NCT03474874

CLINICAL PROTOCOL

Protocol Title:	Human Repeated Insult Patch Test
Protocol Number:	NNAU01-001
Clinical Trial Number:	C18-0595
Test Materials:	NeoMatriX™ Saline Negative control 0.4% SLS Positive Control
Testing Facility:	Consumer Product Testing Company, Inc. 70 New Dutch Lane Fairfield, NJ 07004 (973) 808-7111
Sponsor:	NeXtGen Biologics, Inc. 101 SE 2nd Place, #E201H Gainesville, FL 32601
Principal Investigator:	Michael Caswell, Ph.D., CCRC, CCRA Vice President, Clinical Evaluations
Sub-Investigators:	Joy Frank, R.N. Executive Vice President, Clinical Evaluations Richard R. Eisenberg, M.D. Board Certified Dermatologist, Medical Director

PROTOCOL ACCEPTANCE:

For Consumer Product Testing Co., Inc.:

Michael Caswell, Ph.D., CCRC, CCRA	VP, Clinical Evaluations	13Feb2018 Date
Joy Frank, R.N.	Executive VP, Clinical Evaluations	2/13/18 Date

For Sponsor:

Name	VP Clinical Operations Title	13Feb2018 Date

CONFIDENTIAL

TABLE OF CONTENTS

ABBREVIATIONS

AE – Adverse Event

CFR – Code of Federal Regulations

CPT – Consumer Product Testing Company, Inc.

CRF – Case Report Forms

GCP – Good Clinical Practice

HIPAA – Health Insurance Portability and Accountability Act

ICF – Informed Consent Form

IRB – Institutional Review Board

PI – Principal Investigator or designee

SAE – Serious Adverse Event

SOP – Standard Operating Procedure

DEFINITIONS

Adverse Event (AE): Any negative experience that a participant has during the course of a clinical trial, including new or worsening symptoms or laboratory abnormalities.

Belmont Report: A document entitled "Ethical Principles and Guidelines for the Protection of Human Subjects of Research" that was produced by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research in 1978. The Belmont Report identifies three fundamental ethical principles for all human subjects' research: respect for persons, beneficence, and justice.

Blinding: When research participants are unaware of the assigned "treatment." In a single-blinded trial, the subjects do not know what treatment they are receiving. In a double-blinded trial, the subjects AND the investigators are unaware of the treatment assigned, as are the monitors and statisticians in some cases.

Case Report Form (CRF): A record of information collected on each subject during the clinical trial.

Clinical Investigation: A systematic trial designed to evaluate a test material in humans.

Clinical Research: A trial in human subjects.

Clinical Trial: Any prospective investigation in which the applicant or investigator determines the method of assigning the test material or other interventions to one or more human subjects.

Declaration of Helsinki: A series of guidelines adopted by the 18th World Medical Assembly in Helsinki, Finland in 1964. Recommendations include the procedures required to ensure subject safety in clinical trials, including informed consent and Ethics Committee reviews.

Ethics Committee: An independent group of medical and nonmedical people who verify the integrity of a trial and ensure the safety, integrity, and human rights of the subjects.

Exclusion Criteria: Characteristics that would prevent a subject from being eligible to participate in a research trial, as specified in the protocol.

Good Clinical Practices (GCPs): International ethical and scientific quality standards for the design, conduct, monitoring, recording, auditing, analysis, and reporting of trials.

Health Insurance Portability and Accountability Act (HIPAA): Legislation passed in 1996 that includes a privacy rule creating national standards to protect personal health information.

Inclusion Criteria: A list of requirements that a subject must meet to be eligible to participate in a research trial, as specified in the protocol.

Informed Consent: The verification of a person's willingness to volunteer in a research trial. The verification is requested only after the person has received complete, objective information about the research, including its objectives, potential benefits, risks and inconveniences, alternative therapies that may be available (if applicable), and the subject's rights and responsibilities in accordance with the current revision of the Declaration of Helsinki (as amended). Consent is given by executing the Informed Consent Form (ICF).

Institutional Review Board (IRB): An independent group of professionals designated to review and approve the clinical protocol, Informed Consent Forms, trial advertisements, and patient brochures to ensure that the trial is safe and effective for human participation. The IRB also ensures that the trial adheres to FDA regulations.

Investigator: A medical professional, usually a physician but also sometimes a nurse, pharmacist, or other professional, under whose direction a test material is given or dispensed. A principal investigator (PI) is responsible for the overall conduct of the clinical trial.

MedWatch Program: A national educational/promotional initiative to educate health professionals about the importance of reporting serious adverse events and important product problems, to facilitate reporting to the FDA if they choose to do so, and to provide feedback to the health professional community as new safety information becomes available.

Monitor: The Sponsor or CRO representative who reviews trial records to determine that it is being conducted according to the protocol.

Monitoring: Reviewing a clinical trial, ensuring that conduct, proper records, and reports are in accordance with the approved protocol, standard operating procedures, GCPs, and regulatory requirements.

Protocol: A detailed plan that sets forth the objectives, design, and methods for a clinical trial.

Protocol Amendment: Changes or clarifications made in writing to the original protocol.

Quality Assurance: Systems and procedures designed to ensure that a trial is being performed in compliance with the approved protocol, standard operating procedures, GCPs, and that the data being generated are accurate.

Randomization: A method of assigning trial test material such that each subject has an equal chance of being assigned to each treatment or control group. Randomization guards against selection bias.

Serious Adverse Event (SAE): Any adverse event (AE) that is fatal, life-threatening, or permanently disabling, or that results in new or prolonged hospitalization, in a congenital anomaly/birth defect, or is an important medical event.

Source Data: All information contained in original records and certified copies of results or observations.

Source Documents: Where medical information is originally recorded, including physician notes, laboratory reports, discharge summaries, autopsy reports, etc.

Sponsor: The entity who takes responsibility for initiation, management, and financing of research.

Standard Operating Procedures (SOPs): Official, detailed, written instructions for the management of clinical trials. SOPs ensure that all the functions and activities of a clinical trial are carried out consistently and efficiently.

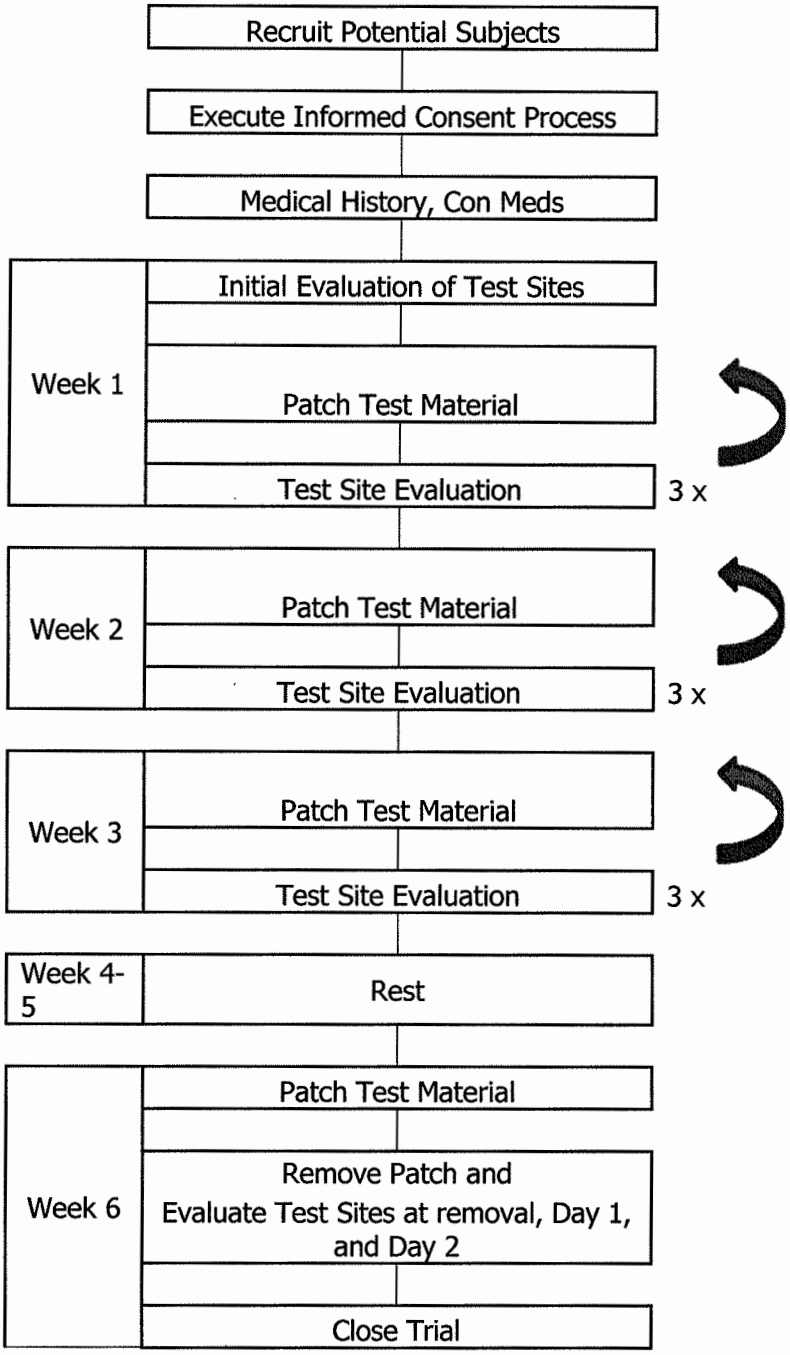
Subject: A patient or healthy person participating in a research trial.

Test Materials: Any material or product that is the subject of testing or a clinical trial. This may also be referred to as a "test article" or "investigational material."

SYNOPSIS

Name of Company: NeXtGen Biologics, Inc.	Name of Investigational Test Materials: NeoMatriX™ Lot: AD17H150932/AD17H150933
Title of Clinical Trial: A Human Repeated Insult Patch Test	
Investigator: Michael Caswell, PhD, CCRA, CCRC	
Sub-Investigators: Joy Frank, RN; Richard Eisenberg, MD	
Clinical Trial Center: Consumer Product Testing Company, Inc., 70 New Dutch Lane, Fairfield NJ 07004	
Publication (reference): None	
Clinical Trial Period: Approximately 6 weeks; start date to be determined	Phase of Development: I
Clinical Trial Design: This is a single-center repeated insult patch test in healthy male and female subjects aged 18 to 79 years, inclusive.	
Objectives: The first primary objective of this trial is to determine by repetitive epidermal contact, the primary or cumulative irritation potential of a test material. The second primary objective of this trial is to determine by repetitive epidermal contact, the allergic contact sensitization potential of a test material.	
Methodology: Subjects will be patched with a test material, a positive control and a negative control 10 times over 40 days, 9 during Induction Phase and 1 during Challenge Phase. Each patch will be worn for approximately two days. Before each patch application, the test site will be evaluated using the Erythemal Scoring Scale (ESS) and Additional Reaction Scoring. Following a Rest Phase of approximately 10 to 14 days, the subjects will again be patched on a virgin test site with the test material (but not the negative control nor the positive control). After two days of skin contact, the test sites will be evaluated using the ESS and Additional Reaction Scoring on removal day and Days 1 and 2 post-removal. The ESS and Additional Reaction Scoring results will be evaluated to determine the allergic potential of the test material. The three test sites will be as follows: test material; saline negative control; and positive control (0.4% SLS).	
Number of Subjects Planned and Analyzed: Approximately 57 subjects will be enrolled in the trial so that at least 50 subjects will complete the trial. Data from all subjects who complete the Induction Phase will be analyzed for irritant contact dermatitis potential. Data from all subjects who complete the Challenge Phase will be analyzed for allergic contact sensitization potential.	
Diagnosis and Main Criteria for Inclusion: Healthy adult male and non-pregnant females aged 18-79 years, inclusive.	
Test Material, Dose and Mode of Administration, Batch Number: The test material, approximate 8 mm disc of NeoMatriX™, will be applied to the cotton pad of each patch. Patches consisting of the test material and controls will be applied to specific test sites on the back of each subject.	
Duration of Treatment: Fresh patches of test material and controls during the Induction Phase (approximately 3 weeks); no patches during the Rest Phase (approximately 2 weeks); and one patch of test material during Challenge Phase (approximately 1 week). No negative control nor positive control will be applied during the Challenge Phase.	
Criteria for Evaluation: Irritant contact dermatitis potential and allergic contact sensitization potential will be assessed through the evaluation of the test sites of application using the ESS and Additional Reaction Scoring.	
Statistical Methods: The ESS scores and Additional Reaction Scoring scores will be tabulated. The incidence of AEs, new-onset AEs, will be summarized. Maximum intensity and duration of AEs will be summarized by treatment group.	

FLOW CHART OF TRIAL DESIGN



1 Background

A repeated insult patch test is a test devised to ascertain if an agent has the potential to cause contact irritation or contact allergy in the skin (Reference 12.1 and 12.2). Allergy is only elicited in immunologically competent individuals who have become sensitized through exposure to the agent following repeated cutaneous patch applications.

2 Trial Objective

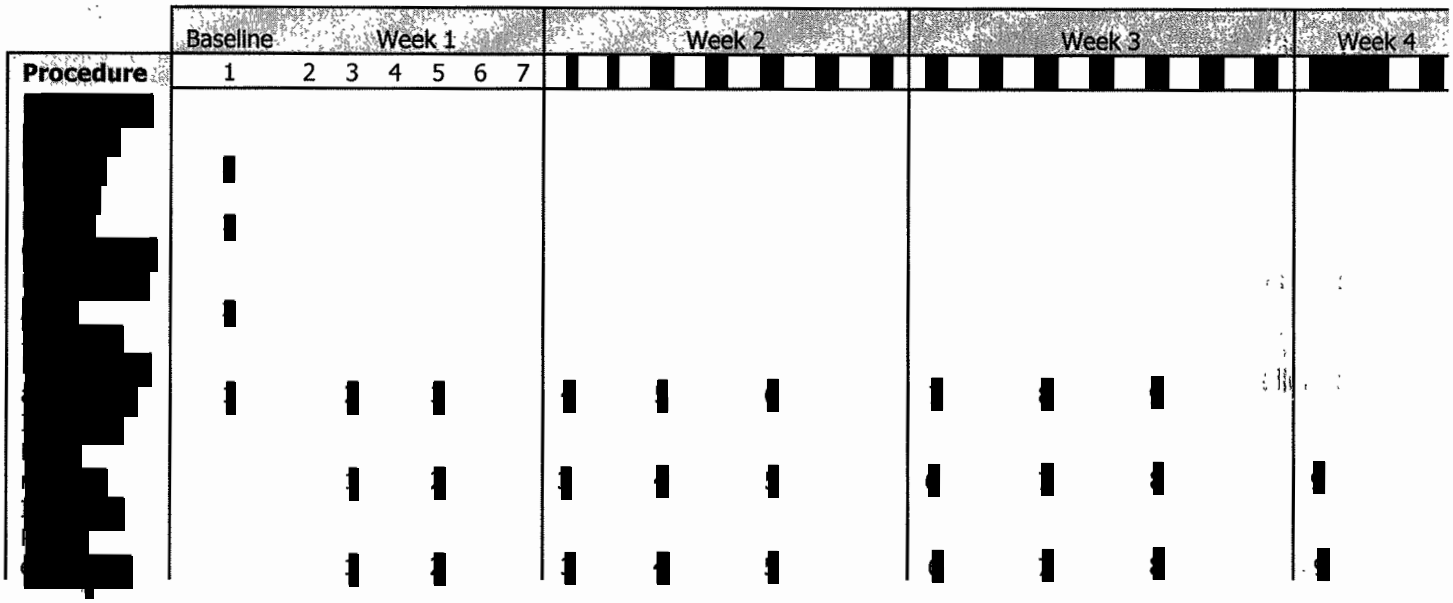
The first primary objective of this trial is to determine by repetitive epidermal contact, the primary or cumulative irritation potential of a test material.

The second primary objective of this trial is to determine by repetitive epidermal contact, the allergic contact sensitization potential of a test material.

3 Proposed Schedule

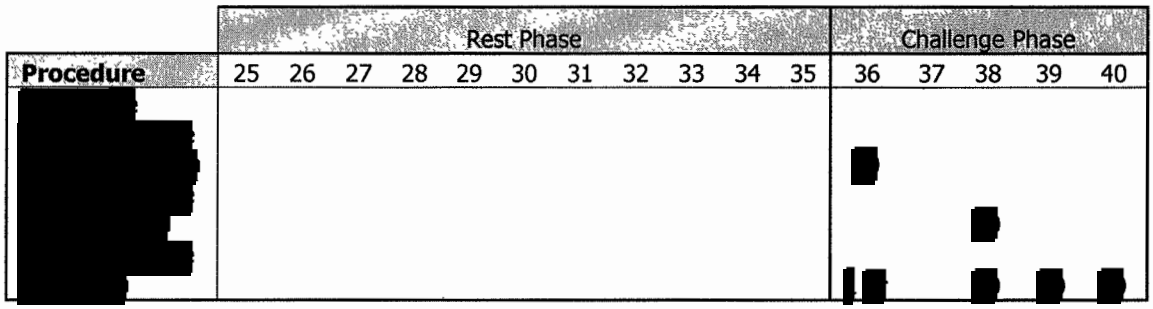
Proposed trial initiation and termination dates will be established prior to the start of testing. The summary schedule of Induction Phase visits is shown in the table below.

Induction Phase Visits



The summary schedule of Rest Phase and Challenge Phase visits is shown in the table below.

Rest Phase and Challenge Phase Visits



4 Test Materials

4.1 Identification

The Sponsor's coded test material will be uniquely identified by a CPT trial number. CPT will record the test material name, physical description, lot number (if applicable), Sponsor and date received into the log-in database.

4.2 Storage

[redacted]

4.3 Controls

[redacted]

4.4 Disposition

At the conclusion of the trial, all remaining test material will be retained by CPT for 30 days and then discarded in accordance with local, state and federal laws and regulations unless the Sponsor has arranged for a different disposition in writing.

5 Selection and Withdrawal of Subjects

5.1 Number of Subjects

At least 50 subjects will complete the trial. Subjects who meet all of the inclusion criteria (Section 5.2) and none of the exclusion criteria (Section 5.3) will qualify for the trial.

5.2 Inclusion Criteria

1. Subjects must be 18-79 years of age (inclusive);
2. Subjects must understand and execute an Informed Consent Form that includes a HIPAA statement;
3. Subjects must be considered dependable and able to follow directions; and
4. Subjects must receive a copy of their executed Informed Consent Form.

5.3 Exclusion Criteria

1. Subjects who are in ill health, i.e., a febrile illness lasting more than 24 hours in the six days prior to first patch application;
2. Subjects who are taking medications other than birth control, which could influence the purpose, integrity or outcome of the trial;
3. Female subjects who are pregnant, planning to become pregnant or lactating during the course of the trial;
4. [redacted]

9. Subjects with a significant past medical history of hepatic, renal, cardiac, pulmonary, digestive, hematological, neurological, locomotor or psychiatric disease;
10. Subject with a history of asthma only if requiring regular medication or hay fever that required prescription treatment in two or more of the previous three years;
11. Subjects with a history of multiple drug hypersensitivity;
12. Subjects with immunization less than 10 days prior to the test patch application;
13. Subjects with a medical history indicating atopy;
14. Subjects with a sensitization or questionable sensitization in a RIPT.

5.4 Prohibitions and Restrictions

1. No use of aspirin, excluding a daily dose of 81 mg, or non-steroidal anti-inflammatory drugs for the duration of the trial;

2. No use of tanning beds or sun lamps or deliberate exposure of the test sites to natural sunlight for the duration of the trial;

3. No immunization during the trial.

5.4 Withdrawal of Subjects

The subject is free to withdraw their consent to participate in the trial at any time and for any reason, in accordance with the principles of the World Medical Association Declaration of Helsinki (as amended) and of the Belmont Report. The PI also has the right to withdraw a subject from the trial for safety, lack of efficacy or administrative reasons.

Possible reasons why a subject may be withdrawn from the trial include the following:

1. Experiences a serious or intolerable AE;
2. Develops, during the course of the trial, symptoms or conditions listed in the exclusion criteria, including pregnancy;
3. Takes medications that are contraindicated, as described in the exclusion criteria;
4. Incurs a protocol violation such as failure to comply with the specified treatment regimen or failure to comply with the visit schedule; or
5. Requests an early discontinuation due to:
   - A clinical reaction for which the PI did not consider removal from the trial to be necessary;
   - Other (non-specific) subject-initiated reason

5.5 Disposition of Withdrawn Subjects

The date the subject is withdrawn from the trial and the reason for discontinuation will be recorded on the CRF. All evaluations scheduled for the final trial visit will be completed as soon as possible after the subject is withdrawn from the trial.

When a subject fails to return for scheduled trial visits, the PI or designee will make a reasonable effort to contact the subject and determine why the subject failed to return. This information will be recorded on the CRFs. The PI will encourage all subjects who decide to withdraw from the trial to complete all evaluations, which may be necessary to assure that the subject is free of untoward effects, and to seek appropriate follow-up for any continuing problem.

6 Methodology

[redacted]

6.1 Design

This is a single-center RIPT in healthy male and female subjects aged 18 to 79 years, inclusive. Subjects will be screened for eligibility within 7 days prior to the first dose administration. Subjects will be asked to appear at the Testing Facility on Day 0 for the first application of patches. During the Induction Phase subjects will be patched 9 times in 21 days. Evaluations of the test sites will occur prior to patch application. The scores of these evaluations will be analyzed for irritant contact dermatitis potential.

After an approximately 2 week Rest Phase, subjects will return to the Testing Facility for the Challenge Phase. Virgin sites on the subjects' back will receive patches. The patches will remain on the test sites for two days of continuous skin contact. Evaluations of the sites will occur the day of patch removal and 1 day and 2 days after patch removal. The scores of these evaluations will be analyzed for allergic contact sensitization potential.

6.2 Patch

Prior to the initiation of the trial, the test material will be supplied as an 8mm disc packaged [redacted]

6.3 Test Procedure

[redacted]

greater require discontinuation of further applications at that test site. Application

[redacted]

6.3.2 Challenge Phase

[redacted]

6.3.3 Re-Challenge Phase

In the event of a significant reaction occurring during the Challenge phase, the PI may decide to schedule a Re-Challenge Patch test for confirmatory purposes. This follow-up investigation will be conducted approximately 2 weeks after the completion of the Challenge Phase. The application of the patch to a virgin test site on the back will be identical to the Challenge Phase. Additionally, the subject may conduct repetitive applications to the anti-cubital fossa for 4 consecutive days. Observations of both test sites will be recorded Days 1, 2 and 3 post application.

6.4 Evaluation

6.4.1 ESS

Erythema at the test site is evaluated according to the ESS shown below. Any score of 2 through 4 will be captured as an AE.

6.4.2 Additional Reaction Scoring

If present, each additional reaction sequela is evaluated according to the following letter scale and a corresponding numerical scale to indicate severity shown below. Any Severity Score of 2 through 4 will be captured as an AE.

7 Statistical Methods

None anticipated.

8 Safety

An adverse event (AE) is any unfavorable and unintended sign, symptom, or disease that may or may not be considered related to the test material. This includes unfavorable or unintended change in body structure (signs), body function (symptoms), abnormal or severely altered laboratory result, or worsening of any pre-existing condition that occurs during the course of the trial.

[redacted]

Also, each subject will be carefully monitored for the development of any AEs. This information may be obtained from signs and symptoms detected during each examination, observations by the trial personnel or spontaneous reports from the subjects. This includes AEs resulting from concurrent illnesses, reactions to concomitant medications or progressive disease states.

All AEs, whether volunteered, elicited or noted during examination, shall be recorded on the subject's CRF using the Common Terminology Criteria for Adverse Events (CTCAE) v.4.

The PI will evaluate all AEs for their relationship to, or association with the test material (or other causes) and their intensity. Additionally, the actions taken (*e.g.*, reduction of test material concentration, discontinuation of test material application, administration of treatment, *etc.*) and the resulting outcome of the AE will be indicated on a CRF (*e.g.,* Sponsor, CPT, MedWatch or other appropriate Form).

Any subject who is withdrawn from the trial due to an AE will be followed until the outcome of the event is determined, and the PI will prepare a written summary of the event and document the available follow-up information on a CRF.

8.1 Relationship to Test Materials

The relationship or association of the AE to a test material will be characterized as unlikely, possible or probable (Reference 12.3). Assessments shall be recorded on the CRF.

Causality Term	Assessment Criteria
Probable	Event or laboratory test abnormality, with plausible time relationship to test material intake
	Unlikely to be attributed to condition (or disease) or other products in use by subject
	Response to withdrawal clinically reasonable
	Rechallenge satisfactory or not required
Possible	Event or laboratory test abnormality, with reasonable time relationship to test material intake
	Could also be explained by condition (or disease) or other products in use by subject
	Response to withdrawal unclear or lacking
Unlikely	Event or laboratory test abnormality, with a time to test material intake that makes a relationship improbable (but not impossible)
	Condition (or disease) or other products provide plausible explanations

For safety analyses, AEs that are classified as a possible or probable association to a test material shall be considered test material-related AEs.

Follow-up of the AE, after the date of discontinuation of exposure to test material is required if the AE or its sequelae persist. Follow-up is required until the event or its sequelae resolve or stabilize at a level acceptable to the PI and to the Medical Monitor.

8.2 Severity of Adverse Event

The severity of each AE will be graded using the following criteria:

Grade	Description
1	Mild - Minor AEs requiring no specific medical intervention including asymptomatic laboratory findings only, or findings of marginal clinical relevance.
2	Moderate - AEs requiring minimal, local, and/or noninvasive intervention.
3	Severe - Severe and undesirable AEs involving significant symptoms requiring hospitalization or invasive intervention; transfusion; elective interventional radiological procedure; or therapeutic endoscopy or operation.
4	Life-threatening or debilitating - AEs complicated by acute, life-threatening metabolic or cardiovascular complications such as circulatory failure, hemorrhage, or sepsis. Also, life-threatening physiologic consequences; need for intensive care or emergent invasive procedure; emergent interventional radiological procedure, therapeutic endoscopy or operation.
5	Death

If the Grade changes within a day, the maximum Grade shall be recorded. If the Grade changes over a longer period of time, the changes shall be recorded as separate events (having separate onset and stop dates for each grade).

8.3 Serious Adverse Events

The PI will evaluate all serious AEs as to their intensity, relation to test material, outcome, and action taken. An SAE is defined as any AE that suggests a significant clinical hazard, contraindication, side effect, or precaution. This includes any event which:

- Results in death;
- Is life-threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Results in a congenital anomaly/birth defect;
- Is an important medical event based on medical judgment, which jeopardizes the subject and requires medical or surgical intervention to prevent one of the outcomes listed above.

ANY SAE, INCLUDING DEATH DUE TO ANY CAUSE, WHICH OCCURS DURING THE TRIAL, WHETHER OR NOT RELATED TO THE TEST MATERIAL, MUST BE REPORTED TO THE SPONSOR OR MEDICAL MONITOR WITHIN 24 HOURS OF WHEN THE PI BECAME AWARE OF THE SAE.

Dayna Healy
dhealy@nextgenbiologics.com

The PI must complete an AE form and send the form to the Medical Monitor or Sponsor within 24 hours of when the PI became aware of the SAE.

CPT may supply MedWatch Forms for SAE reporting, but the responsibility for reporting SAEs to FDA rests with the Sponsor or Medical Monitor. If additional information regarding a previously submitted SAE is obtained, a follow-up SAE report will be completed and sent to the Sponsor or Medical Monitor as indicated above. A copy of safety reports that are filed with the FDA will be sent to each PI participating in any ongoing trials the Sponsor is conducting with the same test material.

The PI will promptly notify the IRB for only the following AEs.

- A single occurrence of a serious event that is uncommon and strongly associated with drug exposure.
- A single occurrence, or more often a small number of occurrences of a serious, event that is not commonly associated with drug exposure, but uncommon in the clinical trial populations.
- Multiple occurrences of an AE that, based on an aggregate analysis, is determined to be an unanticipated problem. There should be a determination that the series of AEs represents a signal that the AEs were not just isolated occurrences and involve risk to human subjects.
- An SAE that is described in the investigator's brochure, protocol, or informed consent documents, but occurs at a specificity that is inconsistent with prior observations.
- An SAE that is described or addressed in the investigator's brochure, protocol or informed consent documents, but for which the rate of occurrence in the trial represents a clinically significant increase in the expected rate of occurrence.
- Any other AE or safety finding that would cause the sponsor to modify the investigator's brochure, clinical trial protocol, or informed consent documents, or would prompt other action by the IRB to ensure the protection of human subjects.

8.4 Management of Adverse Events

All AEs will be reported from the time a signed and dated informed consent form is obtained until completion of the last trial-related procedure. Those AEs meeting the definition of SAEs must be reported using the Adverse Event Form, including SAEs spontaneously reported to the PI within 30 days after the subject has completed the trial (including post-trial follow up). The Sponsor assumes responsibility for appropriate reporting of adverse events to the appropriate regulatory authorities.

All pregnancies occurring during clinical trials must be reported to the Sponsor, or its designee, by the PI within 24 hours of observation or notification of the occurrence. All efforts should be made to obtain follow-up information regarding the outcome of pregnancy and any postnatal sequelae in the infant. Although the occurrence of pregnancy is not an SAE, complications or serious outcomes of the pregnancy must be reported as appropriate. Events that meet the criteria for an SAE must be reported. Pregnancy is considered an exclusion criterion in this trial. Any trial subject who becomes pregnant during trial participation must promptly discontinue further administration of the test material.

Symptomatic treatment of suspected AEs shall be initiated as medically indicated. Any such treatment must be recorded on the CRF. Interruption or discontinuation of test material application may also be required in some circumstances. Causes of AEs other than the trial test material (such as intercurrent illness, other medications, or treatments) shall be excluded before adjustment, interruption, or discontinuation of the trial test material. If there is doubt concerning the cause of a serious or potentially serious AE, exposure to the trial test material shall be discontinued.

8.5 Test Material Deficiency

Any inadequacy of the test material with respect to its identity, quality, durability, reliability, or performance will be considered a deficiency. Test material deficiencies can include but are not limited to malfunctions, use errors, and inadequate labeling.

Any deficiency identified with the test material through the trial will be recorded on the appropriate CRF along with the date of occurrence and a full description of the deficiency. Any AE occurring as a result of the deficiency will be recorded on the AE CRF page as described (Section 7).

9 Source Data and Documents

All data reflecting subject experiences with the trial regimen will be reported by the PI to the Sponsor. One document serves as both the source and CRF document. Whenever possible, all data and observations shall be recorded on CRFs. The CRFs are peer reviewed by the clinic staff, as well as reviewed by CPT's Quality Assurance Unit.

CRFs include all original records of observations, results and activities necessary to reconstruct and evaluate the trial. CRFs include, for example, ICFs, subject notes, and any other records of procedures performed during the trial. All CRFs are to be executed by the PI in a timely manner. Data is reviewed by looking at the CRFs. Correction of CRFs will be according to the SOPs at CPT.

10 Quality Control and Quality Assurance

10.1 Trial Monitoring by the Sponsor

In accordance with current FDA regulations and GCP guidelines, the Sponsor's Monitor or designee may periodically inspect CRFs, research facilities and clinical laboratory facilities associated with this trial at mutually convenient times during or after completion of the trial (Reference 12.4). The monitoring visits provide the Sponsor with the opportunity to evaluate the progress of the trial, verify the accuracy and completeness of CRFs, assure that all protocol requirements, applicable FDA laws and regulations and PI's obligations are being fulfilled and resolve any inconsistencies in the CRFs.

10.2 Trial Reviewing by CPT Quality Assurance Department

The CPT Quality Assurance Department shall periodically audit the trial for compliance with the approved protocol (or written instructions provided by the Sponsor), CPT SOPs, and all applicable laws and regulations. Quality Assurance shall review trial records, documents, and reports for accuracy, completeness, consistency and compliance with the approved protocol (or written instructions received from the Sponsor), CPT SOPs, and all applicable laws and regulations.

10.3 Data Maintenance

Trial data shall be maintained in accordance with the intent and purpose of GCP guidelines, CPT SOPs and all applicable laws and regulations. Where trial data is entered into electronic databases, audits shall be conducted to verify accuracy of data entries against CRFs. Quality Assurance reviewing will be conducted in accordance with the SOPs of CPT to assure the quality and integrity of the clinical data.

11 Obligations of the Sponsor, the Monitor and the PI

11.1 Ethics

The Sponsor, the Monitor, and the PI will assure that all aspects of this trial are conducted in accordance with all regulations and laws guiding the protection of human subjects (including the regulations requiring informed consent (Reference 12.5). The trial will be conducted in accordance with the Principles of the Declaration of Helsinki (as amended) and the Belmont Report, with GCP, and with the SOPs of CPT.

11.2 Institutional Review Board

Prior to enrollment of subjects into the trial, as required by federal regulations (Reference 12.6), the protocol and ICF will be reviewed and approved by an appropriate IRB. The PI will assure that all aspects of the institutional review will be conducted in accordance with current federal regulations. A letter documenting the IRB approval with the names and titles of the IRB members may be received by the Sponsor upon request. Amendments to the protocol or the ICF will be subject to the same requirements as the originals.

The PI shall submit a progress report at least annually to the IRB of those test material-specific trials approved by the IRB. This report shall include: the total number of test materials evaluated using this protocol; a description of any changes in trial procedures or amendments to the protocol; deviations from the protocol; the number and type of subjects evaluated; the number of subjects who discontinued (and the reasons for discontinuation); the number of subjects who completed the trial; and a description of any AEs.

The PI shall promptly notify the IRB of SAEs or any other information that may have an impact on the safety of the trial.

11.3 Informed Consent

Written informed consent must be obtained from each potential subject prior to entering the trial (Reference 12.5). Potential subjects will be informed of the nature of the trial and shall receive complete answers to any questions raised during the consenting process. A signed ICF shall be provided to each subject. The PI must assure that executed ICFs will be obtained from each subject prior to trial entry, and that the informed consent process will be conducted in accordance with current local, state, and federal laws and regulations. Executed ICFs will be retained by the PI with the CRFs.

11.4 Research Subject Confidentiality

The names and identities of all research subjects shall be maintained in strict confidence by CPT and will not appear on CRFs or other records provided to the Monitor or the Sponsor. While the names and identities of the subjects need not be divulged, the records must be available for inspection. This can be accomplished by redacting the subject's names and replacing the name with the subject's trial ID number. The ICF must include appropriate statements explaining these requirements. If this policy conflicts with local regulatory restrictions or institutional requirements, the Sponsor or Monitor shall notify CPT prior to trial initiation.

11.5 Deviation from the Protocol

The PI will not deviate intentionally from this protocol for any reason without prior approval of the Sponsor, except when the change is necessary to eliminate an apparent immediate hazard to the subjects. In that event, the PI must notify the Sponsor in writing within 5 working days after the change is implemented.

Any other changes to this protocol must be made in the form of a formal amendment to the protocol and must be approved in writing by the PI and the Sponsor prior to implementation.

11.6 Clinical Trial Records

During the trial, the PI will maintain adequate records for the trial. This may include medical records, records detailing the progress of the trial for each subject, laboratory reports, CRFs, executed ICFs, test material disposition records, AE reports and information regarding subject discontinuation or completion of the trial.

Trial documentation may include all CRFs, monitoring logs, correspondence between the Sponsor and the PI, protocols, amendments, and deviations, test material supplies receipt, dispensing and final disposition records, and executed ICFs.

All records pertaining to the conduct of the clinical trial including signed CRFs, ICFs, drug accountability records, and other trial documentation shall be retained in the CPT archives for a minimum of 10 years. At any time prior to the completion of the tenth archival year, the Sponsor may submit a written request to obtain custody of these records and documents once the CPT archive period has been completed. This transfer shall be performed at the expense of the Sponsor. In the absence of such written requests, trial-related records and documents shall be destroyed at the end of the CPT archive period, with no further notice, in a manner that renders them useless.

11.7 Final Report

A Draft Report, describing all procedures used and a summary of the results, will be prepared and sent to the Sponsor following completion of the trial and after review by the sponsor and necessary edits, a Final Report will be prepared and sent to the Sponsor unless otherwise agreed upon by the Sponsor and CPT.

11.8 Communication and Publication of Results

The Sponsor shall retain ownership of all CRFs, data analysis and reports, which result from this trial. All information obtained as a result of the trial will be regarded as confidential.

The Final Report or Report summary is submitted for the exclusive use of the person, partnership, or corporation to whom it is addressed, and neither the Report nor the name of CPT nor any member of its staff, may be used in connection with the advertising or sale of any product or process without prior written authorization by a legally binding officer of CPT.

12 References

12.1 Shanahan RW, Weiss M, Weiss C, Murphy E. "Consumer Testing and Evaluation of Personal Care Products," in *The Chemistry and Manufacture of Cosmetics/ Volume I – Basic Science, 3rd Edition,* M. Schlossman,Ed., Allured Publishing Corp, Carol Stream, IL, 2001, pp. 433-452.

12.2 McNamee PM, Api AM, Basketter DA, Gerberick GF, Gilpin DA, Hall BM, Jowsey I, & Robinson MK. A review of critical factors in the conduct and interpretation of the human repeat insult patch test. *Regulatory Toxicology and Pharmacology, 2008;* 52:24-34.

12.3 Guidance for Industry: Good pharmacovigilance practices and pharmacoepidemiologic assessment, DHHS, FDA, March 2005

12.4 Guidance for Industry: Oversight of clinical investigations – A risk-based approach to monitoring, DHHA, FDA, August 2013

12.5 Informed Consent of Human Subjects 21 CRF Part 50 Subpart B

12.6 Institutional Review Boards, 21 CFR, Part 56