitating membrane)	1
Obvious swelling with lids partial eversion of lids	2[a]
Swelling with lids about half-closed	3[a]
Swelling with lids about half-closed to completely closed	4[a]
Discharge	
No discharge	0
Any amount different from normal (does not include small amounts observed in inner canthus of normal animals)	1
Discharge with moistening of the lids and hairs just adjacent to lids	2
Discharge with moistening of lids and hairs, and considerable area around the eye.	3

[a] Positive result.

SECTION 2

TEST REPORT/STUDY PERSONNEL

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P.O. Box 140 • 1001 Proctor Drive • Elkhorn, WI 53121-0140
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OCULAR-A

REPORT TO: Mr. Brad Burnam
Global Health Solutions, LLC
5959 Topanga Canyon Blvd. #170
Woodland Hills, CA 91367

TEST ARTICLE: Global Health Solutions
Eye Care Candidate Formula
Lot No. OV-02
P.O. NO.: PO000000025

DATE RECEIVED: 01-24-2018

TEST INITIATION DATE: 02-06-2018 TEST COMPLETION DATE: 02-16-2018

TEST PROCEDURE: Ocular Irritation Test - Direct Exposure (GLP)
ANSI/AAMI/ISO 10993-10:2010/(R)2014
Ref. Geneva Laboratories Proc. No.: CL1003P

OBJECTIVE: To assess the potential of the test material to produce ocular irritation.

CONCLUSION: Under the conditions of this study, the test article is classified as a:

X Non-irritant
N/A Irritant

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

ANALYST: Amalia Clseby DATE: 02/16/2018

ACCEPTED BY: _____ DATE: 02-16-2018
Technical Reviewer

QA SIGNATURE: _____ DATE: 02-16-2018

TEST SYSTEM:

A. Animals used in Study:

Species: Rabbit (Oryctolagus cuniculus)
Strain: New Zealand White (NZW)
Supplier: Bakkom Rabbitry
Sex: Female, nulliparous and not pregnant
Acclimation: Minimum of five (5) days
Age at test initiation: Young adult, no particular age was prescribed for this test.
Number: Three (3)
Weight: 2.0 kg to 3.0 kg
Identification: Individually numbered ear tags
Health Status: Clinically healthy, not previously used in other eye irritation studies. Animals were observed daily for any health irregularities.
Study Assurances: Facility is registered with the United States Department of Agriculture (USDA). This procedure was approved and is reviewed annually by the Geneva Laboratories, Inc. IACUC (Institutional Animal Care and Use Committee).

B. Animal Husbandry:

Housing: Housed 1 or 2 to an enclosure
Cages: Multi-stacking galvanized steel hutches, identified with a cage card stating the sex, arrival date, supplier, ID number, Job Number and study.
Bedding: Non-contact cage tray liners
Diet: N/A Teklad Global High Fiber Rabbit Diet No. 2031
X Teklad Certified Global High Fiber Rabbit Diet No. 2031C
Water: Municipal water source, ad libitum, monitored monthly for microbial count.
Animal Room Target Temperature: 16-22°C
Animal Room Target Humidity: 30-70%
Lighting: 12-hour light/dark cycle controlled using an automatic timer.
Animal rooms were maintained as a limited access facility.

JUSTIFICATION OF TEST SYSTEM:

The New Zealand White Rabbit has been utilized historically for ocular irritation studies. The rabbit is the preferred species according to ANSI/AAMI/ISO 10993-10 guidelines.

STATISTICAL METHODS: None.

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

CONTROL: The untreated left eye of each animal served as the control.

TEST METHODS:

A. Direct Application:

The test article was dosed as neat (undiluted) product from the final packaging as supplied by the Sponsor unless otherwise specified.

B. Test Procedure:

Not more than twenty-four (24) hours before instillation, the eyes of each animal were visually examined for ocular abnormalities. If any abnormalities were observed, the rabbit was replaced.

Initial testing was performed in one (1) animal. If a well-defined positive response (Table I) occurred, testing in further animals was not necessary and the test article was categorized as an irritant. If no response was seen on initial testing, then testing was performed on two (2) additional animals.

The lower lid of the right eye was gently pulled away from the eyeball to form a cup. A 0.1 mL volume of test article was instilled into the eyecup. The lids were then gently held together for about one (1) second.

The left eye remained untreated and served as the negative control.

The eyes were examined at 1 (±6 minutes), 24 (±2 hours), 48 (±2 hours), and 72 (±2 hours) after instillation. The grades of ocular reaction according to Table I were recorded for each rabbit at each time point (Table II).

DOSAGE OF TEST/CONTROL ARTICLES AND ROUTE OF ADMINISTRATION:

0.1 mL of test article was applied to the right eye for a one (1) time application. The left eye remained untreated to serve as a negative control.

DESCRIPTION OF CALCULATIONS PERFORMED ON DATA: None.

COMMENTS: None

EVALUATION OF RESULTS:

The differences of the ocular reactions observed between the test and control eyes were compared.

A well-defined positive response (Table I) in the initially treated animal eliminates the need for testing in the additional two animals.

If the treated eye in more than one animal shows a positive result (Table I) at any observation, the test article is considered an eye irritant.

If only one of the three eyes shows mild or moderate reaction, or there is uncertainty in the observed reaction, treat further animals. When further animals are treated, the test article is considered an eye irritant when more than half the eyes treated with the test article show a positive response (Table I) at any observation.

If a severe reaction in only one animal is observed at any time point, the test article is considered an eye irritant.

RESULTS:

A. General Health/Mortality Observations During the Study Period:

There were no deaths or abnormal health observations recorded during the study period.

B. Observations of Ocular Reactions: See Table II

Table I
System for Grading Ocular Lesions

Reaction	Numerical Grading
1. Cornea	
Degree of opacity (most dense area)	
No opacity	0
Scattered or diffuse areas, details of iris clearly visible	1*
Easily discernible translucent areas, details of the iris slightly obscured	2*
Opalescent areas, no details of iris visible, size of pupil barely discernible	3*
Opaque, detail of iris not visible	4*
2. Iris	
Normal	0
Folds above normal, congestion swelling, circumcorneal injection (any or all or combination of these), iris still reacting to light (sluggish reaction is positive)	1*
No reaction to light, haemorrhage, gross destruction (any or all of these)	2*
3. Conjunctivae	
Redness (refers to palpebral and bulbar conjunctiva excluding cornea and iris)	
Vessels normal	0
Vessels definitely injected above normal	1
More diffuse, deeper crimson red, individual vessels not easily discernible	2*
Diffuse beefy red	3*
Chemosis	
No swelling	0
Any swelling above normal (include nictitating membrane)	1
Obvious swelling with partial eversion of lids	2*
Swelling with lids about half-closed	3*
Swelling with lids about half-closed to completely closed	4*

*Positive Result

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TABLE II
Grades for Ocular Lesions

Direct Application

CORNEA

Rabbit #	14997		14996		14998	
	Test	Control	Test	Control	Test	Control
1 Hour	0	0	0	0	0	0
24 Hours	0	0	0	0	0	0
48 Hours	0	0	0	0	0	0
72 Hours	0	0	0	0	0	0

IRIS

Rabbit #	14997		14996		14998	
	Test	Control	Test	Control	Test	Control
1 Hour	0	0	0	0	0	0
24 Hours	0	0	0	0	0	0
48 Hours	0	0	0	0	0	0
72 Hours	0	0	0	0	0	0

Scoring Values: 0, 1*, 2, 3 and 4

*A score of ≥1 on Cornea or Iris indicates a positive response.

TABLE II (cont.)
Grades for Ocular Lesions

Direct Application

CONJUNCTIVAE

Rabbit #	14997		14996		14998	
	Test	Control	Test	Control	Test	Control
1 Hour	1	0	1	0	1	0
24 Hours	0	0	0	0	0	0
48 Hours	0	0	0	0	0	0
72 Hours	0	0	0	0	0	0

CHEMOSIS

Rabbit #	14997		14996		14998	
	Test	Control	Test	Control	Test	Control
1 Hour	1	0	1	0	1	0
24 Hours	0	0	0	0	0	0
48 Hours	0	0	0	0	0	0
72 Hours	0	0	0	0	0	0

Scoring Values: 0, 1, 2*, 3 and 4

*A score of ≥2 on Redness or Chemosis indicates a positive response.

GENEVA LABORATORIES, INC.

Toxicology Department Personnel

Dr. Colleen Stewart -- Director of Veterinary Medicine

Sandra Ott -- Study Director

Scott Roberts -- Senior Analyst

Annali Isely -- Analyst

E. Jane Lewis -- QA Toxicology

Paul Norland -- QA Manager

SECTION 3

QUALITY ASSURANCE AUDIT REPORT & STATEMENT

GLP0006*

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

SPONSOR: Global Health Solutions, LLC
5959 Topanga Canyon Blvd. #170
Woodland Hills, CA 91367

TEST ARTICLE: Global Health Solutions
Eye Care Candidate Formula
Lot No.: OV-02

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

REFERENCE: Geneva Laboratories Proc. No.: CL1003P

TEST SYSTEM: New Zealand White Rabbits

TEST STATUS: Study Initiated: 01-26-2018
Test Initiated: 02-06-2018
Test Completed: 02-16-2018
Study Completed: 02-19-2018

AUDIT DATES: See Table I

COMMENTS INCLUDING DEVIATIONS AND PROBLEMS: Under the conditions of this study, the test sample is non-irritant.

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). The Quality Assurance Department is independent of and impartial to: The Testing Department, inspection of data and reporting of the results pertaining to this study.

QA AUDITOR: _____ DATE: 02-19-2018

QA MANAGEMENT: _____ DATE: 02/19/2018

GLP0006*

TABLE I

QUALITY ASSURANCE STATEMENT

INSPECTED BY INSPECTION DATE	STUDY SEGMENT INSPECTED	DATE FINDINGS WERE WRITTEN FOR MANAGEMENT AND STUDY DIRECTOR
E.J.L./02-06-2018	Sample Preparation	02-06-2018
E.J.L./02-06-2018	Pre Test Application	02-06-2018
E.J.L./02-06-2018	1 Hour Score	02-06-2018
E.J.L./02-07-2018	24 Hour Score	02-07-2018
E.J.L./02-08-2018	48 Hour Score	02-08-2018
E.J.L./02-09-2018	72 Hour Score	02-09-2018
E.J.L./02-13-2018	Test Application	02-13-2018
E.J.L./02-13-2018	1 Hour Score	02-13-2018
E.J.L./02-14-2018	24 Hour Score	02-14-2018
E.J.L./02-15-2018	48 Hour Score	02-15-2018
E.J.L./02-16-2018	72 Hour Score	02-16-2018
E.J.L./02-16-2018	Raw Data Review	02-16-2018
E.J.L./02-19-2018	Final Report Review	02-19-2018

*E.J.L. - E. Jane Lewis

QA AUDITOR: E Jane Lewis DATE: 02-19-2018

QA MANAGEMENT: [signature] DATE: 02/19/2018

SECTION 4

COMPLIANCE/ARCHIVE STATEMENTS

GLP0001*

GENEVA LABORATORIES, INC.
STUDY DIRECTOR COMPLIANCE STATEMENT

SPONSOR: Global Health Solutions, LLC
5959 Topanga Canyon Blvd. #170
Woodland Hills, CA 91367

PROTOCOL: Ocular Irritation Test (Direct Application)
[ANSI/AAMI/ISO 10993-10:2010/(R)2014]

TEST ARTICLE: Global Health Solutions
Eye Care Candidate Formula
Lot No.: OV-02

STUDY INITIATION DATE: 01-26-2018 STUDY COMPLETION DATE: 02-19-2018

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.

STUDY DIRECTOR: _____ DATE: 02-19-2018
Toxicology

GLP0002*

GENEVA LABORATORIES, INC.
GLP COORDINATOR ARCHIVE STATEMENT

SPONSOR: Global Health Solutions, LLC
5959 Topanga Canyon Blvd. #170
Woodland Hills, CA 91367

PROTOCOL: Ocular Irritation Test (Direct Application)
[ANSI/AAMI/ISO 10993-10:2010/(R)2014]

TEST ARTICLE: Global Health Solutions
Eye Care Candidate Formula
Lot No.: OV-02

STUDY INITIATION DATE: 01-26-2018 STUDY COMPLETION DATE: 02-19-2018

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: Rachelle Hrachu DATE: 02-19-2018