Traditional 510(k) for MammoGRIP™

July 17, 2015

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1.0 Medical Device User Fee Cover Sheet

The Medical Device User Fee Cover Sheet is provided on the following page.

2.0 CDRH Premarket Review Submission Cover Sheet

The CDRH Premarket Review Submission Cover Sheet is provided on the following page.

3.0 510(k) Cover Letter

The cover letter is provided on the following page.

MammoGRIP™
Saving Lives One Image At A Time

July 16, 2015

U.S. Food and Drug Administration
Center for Devices and Radiological Health
Document Mail Center – WO66-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

RE: Traditional 510(k) Notification for the MammoGRIP™ device

In accordance with 21 CFR Part 807, Subpart E, enclosed are one paper copy and one eCopy of a Traditional 510(k) Premarket Notification for the device identified above. The eCopy is an exact duplicate of the paper submission. MammoGRIP LLC is seeking clearance to release a new mammography positioning aid into commercial distribution in the United States. This submission demonstrates that the MammoGRIP device is substantially equivalent to devices in commercial distribution in the United States.

Prior submissions related to this device are outlined below and are discussed in Section 4.0 of this premarket notification:

- C140029 – Section 513(g) Request for Information
- Q141350 – Pre-Submission Meeting Request

This premarket notification has been formatted in accordance with the following FDA guidance documents:

- Refuse to Accept Policy for 510(k)s (December 31, 2012),
- eCopy Program for Medical Device Submissions (December 31, 2012) and
- Format for Traditional and Abbreviated 510(k)s (August 12, 2005).

Principal Factors About the Design and Use of the MammoGRIP device		
Question	**YES**	**NO**
Is the device intended for prescription use (21 CFR 801 Subpart D)?	X	
Is the device intended for over-the-counter use (21 CFR 807 Subpart C)?		X
Does the device contain components derived from a tissue or other biologic source?		X
Is the device provided sterile?		X
Is the device intended for single use?	X	
Is the device a reprocessed single use device?		X
Does the device contain a drug?		X
Does the device contain a biologic?		X
Does the device use software?		X
Does the submission include clinical information?		X

MammoGRIP™
Saving Lives One Image At A Time

Is the device implanted?		X

This submission contains technical, commercial and confidential trade secret information, and MammoGRIP LLC respectfully requests the maximum protection provided by law, in accordance with 21 CFR 807.95.

Sincerely,

Nancy DeRobertis
CEO
MammoGRIP LLC

Enclosures

4.0 Prior FDA Submissions/Feedback

The following submissions have been made for the MammoGRIP device and summaries are provided below:

- C140029 – Section 513(g) Request for Information (received April 1, 2014)
- Q141350 - Pre-Sumission Meeting Request (dated October 14, 2014)

4.1 513(g) Request for Information

A 513(g) Request for Information was filed in January 2014 to determine the regulatory classification of MammoGRIP. A copy of the 513(g) response from the agency is provided in Appendix 1, which states that MammoGRIP™ is considered an accessory to mammography and is therefore a Class II device under Title 21 of the Code of Federal Regulations (CFR) 892.1710.

MammoGRIP will not be labeled as a hand sanitizer and therefore is not subject to regulation as a combination product.

4.2 Pre-Submission Q-Sub

The Q141350 Pre-Submission Meeting Request was filed on October 14, 2014. The comments from the agency in response to each question of the pre-submission meeting are summarized below along with a response from the applicant, MammoGRIP LLC. The complete FDA pre-submission meeting response is provided in Appendix 2.

Question 1

Agency comments:

- We recommend that you provide biocompatibility testing for your device.
- Please provide the complete device formulation for MammoGRIP
- Please clarify what additional ingredients you are adding, if any.

Response

Biocompatibility testing was performed on the MammoGRIP device and the results are presented in Section 16.0.

MammoGRIP is identical in formulation to a currently marketed hand sanitizer and no additional ingredients are added to create MammoGRIP. The formulation for MammoGRIP is discussed in Section 12.3.

Question 2

No response required.

Question 3

Agency comments:

Your claim that your device can "increase the amount of breast tissue visualized" will require supporting performance data in a clinical study.

Your claim that your device can facilitate "less manipulation of the breast" would also require supporting performance data.

We recommend that you remove this claim from your IFU, or that you propose an appropriate clinical study.

Response

The revised IFU is presented in Section 14.0.

Question 4

Agency comments:

- It is not clear from your submission whether your device comes with specific manipulation techniques or if it is intended for use with standard positioning techniques. Please clarify.
- Please provide an estimate of the number of times your device would be applied per day, and provide an assessment of the risk to the technologist regarding these repeated uses.
- Please demonstrate that a residue is not imparted onto the patient's skin, or provide a rationale of why MammoGRIP would not [affect the image].

Response

The MammoGRIP device is intended to be used with standard positioning techniques and the Instructions for Use have been clarified to include this information (see Section 14.0).

The risk to the technologist is discussed in Section 16.2.

The radiolucency of MammoGRIP is discussed in Section 19.2. Images presented demonstrate MammoGRIP does not cause image artifact or alter the image.

Question 5

No response required. The indication for use statement has been revised to remove performance claims.

5.0 Indications for Use Statement

The Indications for Use form (FDA Form 3881) is provided on the next page.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date: January 31, 2017
See PRA Statement below.

510(k) Number *(if known)*

Device Name
MammoGRIP

Indications for Use *(Describe)*
MammoGRIP aids in positioning during radiologic visualization of the breast.

Type of Use *(Select one or both, as applicable)*

☒ Prescription Use (Part 21 CFR 801 Subpart D) ☐ Over-The-Counter Use (21 CFR 801 Subpart C)

CONTINUE ON A SEPARATE PAGE IF NEEDED.

This section applies only to requirements of the Paperwork Reduction Act of 1995.

DO NOT SEND YOUR COMPLETED FORM TO THE PRA STAFF EMAIL ADDRESS BELOW.

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Office of Chief Information Officer
Paperwork Reduction Act (PRA) Staff
PRAStaff@fda.hhs.gov

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB number."

6.0 510(k) Summary

Submitter:	MammoGRIP LLC
Contact Person:	Erika Huffman Medical Research Manager, Regulatory NAMSA 4050 Olson Memorial Hwy. Suite 450 Minneapolis, MN 55422 Phone: +1-763-588-9857 Fax: +1-763-287-3836 ehuffman@namsa.com
Date Prepared:	July 17, 2015
Trade Name:	MammoGRIP™
Common Name:	Mammography positioning aid
Classification Name:	Accessory to X-Ray Mammographic System, 21 CFR Part 892.1710
Regulatory Class:	Class II
Product Code:	IZH
Predicate Device:	K062141-MammoPad Radiolucent Cushion *This predicate device has not been subject to a design-related recall.*
Device Description:	MammoGRIP™ is a non-medicated, 0.1% benzalkonium chloride foam solution intended to be used during mammography to facilitate breast positioning. When MammoGRIP is applied to the technician's hands, it imparts a slightly tacky or sticky surface while it is still damp, thereby allowing the technician to have a better grip of the dry breast tissue for optimal positioning in the field of view of the mammography machine. MammoGRIP is intended to be used with standard mammogram positioning techniques.
Indications for Use:	MammoGRIP aids in positioning during radiologic visualization of the breast.
Comparison of the Technological Characteristics with the Predicate Device:	The MammoGRIP device is similar to the MammoPad device in the following ways: • Each of the devices is intended to be used as an aid to positioning during radiologic visualization of the breast. • Each of the devices is radiolucent. • Each of the devices is provided non-sterile.

	The MammoGRIP device is differerent from the predicate device in the following ways: • Physical Form
Performance Data:	The MammoGRIP device meets the following biocompatibility standards: • Intracutaneous Injection Test (Irritation) per ISO 10993-10 • Kligman Maximization Test (Sensitivity) per ISO 10993-10 The following characteristics are verified for each lot: pH, appearance, odor, and benzylkonium chloride content. In addition, radiolucency of the MammoGRIP device has been demonstrated.
Conclusion:	The data provided in this submission support the safety of the MammoGRIP device and demonstrate that the MammoGRIP device is substantially equivalent to the predicate device which is currently marketed for the same intended use.

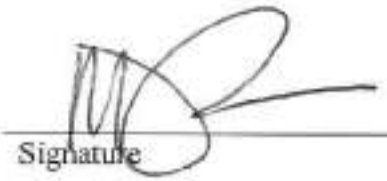
7.0 Truthful and Accurate Statement

PREMARKET NOTIFICATION

TRUTHFUL AND ACCURATE STATEMENT

(As Required by 21 CFR 807.87(k))

I certify that, in my capacity as Chief Executive Officer at MammoGRIP LLC, I believe to the best of my knowledge, that all data and information submitted in the premarket notification are truthful and accurate and that no material fact has been omitted.



Signature

Nancy DeRobertis

Name

7/16/15

Date

8.0 Class III Product Summary and Certification

MammoGRIP is not a class III device, and is not substantially equivalent to a class III device; therefore the Literature Search and Certification requirement of the Safe Medical Devices Amendments (SMDA) of 1990 is not applicable.

9.0 Financial Certification / Disclosure Statement

Clinical studies were not required in support of the premarket notification application, thus financial certifications and/or disclosures are not required.

10.0 Declarations of Conformity

This submission does not contain any declarations of conformity.

11.0 Executive Summary

11.1 Device Description

MammoGRIP™ is a non-medicated, 0.1% benzalkonium chloride foam solution intended to be used during mammography to facilitate breast positioning. When MammoGRIP is applied to the technician's hands, it imparts a slightly tacky or sticky surface while it is still damp, thereby allowing the technician to have a better grip of the dry breast tissue for optimal positioning in the field of view of the mammography machine. MammoGRIP is intended to be used with standard mammogram positioning techniques.

11.2 Indications for Use

MammoGRIP aids in positioning during radiologic visualization of the breast.

11.3 Substantial Equivalence

The MammoGRIP device is substantially equivalent to the following:

- MammoPad Radiolucent Cushion (K062141)

The MammoGRIP device is similar to the MammoPad device in the following ways:

- Each of the devices is intended to be used as an aid to positioning during radiologic visualization of the breast.
- Each of the devices is radiolucent.
- Each of the devices is provided non-sterile.

The MammoGRIP device differs from the MammoPad device in physical form. The MammoGRIP device is a foam solution while the predicate device is a foam pad. However, the intended use, indications for use, and critical functional characteristics such as radiolucency of the subject device are substantially equivalent to those of the predicate device. The differences do not introduce any new questions of safety or effectiveness as discussed in Section 13.0.

11.4 Performance Data

The specifications tested included physical specifications, such as pH and appearance, as well as functional performance such as radiolucency. Details are discussed in Section 19.0.

12.0 Device Description

12.1 Intended Use

MammoGRIP aids in positioning during radiologic visualization of the breast.

12.2 Models and Accessories

MammoGRIP will be provided in two primary packaging configurations: a 1 liter (1000 mL) cartridge (for use with a wall dispenser or mobile stand), and a 50 mL pump bottle. Both are shown in Figure 1 below. A third configuration is a sample kit consisting of the same 50 mL pump bottle, the instructions for use and an order form. The product formulation is identical for all configurations. The available system components and model numbers are listed in Table 1.

Table 1. MammoGRIP System Components

Component	MammoGRIP SKU#
1 liter Cartridge of MammoGRIP	16100-9410-MMG
50 ML Foam Pump of MammoGRIP	16100-50-MMG
Ecoflex touch-free Wall Dispenser	9415-MMG
Ecoflex touch-free Drip Tray	9410-DT-MMG
Ecoflex Mobile Stand	9415-MS-MMG

Figure 1. MammoGRIP 1000 mL and 50 mL Options

12.3 Device Description

MammoGRIP™ is a non-medicated, 0.1% benzalkonium chloride foam solution intended to be used during mammography to facilitate breast positioning. The formulation is shown in Table 2.

The Material Safety Data Sheets (MSDS) are provided in Appendix 3.

Table 2. MammoGRIP Formulation

Ingredient	%wt	Purpose	CAS #
Benzalkonium Chloride 0.1%	0.1-0.13	Active ingredient	8001-54-5
Water	NA-Proprietary	Diluent	7732-18-5
dihydroxypropyl PEG-5 linoleammonium chloride	NA-Proprietary	Foaming surfactant	168677-75-6
glycereth-2 cocoate	NA-Proprietary	Foaming, moisturizing	68201-46-7
behentrimonium chloride	NA-Proprietary	Preservative	17301-53-0
dihydroxyethyl cocamine oxide	NA-Proprietary	NA	61791-47-1

When MammoGRIP is applied to the technician's hands, it imparts a slightly tacky or sticky surface while it is still damp, thereby allowing the technician to have a better grip of the dry breast tissue for optimal positioning in the field of view of the mammography machine. MammoGRIP is intended to be used with standard mammogram positioning techniques and does not interfere with imaging as discussed in Section 19.1.

13.0 Substantial Equivalence

The MammoGRIP device is substantially equivalent to the following:

- MammoPad Radiolucent Cushion (K062141)

Table 3 provides a summary of the pertinent comparison information. The information provided effectively demonstrates the subject device is substantially equivalent to the predicate device.

Table 3. Comparison of MammoGRIP and Predicate Device

Item #	Characteristic	MammoGRIP (Subject Device)	MammoPad (Predicate Device)
1	**510(k) Number Decision Date**	TBD	K062141
2	**Manufacturer**	MammoGRIP LLC	Hologic, Inc. (formerly BioLucent, Inc.)
3	**Classification**	Class II	Class II
4	**Product Code**	IZH	IZH IYX
5	**Regulation**	21 CFR 892.1710	21 CFR 892.1710 21 CFR 892.1100
6	**Model Number(s)**	16100-9410-MMG (1 L volume) 16100-50-MMG (50 mL volume)	MP301
7	**Indications for Use**	MammoGRIP aids in positioning during radiologic visualization of the breast.	Provide padding for patient comfort and aid in positioning during radiologic visualization of the breast using x-ray or scintillation technology.
Functional Characteristics			
8	**Physical Form**	Foam solution	Foam Pad
9	**Radiolucent?**	YES	YES
10	**Biocompatibility**	Meets the following: • Intracutaneous Injection Test (Irritation) per ISO 10993-10 • Kligman Maximization Test (Sensitivity) per ISO 10993-10	Information not available – Product is currently marketed and no Medical Device Reports were found in the FDA MAUDE database to date
11	**Sterility**	Non-sterile	Non-sterile

Table 3. Comparison of MammoGRIP and Predicate Device

Instructions for Use			
12	**Warnings**	• For external use only, not for oral consumption. • In case of eye contact, flush thoroughly with water and/or seek medical attention. • Stop use and consult your doctor if irritation and/or redness develops and persists formore than 72 hours. • If swallowed, get medical help or contact a Poison Control Center right away.	Information not available
13	**Contraindications**	MammoGRIP is not for use with patients with known sensitivity to benzalkonium chloride.	Information not available

The MammoGRIP device is similar to the MammoPad device in the following ways:

- Each of the devices is intended to be used as an aid to positioning during radiologic visualization of the breast.
- Each of the devices is radiolucent.
- Each of the devices is provided non-sterile.

The MammoGRIP device is different from the MammoPad device as outlined in Table 4 below.

Table 4. Summary of Differences between MammoGRIP and MammoPad

Item #	**Characteristic**	**MammoGRIP (Subject Device)**	**MammoPad (Predicate Device)**	**Impact on safety and effectiveness**
8	Physical Form	Foam Solution	Foam Pad	The difference in physical form does not introduce new questions of safety or effectiveness as both products are intended to aid in positioning and are radiolucent which is the critical functional characteristic.

As outlined above, the intended use, indications for use, and critical functional characteristics of the subject device are substantially equivalent to those of the predicate

device. The difference in physical form between the subject device and predicate device does not introduce any new questions of safety or effectiveness over the predicate device as explained in Table 4. The information above demonstrates that the subject device is substantially equivalent to the identified predicate device.

14.0 Proposed Labeling

Device labels and instructions for use have been developed for MammoGRIP in accordance with the requirements stated 21 CFR §801 – Labeling and 21 CFR §1, Subpart B – General Labeling Requirements. The proposed labels for the front and back of the device are shown below in Figure 2 and Figure 3, respectively. The draft Instructions for Use are provided in Figure 4 below. These instructions will be provided as a package insert with each MammoGRIP device.

Figure 2. MammoGRIP Front Label

Figure 3. MammoGRIP Back Label (text only)

Active ingredient: Benzalkonium Chloride 0.1 %

Use
MammoGRIP aids in positioning during radiologic visualization of the breast.

RxOnly

Directions for Use (External Use only by Radiologic Technologist)

Step 1. Pump the MammoGRIP dispenser one time onto the palm of your hand and rub your hands together.
Step 2. While hands remain slightly tacky (before product is completely dry), stand patient in center, facing mammographic unit with hips & feet facing straight towards machine.

Step 3. Remove one side of gown & begin positioning per standard positioning techniques.

Step 4. Once the breast is pulled up and out, make sure to always bring the opposite breast forward onto the bucky but draping enough to the side that there are no folds in cleavage. MammoGRIP acquires maximum breast tissue by pulling in the superior and medial breast tissue from on top of the breast and holding it in place. Without the use of MammoGRIP, the tissue normally would have retracted once compression was applied.

Step 5. Repeat application before every view, repeat steps 1 thru 4

Inactive Ingredients

Water
dihydroxypropyl PEG-5 linoleammonium chloride
glycereth-2 cocoate
behentrimonium chloride
dihydroxyethyl cocamine oxide

Distributed by: B4 Brands, Lisbon, Iowa 52253

For Questions or Comments: Please go to www.mammogrip.com

Figure 4. MammoGRIP Instructions for Use

INDICATIONS FOR USE

MammoGRIP™ aids in positioning during radiologic visualization of the breast.

RxOnly

INSTRUCTIONS FOR USE

MammoGRIP™
Device Description

MammoGRIP™ is an Alcohol-Free solution that is fragrance-free and powered by the active ingredient Benzalkonium Chloride. The product leaves the hands feeling soft, once completely dry, without the strong smell of alcohol or chemical fragrances.

Contraindications

MammoGRIP™ is not for use with patients with known sensitivity to benzalkonium chloride.

Warnings and Precautions

- For external use only, not for oral consumption.

- In case of eye contact, flush thoroughly with water and/or seek medical attention.
- Stop use and consult your doctor if irritation and/or redness develops and persists formore than 72 hours.
- If swallowed, get medical help or contact a Poison Control Center right away.

Directions for Use

Follow the simple 5 step process below.

Step 1. Pump the MammoGRIP dispenser one time onto the palm of your hand and rub your hands together.

Step 2. While hands remain slightly tacky (before product is completely dry), stand patient in center, facing mammographic unit with hips & feet facing straight towards machine.

Step 3. Remove one side of gown & begin positioning per standard positioning techniques.

Step 4. Once the breast is pulled up and out , make sure to always bring the opposite breast forward onto the bucky but draping enough to the side that there are no folds in cleavage. MammoGRIP acquires maximum breast tissue by pulling in the superior and medial breast tissue from on top of the breast and holding it in place. Without the use of MammoGRIP, the tissue normally would have retracted once compression was applied.

Step 5. Repeat application before every view, repeat steps 1 thru 4

15.0 Sterilization and Shelf-Life

15.1 Sterilization

This section is not applicable. The MammoGRIP device is non-sterile when used.

15.2 Packaging

MammoGRIP will be provided in two primary packaging configurations: a 1 liter (1000 mL) cartridge (for use with a wall dispenser or mobile stand), and a 50 mL pump bottle. Both sizes are shipped by the case in an appropriately sized cardboard box (4 units/case for the large size and 36 units/case for the small size). Instructions for use will be included.

The sample kit will be packaged in a cardboard box and will include the 50 mL pump, instructions for use, and an order form.

15.3 Shelf-Life/Stability

MammoGRIP is proposed to be labeled with a 2 year shelf life. Stability testing performed on product with an identical formulation and stored in identical containers under identical conditions has been performed and the results are fully applicable to MammoGRIP.

The stability testing is performed by aging the product at 40 °C for 0, 30, 60, and 90 days. At each timepoint, testing is performed per the Aerobic plate counting method (reference FDA BAM Ch. 23) to determine the presence of microorganisms. The samples are then tested to confirm they meet the pre-defined specifications for concentration of active ingredient (using high-performance liquid chromatography), pH, appearance and smell as listed in Table 5.

Table 5. MammoGRIP Specifications (all timepoints)

Characteristic	Acceptance Criteria
Benzylkonium Chloride %	0.10-0.13%
pH	4.5-7.5
Appearance	Clear
Smell	Odorless

16.0 Biocompatibility

The MammoGRIP device is classified according to ISO 10993-1 as: surface, limited contact (< 24 hr) with skin. Because the MG intended use includes the application of a surface device which has limited contact with skin, consideration must be given to all relevant endpoints defined by ISO 10993-1:2009 and FDA Blue Book Memorandum #G95-1, that is: cytotoxicity, sensitization, and irritation.

Table 6 below provides a summary of the testing performed to demonstrate the biocompatibility of the materials used in this device. Full biocompatibility test reports are provided in the appendices indicated.

Table 6. Summary of Biocompatibility Testing

Test Description	NAMSA Report #	Test Result	Appendix
Cytotoxicity (Elution Test) *Per ISO 10993-5*	15T_31655_04	See Section 16.1 below	Appendix 4
Intracutaneous Injection Test (Irritation) *Per ISO 10993-10*	15T_31655_05	**PASS** very slight erythema and no edema; Primary Irritation Index calculated to be 0.8; response categorized as slight	Appendix 5
Kligman Maximization Test (Sensitivity) *Per ISO 10993-10*	15T_31655_06	**PASS** No evidence of delayed sensitization	Appendix 6

16.1 Justification for Cytotoxicity Results

As noted above, MammoGRIP was evaluated to determine the potential for cytotoxicity. This study was conducted based on the requirements of ISO 10993-5: Biological evaluation of medical devices - Part 5: Tests for in vitro cytotoxicity. The test article showed evidence of causing severe cell lysis or toxicity and did not meet the requirements of the test since the cellular reactivity grade was greater than a grade 2 (mild reactivity).

However, as discussed in Section 7.1 of the Biological Risk Assessment provided in Appendix 7, ISO 10993-5:2009 indicates in clause 10 that the results of cytotoxicity test shall be evaluated considering the classification of the device. It goes on to indicate that any cytotoxicity result can be of a concern, but indicates that it is the *potential* for *in vivo* toxicity that is the primary concern and a device cannot be determined unsuitable for a given application based solely on *in vitro* cytotoxicity data. It would be an inaccurate

decision, and an incomplete evaluation, to identify a device as not biocompatible based solely on the result of an *in vitro* test alone without some correlation to an identified *in vivo* effect. Without this correlation, materials commonly used in medical devices such as silver, latex, copper, and acetal resins, which commonly produce a positive cytotoxic response, would be deemed as unfit for device applications. Through further *in vivo* evaluation of devices containing these materials, one can conclude that they are suitable for medical device applications. This also demonstrates that *in vitro* cytotoxicity studies do not provide a perfect correlation to the clinical condition.

Because these *in vitro* tests only expose a single layer of cells in a culture, these results cannot always be directly related to effects on a complex biological system such as living tissue. Hanks *et al*. investigated why conclusions from tissue culture are sometimes different from those obtained from *in vivo* biocompatibility studies.[1] It was concluded that in many cases the *in vitro* tests were too sensitive resulting in many materials being rejected due to *in vitro* test results. Some studies have shown that candidate materials that display moderate *in vitro* cytotoxicity have excellent biocompatibility *in vivo*.[2] Rosengren *et al*. studied this phenomenon further and concluded that there is not a definite negative implication to using a biomaterial exhibiting *in vitro* cytotoxicity.[2] Some clinically effective and widely used materials as noted above have been cytotoxic in *in vitro* cytotoxicity tests but have proven to be successful in long-term clinical implantation. Mimicking a complex biological system in a single *in vitro* experiment is not always straightforward.

Considering the results of the cytotoxicity test and the guidance provided by the ISO 10993-5:2009 regarding the evaluation of cytotoxicity results, it is appropriate to focus on the results of the more clinically relevant and definitive *in vivo* studies conducted on MammoGRIP that are summarized above. In addition, MammoGRIP contains the active ingredient Bezalkonium Chloride which is an anti-microbial so the cytotoxicity of individual cells used in the cytotoxicity biocompatibility screening assay was expected. Other clinically safe anti-microbial agents (i.e. silver, BZT, isopropyl alcohol and ethyl alcohol) show similar results.

MammoGRIP was also subjected to in vivo sensitization and irritation assays. MammoGRIP demonstrated no potential to cause sensitization and only a very slight ability to cause skin irritation. From these results, it can be determined that the in vitro cell cytotoxicity results do not correspond to the *in vivo* results and can be considered an

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[1] Hanks CT, Wataha JC, Sun Z. (1996) In vitro models of biocompatibility: A review, Dent Mater, 12, 186-193.

[2] Rosengren A, Faxius L, Tanaka N, Watanabe M, Bjursten LM. (2005) Comparison of implantation and cytotoxicity testing for initially toxic biomaterials, J Biomed Mater Res, 75A, 115-122.

anomaly. The more definitive *in vivo* primary skin irritation and sensitization tests indicate that MammoGRIP will not cause patient irritation or sensitization responses.

16.2 Technologist Exposure Risk Assessment

The Margin of Safety (MOS) for the patient was calculated to be 10 per the Biological Risk Assessment provided in Appendix 7. The methodology used to estimate the patient MOS is also applicable to the technologist since the worst case exposure for the patient, for purposes of the risk assessment, is the same as the expected exposure of the technologist when MammoGRIP is used as intended during the patient's imaging session.

The patient exposure MOS calculations outlined in the risk assessment (Appendix 7) assumed a worst case of 4 MammoGRIP applications to the hands of the technologists per individual patient imaging session; therefore, with a patient MOS of 10, the estimated maximum safe number of MammoGRIP applications to the hands of the technologist is 40 per day.

17.0 Software

This section is not applicable as the MammoGRIP device does not contain software.

18.0 Electromagnetic Compatibility and Electrical Safety

This section is not applicable as the MammoGRIP device is not electrical.

19.0 Performance Testing - Bench

19.1 Verification

Table 7 lists the specifications for the MammoGRIP device and the range of acceptable values. These parameters are measured for each lot of the product and are used to determine lot acceptance during the manufacturing process. Once accepted, the lot is packaged into the various configurations described in Section 15.2.

Table 7. MammoGRIP Specifications

Characteristic	Acceptance Criteria
pH	4.5-7.5
Appearance	Clear
Smell	Odorless
Benzylkonium Chloride %	0.10-0.13%

19.2 Radiolucency

The MammoGRIP formulation is discussed in detail in Section 12.3 and the ingredients are listed below for reference. These ingredients are not radiopaque nor metallic-based and therefore it can be concluded that MammoGRIP will not affect mammography images.

Ingredient
Benzalkonium Chloride 0.1%
Water
dihydroxypropyl PEG-5 linoleammonium chloride
glycereth-2 cocoate
behentrimonium chloride
dihydroxyethyl cocamine oxide

To further support this conclusion, mammography images for several patients were compared to demonstrate that MammoGRIP does not alter the image or introduce image artifact when used as intended. Images taken previously (e.g. in prior years) without the use of MammoGRIP were compared to current images taken with the use of MammoGRIP. As can be seen in Figure 5 through Figure 7 below, the use of MammoGRIP did not alter the image or create image artifact.

Note: *The red arrows indicate areas of potential concern as noted by the physician (e.g. nodularity, carcinoma, etc.).*

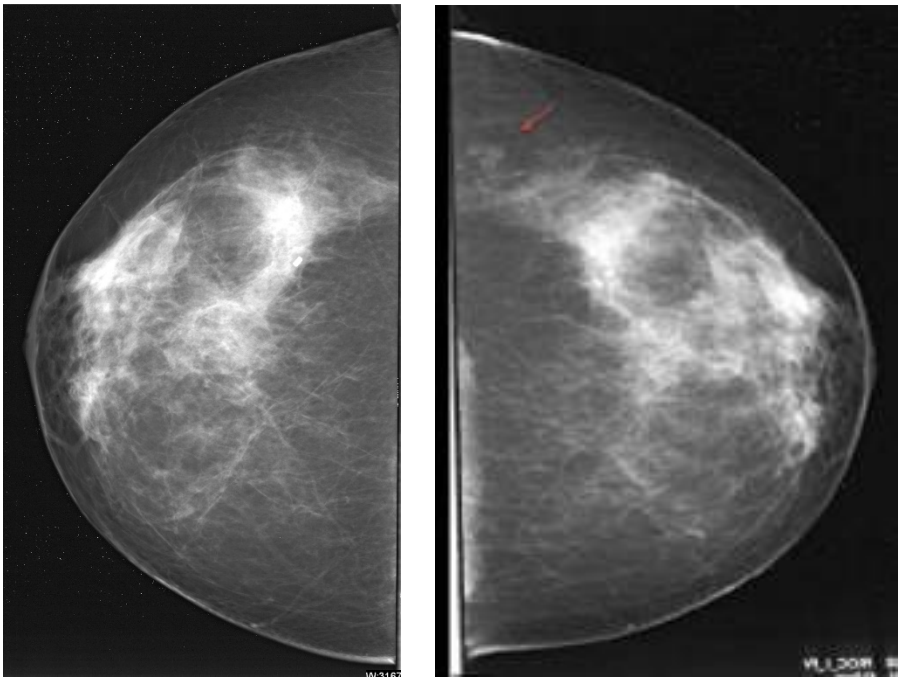


Figure 5. Image Comparision – Patient #1
without (left) and with (right) MammoGRIP
Red arrow indicates area of concern noted by physician, not image artifact

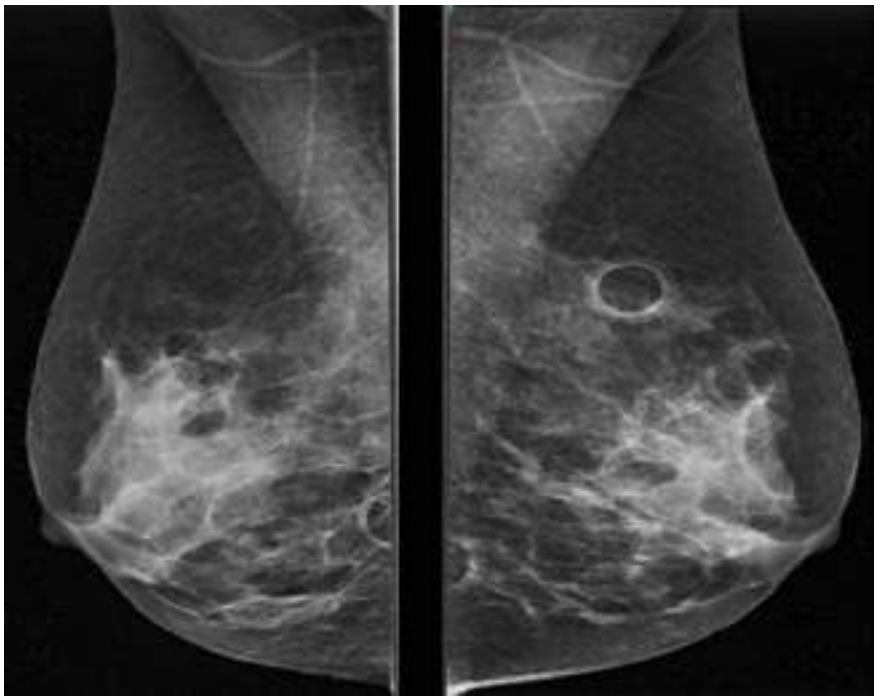


Figure 6. Image Comparison – Patient #2
without (left) and with (right) MammoGRIP

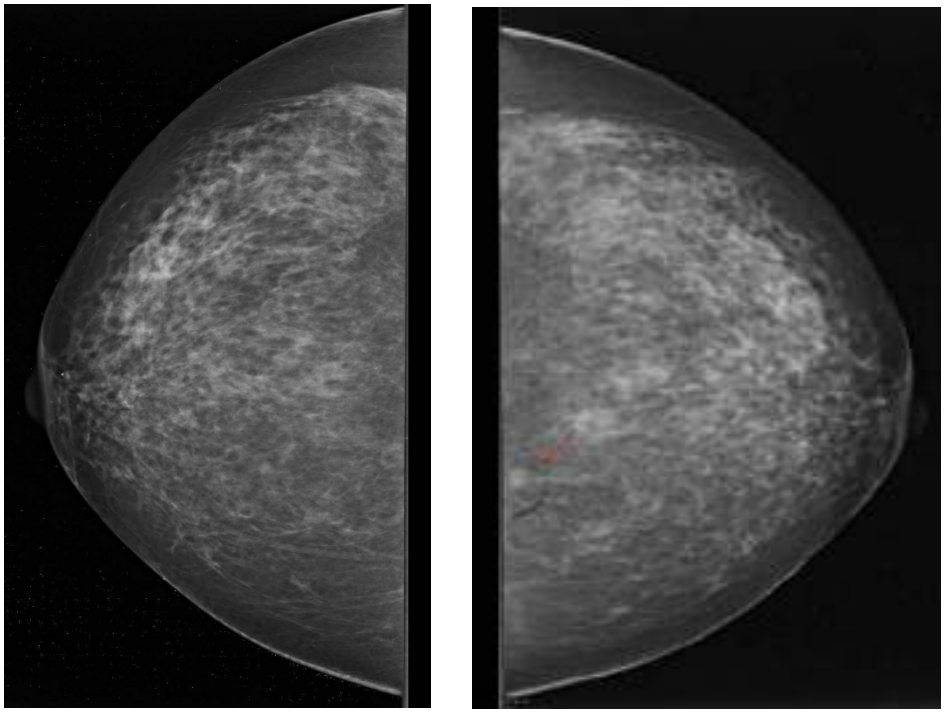


Figure 7. Image comparison – Patient #3
without (left) and with (right) MammoGRIP
Red arrow indicates area of concern noted by physician, not image artifact

19.3 Conclusion

The results described above demonstrate that the MammoGRIP device meets its specifications and performance requirements.

20.0 Performance Testing - Animal

No animal studies were performed in support of the development of this product; therefore this section is not applicable.

21.0 Performance Testing – Clinical

No clinical studies were performed in support of the development of this product; therefore this section is not applicable. Completed Form FDA 3674 is provided on the next page.

Form Approved: OMB No. 0910-0616. Expiration Date: 2/28/2018. See PRA Statement on page 2.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Certification of Compliance

Under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank (42 U.S.C. § 282(j))

(For submission with an application/submission, including amendments, supplements, and resubmissions, under §§ 505, 515, 520(m), or 510(k) of the Federal Food, Drug, and Cosmetic Act or § 351 of the Public Health Service Act.)

SPONSOR / APPLICANT / SUBMITTER INFORMATION

1. Name of Sponsor/Applicant/Submitter
MammoGRIP LLC

2. Date of the Application/Submission Which This Certification Accompanies
07/16/2015

3. Address

Address 1 *(Street address, P.O. box, company name c/o)*
1130 Route 46 West

Address 2 *(Apartment, suite, unit, building, floor, etc.)*

City
Parsippany

State/Province/Region
NJ

Country
USA

ZIP or Postal Code
07054

4. Telephone and Fax Numbers *(Include country code if applicable and area code)*

(Tel): (201) 600-0463

(Fax): (212) 239-7966

PRODUCT INFORMATION

5. For Drugs/Biologics: Include Any/All Available Established, Proprietary and/or Chemical/Biochemical/Blood/Cellular/Gene Therapy Product Name(s).
For Devices: Include Any/All Common or Usual Name(s), Classification, Trade or Proprietary or Model Name(s) and/or Model Number(s)

Accessory to X-Ray Mammographic System, Class II, MammoGRIP

Continuation Page for #5

APPLICATION / SUBMISSION INFORMATION

6. Type of Application/Submission Which This Certification Accompanies

☐ IND ☐ NDA ☐ ANDA ☐ BLA ☐ PMA ☐ HDE ☒ 510(k) ☐ PDP ☐ Other

7. Include IND/NDA/ANDA/BLA/PMA/HDE/510(k)/PDP/ Other Number *(If number previously assigned)*

If BLA was selected in item 6, provide Supplement Number

8. Serial Number Assigned to Application/Submission Which This Certification Accompanies

CERTIFICATION STATEMENT / INFORMATION

9. Check only one of the following boxes *(See instructions for additional information and explanation)*

☒ A. I certify that the requirements of 42 U.S.C. § 282(j), Section 402(j) of the Public Health Service Act do not apply because the application/submission which this certification accompanies does not reference any clinical trial.

☐ B. I certify that the requirements of 42 U.S.C. § 282(j), Section 402(j) of the Public Health Service Act do not apply to any clinical trial referenced in the application/submission which this certification accompanies.

☐ C. I certify that the requirements of 42 U.S.C. § 282(j), Section 402(j) of the Public Health Service Act apply to one or more of the clinical trials referenced in the application/submission which this certification accompanies and that those requirements have been met.

Certification Statement / Information section continued on page 2

CERTIFICATION STATEMENT / INFORMATION *(Continued)*

10. If you checked box C, in number 9, provide the National Clinical Trial (NCT) Number(s) for any "applicable clinical trial(s)," under 42 U.S.C. § 282(J)(1)(a)(i), section 402(j)(1)(a)(i) of the Public Health Service Act, referenced in the application/ submission which this Certification accompanies. *(Add continuation page as necessary.)*

NCT Number(s): _____ _____ _____ _____ _____

Continuation Page for #10

The undersigned declares, to the best of her/his knowledge, that this is an accurate, true, and complete submission of information. I understand that the failure to submit the certification required by 42 U.S.C. § 282(j)(5)(B), section 402(j)(5)(B) of the Public Health Service Act, and the knowing submission of a false certification under such section are prohibited acts under 21 U.S.C. § 331, section 301 of the Federal Food, Drug, and Cosmetic Act.

Warning: A willfully and knowingly false statement is a criminal offense, U.S. Code, title 18, section 1001.

11. Name and Title of the Person who Signs Number 15

Name	Title
Nancy DeRobertis	Chief Executive Officer

12. Address

Address 1 *(Street address, P.O. box, company name c/o)*	13. Telephone and Fax Numbers *(Include country code if applicable and area code)*
1130 Route 46 West	
Address 2 *(Apartment, suite, unit, building, floor, etc.)*	(Tel): (201) 600-0463
City: Parsippany; State/Province/Region: NJ	(Fax): (212) 239-7966
Country: USA; ZIP or Postal Code: 07054	

14. Date of Certification: 7/16/15

15. Signature of Sponsor/Applicant/Submitter or an Authorized Representative *(Sign)* — Sign

This section applies only to requirements of the Paperwork Reduction Act of 1995.

*****DO NOT SEND YOUR COMPLETED FORM TO THE PRA STAFF EMAIL ADDRESS BELOW.*****

The burden time for this collection of information is estimated to average 15 minutes and 45 minutes (depending on the type of application/ submission) per response, including the time to review instructions, search existing data sources, gather and maintain the data needed and complete and review the collection of information. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
Paperwork Reduction Act (PRA) Staff
PRAStaff@fda.hhs.gov

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB number."

Appendix 1. 513(g) Request - FDA Response

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Document Control Center – WO66-G609
Silver Spring, MD 20993-0002

May 20, 2014

Womens Imaging Solutions Enterprises, LLC, dba, WISE
% Irving L. Wiesen, Esq.
Law Offices of Irving L. Wiesen, P.C.
420 Lexington Avenue, Suite 2400
NEW YORK NY 10170

Re: C140029
Device Name: MammoGRIP™
Dated: January 16, 2014
Received: April 1, 2014

Dear Mr. Wiesen:

We have reviewed the above referenced request for information, submitted in accordance with Section 513(g) of the Federal Food, Drug, and Cosmetic Act (Act), regarding the regulatory requirements applicable to the MammoGRIP™. Based on the information provided in your submission, it appears that your device is intended as an aid for positioning patient during a mammographic exam. Thus, we believe the MammoGRIP™ is an accessory to a Mammographic X-ray System. An accessory is a device that in general is regulated under the same classification regulation as the device with which it is used. The Food and Drug Administration (FDA) has classified a Mammographic X-ray System as a class II device under Title 21 of the Code of Federal Regulations (CFR) 892.1710. You will need to submit a premarket notification [510(k)] and receive FDA clearance prior to marketing your device. You may not market this device until you have received a letter from FDA allowing you to do so. If you market the device without conforming to these requirements, you will be in violation of the Act.

Please be advised that Title 21 Code of Federal Regulations, Part 807, Subparts A-D, requires all establishments, whether foreign or domestic, that are engaged in the manufacture, preparation, propagation, compounding, or processing of a device that is imported or offered for import into or distribution in the U.S. to register and list with the FDA. If you have any questions regarding the registration and listing requirements, please call 301-796-7400.

Based on the information provided in your submission, we could not determine whether MammoGRIP™ is also intended to be used as a hand sanitizer. If so, MammoGRIP™ would be a combination product and a Request for Designation (RFD) would need to be submitted to the Office of Combination Products (OCP). OCP is the component of the Food and Drug Administration responsible for determining the classification of a product as a drug, biological product, or device under section 563 of the act as well as assignment of combination products, subject to section 503(g) of the act, to a lead Center within the agency based on primary mode of action. See Staff Manual Guide 1410.701, available at http://www.fda.gov/AboutFDA/ReportsManualsForms/StaffManualGuides/ucm052536.htm.

The RFD process is outlined in 21 CFR Part 3, and 21 CFR 3.7 outlines the information required in an RFD submission. RFD submitters are encouraged to review the agency's guidance "How to Write a Request for Designation (RFD)," prior to submitting an RFD, which is available at http://www.fda.gov/RegulatoryInformation/Guidances/ucm126053.htm. Your RFD should be mailed to the address below:

Office of Combination Products
Food and Drug Administration
WO32, Hub/Mail Room #5129
10903 New Hampshire Avenue
Silver Spring, MD 20993
Tel: (301) 796-8930
Fax: (301) 847-8619

Section 513(g) of the Act requires the agency to provide information about the regulatory requirements applicable to a particular type of device. The response represents my best judgment about how the product would be regulated, based upon our review of the information you have provided, including your description of the product and its intended use. My response to a 513(g) request is not a classification decision for a device and does not constitute FDA clearance or approval for commercial distribution.

If you have any further questions regarding this letter, please contact Dr. Robert Ochs, Chief, Mammography, Ultrasound and Imaging Software Branch, at (301) 796-6661 or for general questions please contact the Division of Industry and Consumer Education at its toll free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/default.htm.

Sincerely yours,

Mary S Pastel

Mary S. Pastel, Sc.D.
Deputy Director for Radiological Health
Office of In Vitro Diagnostics
and Radiological Health
Center for Devices and Radiological Health
Food and Drug Administration

Appendix 2. Pre-Submission (Q-Sub) Meeting Request – FDA Response

Dear Ms. Kvistad,

Thank you for submitting your pre-submission regarding the MammoGRIP for our review. We have the following comments regarding your submission. For more information on the pre-submission process, please refer to the draft guidance document *Medical Devices: The Pre-Submission Program and Meetings with FDA Staff.*

You have identified the following specific questions for FDA feedback *in italics and grey highlighting.*

1. Please comment on the decision to rely on the FDA monograph for benzalkonium chloride rather than conducting additional biocompatibility testing since the formulation and basic use of the MammoGRIP™ product is identical to that of an OTC hand sanitizer.

FDA Feedback: There is not an existing monograph for antiseptic hand rubs (i.e., commonly called hand sanitizers), including those containing benzalkonium chloride. This is noted in the Federal Register notice (Volume 78, No. 242) from 12/17/2013 in which states "We are not, at this time, proposing conditions under which OTC consumer antiseptic hand rubs (commonly called hand sanitizers) or antiseptics intended for use by health care professionals are generally recognized as safe and effective (GRAS/GRAE)." In addition, to our knowledge there is no approved NDA for benzalkonium chloride as a topical antiseptic. Accordingly, we recommend that you provide biocompatibility testing for your device.

We also have the following additional comments:

- Please provide the complete device formulation for MammoGRIP which includes the chemical name of each ingredient, its percent content, a product data sheet, and its purpose.
- The Nobac datasheet that you have provided states that "*Nobac Instant Foaming Hand Sanitizer produces a fast drying, non-stick foam that contains unique non-drying conditioning and moisturizing ingredients, leaves the skin with a soft, refreshing and silky afterfeel…".* However, you state that the MammoGRIP results in a slightly tacky or sticky surface to allow for a better grip of the breast tissue. This discrepancy suggests that when you use Nobac to generate the final formulation of MammoGRIP, you may be adding other ingredients to change the chemical nature of Nobac to yield this "sticky/tacky" property. Please clarify what additional ingredients you are adding, if any.

This information is requested to facilitate our review of the biocompatibility of your device.

2. Please comment on the use of MammoPad® as a predicate product for MammoGRIP™ and MAXVIEW as a comparison device.

FDA Feedback: The MammoPad is an appropriate predicate device because it shares the same intended use as an aid to positioning of the breast during radiographic examination. You describe the MAXVIEW positioning system as being designed to increase the amount of breast tissue pulled into the field of view. You are proposing the MAXVIEW as a comparison device because you are also claiming that your device can increase the amount of breast tissue visualized. However, specifying the MAXVIEW as a comparison or reference device is not necessary to support the substantial equivalence of your device. Rather, the additional claims that you have included in your Indications for Use (IFU) compared to the MammoPad would require supporting performance data.

3. Please comment on the proposed Indications for Use statement for MammoGRIP™ taking into consideration the predicate device, the claims being made for the MAXVIEW feature and the testing performed for MammoGRIP™.

FDA Feedback: As noted in our response to #2, the MammoPad is an appropriate predicate device. There are two claims in your proposed IFU that are not included in the IFU of the MammoPad. Your claim that your device can "increase the amount of breast tissue visualized" will require supporting performance data in a clinical study (please see our comments in #5). Your claim that your device can

facilitate “less manipulation of the breast” would also require supporting performance data. Based on our review of your submission, you have not proposed a study that can demonstrate the effectiveness of your device for this claim. Therefore, we recommend that you remove this claim from your IFU, or that you propose an appropriate clinical study.

4. Please comment on the information presented for MammoGRIP™. Is this data sufficient to support the 510(k)?

FDA Feedback: The information provided in your pre-submission does include many components of a 510(k) submission, but some aspects appear to be missing (e.g., Substantial Equivalence Discussion, 510(k) Summary). For your reference, I have attached the Refuse to Accept Checklist for Traditional 510(k) Submissions that outlines the required elements for our administrative review of 510(k) submissions. Please note that it is not possible to determine whether your device is substantially equivalent during the pre-submission process. As noted in our responses to #1 and #5, we have concerns regarding the device biocompatibility and performance testing you have provided. We also have the following specific comments:

- It is not clear from your submission whether your device comes with specific manipulation techniques or if it is intended for use with standard positioning techniques. Please clarify.
- Your instructions for use specify that your device should be “applied onto the technologist’s hands before positioning a patient for each view of the mammogram” i.e., your device will be applied at least four times per patient examined. Depending on the number of patients a technologist encounters per day, this can represent a significant number of applications of your device. Please provide an estimate of the number of times your device would be applied per day, and provide an assessment of the risk to the technologist regarding these repeated uses.
- Based on our review of your submission, you have not addressed or assessed whether your device could leave a residue on the patients skin. Given that your device imparts a “tacky” property to the technologist’s hands, it is possible that a residue could be transferred to the patient’s breast (skin). Residues on the patient’s skin can lead to artifacts that interfere with interpretation of the mammogram resulting in repeat acquisition or follow-up imaging that otherwise would not be required. For example, patients are usually advised to abstain from using lotions, perfumes and deodorants for this reason. Please demonstrate that a residue is not imparted onto the patient’s skin, or provide a rationale of why it would not.

5. Please comment on the clinical data collected for MammoGRIP™. Is this data sufficient to support the proposed Indications for Use statement?

FDA Feedback: You have provided an observational clinical study comparing the PNL of images prospectively acquired with the MammoGRIP to the PNL measured on prior mammograms. We have several concerns with the study that you have provided. For example, no statistical analysis was performed, and only data from a subset of 12 (of 35) was presented. It is also not clear how many readers measured the PNL, or if they were blinded to whether the images were acquired with or without the MammoGRIP. More generally, we have concerns that the submitted study design may not be appropriate for supporting the claim in your IFU that your device can increase the amount of breast tissue visualized. We are concerned about the following potential sources of bias and uncertainty.

Year-to-year variability in visualized breast tissue: You have proposed to retrospectively use prior mammograms (6 months to 2 years prior) as the “without MammoGRIP” comparator. We recognize that this may be an appropriate comparator as it is preferable to prospectively acquiring an additional set of images on each patient. However, there may be considerable variability in image acquisition factors between the prior and current exams including differing technologists, systems and facilities. Similarly, there may be variability due to patient changes, such as weight. These sources of variability could affect the amount of breast tissue visualized and confound any measures of the effect of MammoGRIP. Please provide a justification or rationale for why prior mammograms are an acceptable comparator, addressing our concerns regarding sources of variability.

A related issue pertains to the degree of breast compression. An increase in amount of breast tissue visualized or PNL could also be attributable to increased breast compression, which may confound measures of the effect of the MammoGRIP. Therefore, we recommend that you perform an analysis regarding the amount of breast compression/breast thickness for each patient in the current vs. prior mammogram acquisitions. Breast thickness is a quantity that is recorded in the DICOM header for digital mammograms, and thus should be readily accessible from the mammogram images in your study.

Hawthorne effect: We are concerned that your study does not have a control(s) arm. In the absence of a control it is not possible to determine whether any observed effect (e.g., increase in PNL) is from your device or if the study suffers from the Hawthorne effect also known as the observer effect. This effect refers to individuals improving or modifying an aspect of their behavior in response to their awareness of being observed. The imaging technologists may have unconsciously changed their positioning efficacy simply because they knew that data was being collected for a study. In the absence of control it is not possible to assess whether the device is effective or whether the observer effect explains the improvement.

For this reason, we recommend that you consider including one or more control arm(s) to your study. For example, you could have two arms: one wherein the MammoGRIP is prospectively used and one wherein a sham device is prospectively used. After satisfying the study inclusion/exclusion criteria, patients would be randomized into the study or control arm(s). The imaging technologists should be blinded when positioning patients as to which arm the patient is in. For each arm, the difference in PNL compared to the previous year mammogram would be evaluated. Appropriate statistical comparisons between the MammoGRIP and control arm(s) would be performed to determine whether any measured change in PNL is statistically significant and can be attributable to use of the MammoGRIP. The preceding paragraph describes a suggested strategy, which you are not obligated to pursue. However, we would request that you describe your approach to minimize this potential bias, and justify your choice of control(s).

There is another related way in which the observer effect may confound your proposed study. As part of current clinical practice, during a current mammogram acquisition technologists usually view the patient's previous mammogram as a guide for breast positioning. Knowing that they are in a study, it is possible that the technologist may try to get extra tissue visualized compared to the previous year mammogram, which is your "without MammoGRIP" comparator. Therefore, we recommend that you consider including an additional purely retrospective analysis, wherein the PNL of the previous two mammograms are compared to one another (e.g., $PNL_{1\ year\ ago} - PNL_{2\ years\ ago}$). The data from this analysis could also help to address our concerns regarding year to year variability noted above.

Study design and statistical plan: Finally, the submitted study data and design lacks sufficient detail and statistical analysis. We recommend that you provide a more detailed study protocol and statistical analysis plan to facilitate our review and enhance our feedback to you. We have the following specific comments:

- As a general principle, the study PI and study participants should be financially independent from the device manufacturer. Based on our review of your submission, Ms. DeRobertis was involved in the development of the MammoGRIP and is also the study Principal Investigator. We recommend an independent study PI.
- The objective of the study should be clearly stated, along with a statement of the hypothesis to be tested.
- Although this is a low-risk study, it should be conducted under IRB approval. In addition, to minimize bias the study technologists should not be aware of the exclusion criteria of the study, and thus should not be the study consenters.
- The inclusion and exclusion criteria for the study should be specified. For example:
    - Inclusion criteria should include patients previously imaged at the same facility
    - Exclusion criteria should include: patients with weight fluctuation of more than 10 pounds from the previous mammogram; patients with any breast intervention since the previous mammogram

- The study design and statistical plan should be pre-specified, e.g., a sample size justification, randomization schema, blinded analysis, statistical analysis of study results etc.
- You have proposed using the PNL as a quantitative metric for evaluating the amount of breast tissue visualized. We have the following comments:
    - We are concerned that there may be considerably variability in the measurement of PNL. Therefore, we recommend that several readers measure the PNL in a blinded fashion. Alternatively, you could justify using one reader if you could demonstrate that there is low variability for this measurement and/or if you are using a semi-automated approach with software.
    - As an alternative measure to PNL, you may consider using software that can automatically or semi-automatically estimate the 2D area of a mammogram if you would like perform an area-based comparison.
    - The quantification of breast tissue (PNL or area) should be performed on both CC and MLO views for each patient. For PNL, such data should be analyzed to ensure that PNL_{MLO}-PNL_{CC} < 1cm. There may be some correlation between the 4 measurements (i.e., they are not independent measures), and such correlation should be accounted for in the statistical analysis.
- Depending on the claims that you are pursuing, you may also consider comparing call-back rates with and without the MammoGRIP.

Please note that these comments just represent our feedback based on the information you have provided in your submission. You are welcome to proposed alternative study designs based on your desired claims and endpoints. We are happy to discuss this feedback with you in a follow-up teleconference.

Please do not hesitate to contact Sanaz (Sunny) Jansen at 240-402-5259 or Sanaz.Jansen@fda.hhs.gov if you have any questions or concerns, or would like additional clarification on the rationale behind these comments.

Appendix 3. Material Safety Data Sheets (MSDS)

SAFETY DATA SHEET

1. Identification

Product identifier **Benzalkonium Chloride**

Other means of identification

Catalog number 1051001

Recommended use Specified quality tests and assay use only.

Recommended restrictions Not for use as a drug. Not for administration to humans or animals.

Manufacturer/Importer/Supplier/Distributor information

Company name U. S. Pharmacopeia

Address 12601 Twinbrook Parkway
Rockville
MD
20852-1790
US

Telephone RS Technical Services 301-816-8129

Website www.usp.org

E-mail RSTECH@usp.org

Emergency phone number CHEMTREC within US & Canada 1-800-424-9300
CHEMTREC outside US & Canada +1 703-527-3887

2. Hazard(s) identification

Physical hazards Not classified.

Health hazards Skin corrosion/irritation Category 1
Serious eye damage/eye irritation Category 1

OSHA hazard(s) Not classified.

Label elements

Signal word Danger

Hazard statement Causes severe skin burns and eye damage. Causes serious eye damage.

Precautionary statement

Prevention Do not breathe mist or vapor. Wash thoroughly after handling. Wear protective gloves/protective clothing/eye protection/face protection.

Response If swallowed: Rinse mouth. Do NOT induce vomiting. If on skin (or hair): Take off immediately all contaminated clothing. Rinse skin with water/shower. Wash contaminated clothing before reuse. If inhaled: Remove person to fresh air and keep comfortable for breathing. If in eyes: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing. Immediately call a poison center/doctor.

Storage Store locked up.

Disposal Dispose of contents/container in accordance with local/regional/national/international regulations.

Hazard(s) not otherwise classified (HNOC) Not classified.

Environmental hazards Hazardous to the aquatic environment, acute hazard Category 2
Hazardous to the aquatic environment, long-term hazard Category 2

Supplemental information

Hazard statement Toxic to aquatic life. Toxic to aquatic life with long lasting effects.

Precautionary statement

Prevention Avoid release to the environment.

Response	Collect spillage.
Disposal	Dispose of contents/container in accordance with local/regional/national/international regulations.

3. Composition/information on ingredients

Mixture

Hazardous components

Chemical name	Common name and synonyms	CAS number	%
Benzalkonium Chloride		8001-54-5	10

Non-hazardous components

Chemical name	Common name and synonyms	CAS number	%
Water		7732-18-5	90

4. First-aid measures

Inhalation	Remove victim to fresh air and keep at rest in a position comfortable for breathing. Call a physician or poison control center immediately.
Skin contact	Take off immediately all contaminated clothing. Rinse skin with water/shower. Call a physician or poison control center immediately. For minor skin contact, avoid spreading material on unaffected skin.
Eye contact	Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing. Call a physician or poison control center immediately.
Ingestion	Call a physician or poison control center immediately. Rinse mouth. Do not induce vomiting. If vomiting occurs, keep head low so that stomach content doesn't get into the lungs.
Most important symptoms/effects, acute and delayed	Corrosive effects. Gastrointestinal disturbances. Respiratory depression.
Indication of immediate medical attention and special treatment needed	Treatment for overdose of quaternary ammonium compounds should be symptomatic and supportive and may include the following: 1. If ingested, dilute with 8 ounces of milk or water, unless contraindicated. Suction gastric contents through a nasogastric or orogastric tube. Control seizures and protect airway before initiating. 2. Treat hypotension by infusing 10 - 20 mL/kg isotonic fluid. If hypotension persists, administer dopamine or norepinephrine. 3. If inhaled, administer oxygen and assist ventilation as needed. Treat bronchospasm with inhaled beta2 agonist and oral or parenteral corticosteroids. [Meditext 2009]
General information	Remove from exposure. Remove contaminated clothing. For treatment advice, seek guidance from an occupational health physician or other licensed health-care provider familiar with workplace chemical exposures. In the United States, the national poison control center phone number is 1-800-222-1222. If person is not breathing, give artificial respiration. If breathing is difficult, give oxygen if available. Persons developing serious hypersensitivity (anaphylactic) reactions must receive immediate medical attention.

5. Fire-fighting measures

Suitable extinguishing media	Water fog. Foam. Dry chemical powder. Carbon dioxide (CO2).
Unsuitable extinguishing media	Do not use water jet as an extinguisher, as this will spread the fire.
Specific hazards arising from the chemical	No unusual fire or explosion hazards noted.
Special protective equipment and precautions for firefighters	Wear suitable protective equipment.

6. Accidental release measures

Personal precautions, protective equipment and emergency procedures	Keep unnecessary personnel away. Do not touch damaged containers or spilled material unless wearing appropriate protective clothing. Ensure adequate ventilation. Avoid inhalation of vapors. Wear appropriate personal protective equipment.
Methods and materials for containment and cleaning up	Absorb spillage with suitable absorbent material. For waste disposal, see section 13 of the SDS. Clean surface thoroughly to remove residual contamination.

7. Handling and storage

Precautions for safe handling	As a general rule, when handling USP Reference Standards, avoid all contact and inhalation of dust, mists, and/or vapors associated with the material. Clean equipment and work surfaces with suitable detergent or solvent after use. After removing gloves, wash hands and other exposed skin thoroughly. Use of a designated area is recommended for handling of potent materials.
Conditions for safe storage, including any incompatibilities	Store in tight container as defined in the USP-NF. This material should be handled and stored per label instructions to ensure product integrity.

8. Exposure controls/personal protection

Biological limit values	No biological exposure limits noted for the ingredient(s).
Exposure guidelines	No exposure standards allocated.
Appropriate engineering controls	Airborne exposure should be controlled primarily by engineering controls such as general dilution ventilation, local exhaust ventilation, or process enclosure. Local exhaust ventilation is generally preferred to general exhaust because it can control the contaminant at its source, preventing dispersion into the work area. An industrial hygiene survey involving air monitoring may be used to determine the effectiveness of engineering controls. Local exhaust ventilation such as a laboratory fume hood or other vented enclosure is recommended, particularly for grinding, crushing, weighing, or other dust-generating procedures. Effectiveness of engineering controls intended for use with highly potent materials should be assessed by use of nontoxic surrogate materials. Local exhaust ventilation such as a laboratory fume hood or other vented enclosure is recommended, particularly for aerosol-generating procedures.

Individual protection measures, such as personal protective equipment

Eye/face protection	Safety glasses with sideshields are recommended. Face shields or goggles may be required if splash potential exists or if corrosive materials are present. Approved eye protection (e.g., bearing the ANSI Z87 or CSA stamp) is preferred. Maintain eyewash facilities in the work area.
Skin protection	
Hand protection	Chemically compatible gloves. For handling solutions, ensure that the glove material is protective against the solvent being used. Use handling practices that minimize direct hand contact. Employees who are sensitive to natural rubber (latex) should use nitrile or other synthetic nonlatex gloves. Use of powdered latex gloves should be avoided due to the risk of latex allergy. To reduce the risk of contamination of skin and surfaces, wear two pairs of gloves. Remove the outer gloves after handling and cleanup of the material, and remove the inner gloves only after removing other personal protective equipment.
Other	For handling of laboratory scale quantities, a disposable lab coat or isolation gown over street clothes is recommended. Where significant quantities are handled, work clothing and booties may be necessary to prevent take-home contamination.
Respiratory protection	Where respirators are deemed necessary to reduce or control occupational exposures, use NIOSH-approved respiratory protection and have an effective respirator program in place (applicable U.S. regulation OSHA 29 CFR 1910.134).
Thermal hazards	Not available.
General hygiene considerations	Handle in accordance with good industrial hygiene and safety practice.

9. Physical and chemical properties

Appearance	Clear, colorless to light-yellow liquid.
Physical state	Liquid.
Form	Liquid.
Odor	Odorless or faint, aromatic odor.
Odor threshold	Not available.
pH	6 - 9
Melting point/freezing point	Not available.
Initial boiling point and boiling range	Not available.
Evaporation rate	Not available.
Flammability (solid, gas)	Not applicable.
Upper/lower flammability or explosive limits	
Flammability limit - lower (%)	Not available.
Flammability limit - upper (%)	Not available.
Explosive limit - lower (%)	Not available.
Explosive limit - upper (%)	Not available.
Vapor density	Not available.
Relative density	Not available.
Solubility in water	Not available.
Partition coefficient (n-octanol/water)	Not available.
Auto-ignition temperature	Not available.
Decomposition temperature	Not available.

Viscosity Not available.

Other information

Chemical family Quaternary ammonium compound.

10. Stability and reactivity

Reactivity No reactivity hazards known.

Chemical stability Material is stable under normal conditions.

Possibility of hazardous reactions No dangerous reaction known under conditions of normal use.

Conditions to avoid None known.

Incompatible materials Strong oxidizing agents. Strong bases. Acid anhydrides. Acid chlorides.

Hazardous decomposition products NOx, Cl-. Irritating and/or toxic fumes or gases. Emits toxic fumes under fire conditions.

11. Toxicological information

Information on likely routes of exposure

Ingestion Based on available data, the classification criteria are not met.

Inhalation May cause irritation to the respiratory system.

Skin contact Causes severe skin burns.

Eye contact Causes severe eye burns. Causes serious eye damage.

Symptoms related to the physical, chemical, and toxicological characteristics Burning pain and severe corrosive skin damage. Acute eye irritation/corrosion. Burning in mouth, throat, and/or stomach. Nausea. Vomiting. Diarrhea. Salivation. Mouth ulcers. Difficulty breathing. Bluish skin. Muscle weakness. Dizziness. Headache. Restlessness.

Delayed and immediate effects of exposure Respiratory depression. Cyanosis. Metabolic acidosis. Hypotension.

Medical conditions aggravated by exposure Asthma. Pre-existing skin conditions or damage.

Acute toxicity

Components	Species	Test Results
Benzalkonium Chloride (CAS 8001-54-5)		
Acute		
Dermal		
LD50	Rat	1420 mg/kg
		930 mg/kg
Oral		
LD50	Mouse	150 mg/kg
	Rat	240 mg/kg

Skin corrosion/irritation Causes severe skin burns and eye damage.

Serious eye damage/eye irritation Causes severe eye burns. Causes serious eye damage.

Local effects

Benzalkonium Chloride

Eye irritancy test, 10% benzalkonium chloride solution.
Result: Corneal clouding; epithelial hyperplasia after 21 days.
Species: Monkey
Eye irritancy test, 10% benzalkonium chloride solution.
Result: Corneal damage.
Species: Rabbit
Skin irritancy test, 5% benzalkonium chloride solution.
Result: Necrosis of epidermis.
Species: Guinea pig

Respiratory sensitization Due to lack of data the classification is not possible.

Skin sensitization Due to lack of data the classification is not possible.

Sensitization Asthma and contact dermatitis following occupational exposure to this material have been reported.

Germ cell mutagenicity Due to lack of data the classification is not possible.
Data from germ cell mutagenicity tests were not found.

Mutagenicity

Benzalkonium Chloride

B. Subtilis rec-assay.
Result: Negative.

Mutagenicity

Benzalkonium Chloride

DNA polymerase assay in E. Coli.
Result: Repairable DNA damage.
In vitro chromosome aberration assay in Syrian hamster embryo cells.
Result: Negative.
In vitro micronucleus assay in human lymphocytes.
Result: Positive.
S. typhimurium reverse mutation assay.
Result: Negative.

Carcinogenicity

Based on available data, the classification criteria are not met.
This material is not considered to be a carcinogen by IARC, NTP, or OSHA.

Benzalkonium Chloride

Carcinogenicity studies in rats and guinea pigs, administered orally.
Result: Not carcinogenic
Lifetime carcinogenicity studies in mice and rabbits, administered dermally.
Result: No skin tumors were induced

Reproductive toxicity

Based on available data, the classification criteria are not met.

Reproductivity

Benzalkonium Chloride

100 mg/kg/day Reproduction and development study., administered intravaginally during early gestation.
Result: No teratogenicity noted.
Species: Mouse
50 - 200 mg/kg Reproduction and development study., administered intravaginally.
Result: Embryotoxicity and fetotoxicity at high doses; no teratogenicity.
Species: Rat

Specific target organ toxicity - single exposure

Based on available data, the classification criteria are not met.

Specific target organ toxicity - repeated exposure

Based on available data, the classification criteria are not met.

Aspiration hazard

Due to lack of data the classification is not possible.

12. Ecological information

Ecotoxicity

Toxic to aquatic life with long lasting effects.

Components		Species	Test Results
Benzalkonium Chloride (CAS 8001-54-5)			
Aquatic			
Fish	LC50	Bluegill (Lepomis macrochirus)	0.223 - 0.46 mg/l, 96 hours

Persistence and degradability

No data is available on the degradability of this product.

Bioaccumulative potential

Not available.

Mobility in soil

Not available.

Other adverse effects

Not available.

13. Disposal considerations

Disposal instructions

Dispose in accordance with all applicable regulations. Under RCRA, it is the responsibility of the user of the product to determine, at the time of disposal, whether the product meets RCRA criteria for hazardous waste.

Local disposal regulations

Not available.

Hazardous waste code

Not available.

Waste from residues / unused products

Dispose of in accordance with local regulations. Empty containers or liners may retain some product residues. This material and its container must be disposed of in a safe manner (see: Disposal instructions).

Contaminated packaging

Empty containers should be taken to an approved waste handling site for recycling or disposal. Since emptied containers may retain product residue, follow label warnings even after container is emptied.

14. Transport information

DOT

UN number UN1760
UN proper shipping name Corrosive liquid, n.o.s. (Benzalkonium chloride 10% solution), MARINE POLLUTANT
Transport hazard class(es) 8

Subsidiary class(es)	Not available.
Packing group	III

IATA

UN number	UN1760
UN proper shipping name	Corrosive liquid, n.o.s. (Benzalkonium chloride 10% solution)
Transport hazard class(es)	8
Subsidiary class(es)	-
Packaging group	III
Transport in bulk according to Annex II of MARPOL 73/78 and the IBC Code	No information available.
General information	DOT Regulated Marine Pollutant. IMDG Regulated Marine Pollutant.

DOT

IATA

Marine pollutant

15. Regulatory information

US federal regulations

CERCLA/SARA Hazardous Substances - Not applicable.

One or more components are not listed on TSCA.

Superfund Amendments and Reauthorization Act of 1986 (SARA)

Hazard categories	Immediate Hazard - Yes Delayed Hazard - No Fire Hazard - No Pressure Hazard - No Reactivity Hazard - No
SARA 302 Extremely hazardous substance	No
SARA 311/312 Hazardous chemical	No

Other federal regulations

Safe Drinking Water Act (SDWA)	Not regulated.

Food and Drug Administration (FDA)	Not regulated.
US state regulations	California Safe Drinking Water and Toxic Enforcement Act of 1986 (Proposition 65): This material is not known to contain any chemicals currently listed as carcinogens or reproductive toxins.

International Inventories

Country(s) or region	Inventory name	On inventory (yes/no)*
Australia	Australian Inventory of Chemical Substances (AICS)	Yes
Canada	Domestic Substances List (DSL)	Yes
Canada	Non-Domestic Substances List (NDSL)	No
China	Inventory of Existing Chemical Substances in China (IECSC)	Yes
Europe	European Inventory of Existing Commercial Chemical Substances (EINECS)	No
Europe	European List of Notified Chemical Substances (ELINCS)	No
Japan	Inventory of Existing and New Chemical Substances (ENCS)	No
Korea	Existing Chemicals List (ECL)	Yes
New Zealand	New Zealand Inventory	Yes
Philippines	Philippine Inventory of Chemicals and Chemical Substances (PICCS)	Yes
United States & Puerto Rico	Toxic Substances Control Act (TSCA) Inventory	No

*A "Yes" indicates that all components of this product comply with the inventory requirements administered by the governing country(s)

16. Other information, including date of preparation or last revision

Issue date	12-18-2014
Version #	01
Further information	Not available.
Disclaimer	USP Reference Standards are sold for chemical test and assay purposes only, and NOT for human consumption. The information contained herein is applicable solely to the chemical substance when used as a USP Reference Standard and does not necessarily relate to any other use of the substance described, (i.e. at different concentrations, in drug dosage forms, or in bulk quantities). USP Reference Standards are intended for use by persons having technical skill and at their own discretion and risk. This information has been developed by USP staff from sources considered reliable but has not been independently verified by the USP. Therefore, the USP Convention cannot guarantee the accuracy of the information in these sources nor should the statements contained herein be considered an official expression. NO REPRESENTATION OR WARRANTY, EXPRESS OR IMPLIED, INCLUDING THE WARRANTIES OF MERCHANTABILITY AND FITNESS FOR A PARTICULAR PURPOSE is made with respect to the information contained herein.

SAFETY DATA SHEET

Version 5.2
Revision Date 02/24/2014
Print Date 07/16/2015

1. PRODUCT AND COMPANY IDENTIFICATION

1.1 Product identifiers

Product name : Distilled water

Product Number : 07-6061
Brand : Katayama OEM Partner
REACH No. : A registration number is not available for this substance as the substance or its uses are exempted from registration, the annual tonnage does not require a registration or the registration is envisaged for a later registration deadline.
CAS-No. : 7732-18-5

1.2 Relevant identified uses of the substance or mixture and uses advised against

Identified uses : Laboratory chemicals, Manufacture of substances

1.3 Details of the supplier of the safety data sheet

Company : Sigma-Aldrich
3050 Spruce Street
SAINT LOUIS MO 63103
USA

Telephone : +1 800-325-5832
Fax : +1 800-325-5052

1.4 Emergency telephone number

Emergency Phone # : (314) 776-6555

2. HAZARDS IDENTIFICATION

2.1 Classification of the substance or mixture

Not a hazardous substance or mixture.

2.2 GHS Label elements, including precautionary statements

Not a hazardous substance or mixture.

2.3 Hazards not otherwise classified (HNOC) or not covered by GHS - none

3. COMPOSITION/INFORMATION ON INGREDIENTS

3.1 Substances

Formula : H2O H_2O
Molecular Weight : 18.02 g/mol
CAS-No. : 7732-18-5
EC-No. : 231-791-2

No ingredients are hazardous according to OSHA criteria.
No components need to be disclosed according to the applicable regulations.

4. FIRST AID MEASURES

4.1 Description of first aid measures

If inhaled
If not breathing give artificial respiration

4.2 Most important symptoms and effects, both acute and delayed
The most important known symptoms and effects are described in the labelling (see section 2.2) and/or in section 11

4.3 Indication of any immediate medical attention and special treatment needed
no data available

5. FIREFIGHTING MEASURES

5.1 Extinguishing media

Suitable extinguishing media
Use extinguishing measures that are appropriate to local circumstances and the surrounding environment.

5.2 Special hazards arising from the substance or mixture
no data available

5.3 Advice for firefighters
no data available

5.4 Further information
The product itself does not burn.

6. ACCIDENTAL RELEASE MEASURES

6.1 Personal precautions, protective equipment and emergency procedures
For personal protection see section 8.

6.2 Environmental precautions
no data available

6.3 Methods and materials for containment and cleaning up
Wipe up with absorbent material (e.g. cloth, fleece).

6.4 Reference to other sections
For disposal see section 13.

7. HANDLING AND STORAGE

7.1 Precautions for safe handling
For precautions see section 2.2.

7.2 Conditions for safe storage, including any incompatibilities
No special storage conditions required.

7.3 Specific end use(s)
Apart from the uses mentioned in section 1.2 no other specific uses are stipulated

8. EXPOSURE CONTROLS/PERSONAL PROTECTION

8.1 Control parameters

Components with workplace control parameters
Contains no substances with occupational exposure limit values.

8.2 Exposure controls

Appropriate engineering controls
Handle in accordance with good industrial hygiene and safety practice.

Personal protective equipment

Skin protection
Handle with gloves. Gloves must be inspected prior to use. Use proper glove removal technique (without touching glove's outer surface) to avoid skin contact with this product. Dispose of contaminated gloves after use in accordance with applicable laws and good laboratory practices. Wash and dry hands.

Full contact
Material: Nitrile rubber
Minimum layer thickness: 0.11 mm
Break through time: 480 min

Material tested:Dermatril® (KCL 740 / Aldrich Z677272, Size M)

Splash contact
Material: Nitrile rubber
Minimum layer thickness: 0.11 mm
Break through time: 480 min
Material tested:Dermatril® (KCL 740 / Aldrich Z677272, Size M)

data source: KCL GmbH, D-36124 Eichenzell, phone +49 (0)6659 87300, e-mail sales@kcl.de, test method: EN374
If used in solution, or mixed with other substances, and under conditions which differ from EN 374, contact the supplier of the CE approved gloves. This recommendation is advisory only and must be evaluated by an industrial hygienist and safety officer familiar with the specific situation of anticipated use by our customers. It should not be construed as offering an approval for any specific use scenario.

Respiratory protection
No special protective equipment required.

Control of environmental exposure
Prevent product from entering drains.

9. PHYSICAL AND CHEMICAL PROPERTIES

9.1 Information on basic physical and chemical properties

a)	Appearance	Form: liquid Colour: colourless
b)	Odour	no data available
c)	Odour Threshold	no data available
d)	pH	6.0 - 8.0 at 25 °C (77 °F)
e)	Melting point/freezing point	0.0 °C (32.0 °F)
f)	Initial boiling point and boiling range	100 °C (212 °F) - lit.
g)	Flash point	not applicable
h)	Evapouration rate	no data available
i)	Flammability (solid, gas)	no data available
j)	Upper/lower flammability or explosive limits	no data available
k)	Vapour pressure	no data available
l)	Vapour density	no data available
m)	Relative density	1.000 g/cm3 at 3.98 °C (39.16 °F)
n)	Water solubility	completely miscible
o)	Partition coefficient: n-octanol/water	no data available
p)	Auto-ignition temperature	no data available
q)	Decomposition temperature	no data available
r)	Viscosity	no data available
s)	Explosive properties	no data available
t)	Oxidizing properties	no data available

9.2 Other safety information
no data available

10. STABILITY AND REACTIVITY

10.1 Reactivity
no data available

10.2 Chemical stability
Stable under recommended storage conditions.

10.3 Possibility of hazardous reactions
no data available

10.4 Conditions to avoid
no data available

10.5 Incompatible materials
no data available

10.6 Hazardous decomposition products
In the event of fire: see section 5

11. TOXICOLOGICAL INFORMATION

11.1 Information on toxicological effects

Acute toxicity
no data available

Inhalation: no data available

Dermal: no data available

no data available

Skin corrosion/irritation
no data available

Serious eye damage/eye irritation
no data available

Respiratory or skin sensitisation
no data available

Germ cell mutagenicity
no data available

Carcinogenicity

IARC: No component of this product present at levels greater than or equal to 0.1% is identified as probable, possible or confirmed human carcinogen by IARC.

ACGIH: No component of this product present at levels greater than or equal to 0.1% is identified as a carcinogen or potential carcinogen by ACGIH.

NTP: No component of this product present at levels greater than or equal to 0.1% is identified as a known or anticipated carcinogen by NTP.

OSHA: No component of this product present at levels greater than or equal to 0.1% is identified as a carcinogen or potential carcinogen by OSHA.

Reproductive toxicity
no data available

no data available

Specific target organ toxicity - single exposure
no data available

Specific target organ toxicity - repeated exposure
no data available

Aspiration hazard
no data available

Additional Information
RTECS: ZC0110000

To the best of our knowledge, the chemical, physical, and toxicological properties have not been thoroughly investigated.

12. ECOLOGICAL INFORMATION

12.1 Toxicity
no data available

12.2 Persistence and degradability
not applicable

12.3 Bioaccumulative potential
no data available

12.4 Mobility in soil
no data available

12.5 Results of PBT and vPvB assessment
PBT/vPvB assessment not available as chemical safety assessment not required/not conducted

12.6 Other adverse effects

no data available

13. DISPOSAL CONSIDERATIONS

13.1 Waste treatment methods

Product
Taking into account local regulations the product may be disposed of as waste water after neutralisation.

14. TRANSPORT INFORMATION

DOT (US)
Not dangerous goods

IMDG
Not dangerous goods

IATA
Not dangerous goods

15. REGULATORY INFORMATION

REACH No. : A registration number is not available for this substance as the substance or its uses are exempted from registration, the annual tonnage does not require a registration or the registration is envisaged for a later registration deadline.

SARA 302 Components
SARA 302: No chemicals in this material are subject to the reporting requirements of SARA Title III, Section 302.

SARA 313 Components
SARA 313: This material does not contain any chemical components with known CAS numbers that exceed the threshold (De Minimis) reporting levels established by SARA Title III, Section 313.

SARA 311/312 Hazards
No SARA Hazards

Massachusetts Right To Know Components
No components are subject to the Massachusetts Right to Know Act.

Pennsylvania Right To Know Components

	CAS-No.	Revision Date
Water	7732-18-5	

New Jersey Right To Know Components

	CAS-No.	Revision Date
Water	7732-18-5	

California Prop. 65 Components

This product does not contain any chemicals known to State of California to cause cancer, birth defects, or any other reproductive harm.

16. OTHER INFORMATION

HMIS Rating

Health hazard:	0
Chronic Health Hazard:	
Flammability:	0
Physical Hazard	0

NFPA Rating

Health hazard:	0
Fire Hazard:	0
Reactivity Hazard:	0

Further information

The above information is believed to be correct but does not purport to be all inclusive and shall be used only as a guide. The information in this document is based on the present state of our knowledge and is applicable to the product with regard to appropriate safety precautions. It does not represent any guarantee of the properties of the product. Sigma-Aldrich Corporation and its Affiliates shall not be held liable for any damage resulting from handling or from contact with the above product. See www.sigma-aldrich.com and/or the reverse side of invoice or packing slip for additional terms and conditions of sale.

Preparation Information

Sigma-Aldrich Corporation
Product Safety – Americas Region
1-800-521-8956

Version: 5.2 Revision Date: 02/24/2014 Print Date: 07/16/2015

Safety Data Sheet
Cola®Quat SLCC

SECTION 1 – IDENTIFICATION

GHS Product Identifier | Trade Name:	Cola®Quat SLCC
CAS Number:	168677-75-6
Uses of the Substance / Mixture:	Surfactant for various applications
Formula:	N/A
Company Name:	Colonial Chemical, Inc.
Company Address:	P.O. Box 111, South Pittsburg, TN 37380 USA
Phone Number:	(P) 423.837.8800 (F) 423.837.3888
Emergency Phone Number:	Colonial Chemical: 423.837.8800 Chemtrec: 800.424.9300

SECTION 2 – HAZARDOUS IDENTIFICATION

Classification:

Classification (Regulation (EC) No 1272/2008)

None

Classification (67/548/EEC, 1999/45/EC)

None

Label Elements:

Hazardous products which must be listed on the label:

None

Globally Harmonized System of Classification and Labeling of Chemicals (GHS)

Precautionary statements:

Prevention

P264 Wash skin thoroughly after handling
P280 Wear protective gloves/eye protection/face protection

Response

P302 + P352 IF ON SKIN: Wash with plenty of soap and water
P305 + P351 + P338 IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing.
P308 IF exposed or concerned: P310 Immediately call a POISON CENTER or doctor/physician.

Storage

P401 Store in an area between 10-30 °C
P404 Store in a closed container
P420 Store away from strong oxidizing agents and reducing agents

Disposal

P501 Dispose of contents/container in accordance with local, regional, national and/or international regulations.

SECTION 3 – COMPOSITION / INFORMATION ON INGREDIENTS

Substance

Chemical nature: Surfactant

Information on Components and Impurities

Chemical Name	GHS Classification	Concentration (%)
Dihydroxypropyl PEG-5 Linoleammonium Chloride	None	proprietary

SECTION 4 – FIRST AID MEASURES

Description of necessary first-aid measures

General advice: Show this safety data sheet to the doctor in attendance. First aider needs to protect himself/herself. Place affected clothing in a sealed bag for subsequent decontamination.

Inhalation: Remove victim to fresh air. Administer oxygen if breathing is difficult. Give artificial respiration if victim is not breathing.

Skin contact: In case of contact with substance, immediately flush skin with running water for at least 20 minutes. Remove and isolate contaminated clothing and shoes. If skin irritation continues: Get medical attention.

Eye contact: In case of contact with substance, immediately flush eyes with running water for at least 20 minutes. If present and easy to do, remove contacts. If eye irritation persists, consult a physician.

Ingestion: Do NOT induce vomiting without medical advice. Drink water as a precaution. Call a physician or poison control center immediately. Never give anything by mouth to an unconscious person.

SECTION 5 – FIREFIGHTING MEASURES

Extinguishing media

Suitable extinguishing media: CO2, Dry Chemical, BC/ABC Extinguishers

Special hazards arising from the substance or mixture

Specific hazards during firefighting: On combustion forms carbon monoxide, carbon dioxide, potassium oxide

Advice for firefighters

Special protective equipment: Self-contained breathing apparatus (EN 133)
Full protective suit

SECTION 6 – ACCIDENTAL RELEASE MEASURES

Personal precautions, protective equipment and emergency procedures

Wear suitable protective equipment. Do not touch damaged containers or spilled material unless wearing suitable protective clothing.

Methods for Cleaning or Taking Up

SMALL SPILLS: Take up with sand or other non-combustible absorbent material and place into containers for later disposal.
LARGE SPILLS: Dike far ahead of spill for later disposal. To avoid gelling and foaming problems, do not use water to flush to industrial sewer. Spills may be reportable to local, state, federal and/or provincial authorities.

Additional advice

Prevent entry into waterways, sewers, basements or confined areas.

SECTION 7 – HANDLING AND STORAGE

Handling

Advice on safe handling and usage: Avoid contact with skin and eyes

Storage

Recommended: Store in original container. Store tightly closed. Store in an area between 10-30 °C

SECTION 8 – EXPOSURE CONTROLS / PERSONAL PROTECTION

Components with workplace control parameters

Components	Value Type	Value	Update	Basis
N/A				

Components with workplace foreign control parameters

Components	Value Type	Value	Update	Basis
N/A				

Control Measures

Engineering measures: Avoid splashes. Apply technical measures to comply with any occupational exposure limits when applicable.

Personal protective equipment

Respiratory protection: In the case of insufficient ventilation, wear suitable respiratory equipment.

Hand protection: Wear appropriate gloves. In EU member states, gloves should satisfy the specification of EU Directive 89/686/EEC and the standard EN 374 derived from it. Please observe instructions provided by the glove supplier regarding permeability and breakthrough time. Also, take into consideration the specific local conditions under which the product is used, such as danger of cuts, abrasion and the contact time. Gloves must be inspected prior to use. Gloves should be discarded and replaced if there is any indication of degradation or chemical breakthrough.

Eye protection: Wear safety goggles. In case of contact through splashing: Wear face-shield and protective suit.

Skin and body protection: Wear appropriate clothing to avoid direct skin contact. Remove and wash contaminated clothing before wearing again.

Hygiene measures: Emergency equipment nearby and immediately accessible, with instructions for use. Ensure that eyewash stations and safety showers are close to the workstation location. Use clean, well-maintained personal protection equipment. Store the personal protection equipment in a clean location away from the work area. Contaminated work clothing should not be allowed out of the workplace. Before re-use, thoroughly clean personal protection equipment. Wash hands before breaks and immediately after handling the product. Shower or bathe at the end of working. When using the product do not eat, drink or smoke.

Protective measures: The protective equipment must be selected in accordance with current CEN standards and in cooperation with the supplier of the protective equipment. Selection of appropriate personal protective equipment should take into account the performance of the protective equipment relative to the task(s) to be performed, conditions present, duration of use, and the potential hazards and/or risks that may occur during use.

SECTION 9 – PHYSICAL AND CHEMICAL PROPERTIES

Appearance

Form:	Liquid
Physical state:	Liquid
Color:	Water White to Light Yellow
Odor:	characteristic

Safety data

pH 1% aqueous:	6.5 – 7.5
Melting point/range:	no data available
Boiling point/boiling range:	~101°C, 215°F
Flash point:	>93°C
Flammability (solid, gas):	no data available
Auto-ignition temperature	no data available
%Volatile by wt:	60.5
Water solubility:	Soluble
Solubility in other solvents	no data available
Partition coefficient: noctanol/water:	no data available

Vapor pressure:	no data available
Evaporation rate:	no data available
Relative vapor density:	> 1
Specific Gravity:	1.0 gm/mL
Oxidation/Reduction Potential:	no data available
Viscosity, dynamic:	no data available
Viscosity, kinematic:	no data available
Explosive properties:	no data available
Thermal decomposition:	no data available
Lower explosion limit:	no data available
Upper explosion limit:	no data available

SECTION 10 – STABILITY AND REACTIVITY

Chemical Stability: Stable at room temperature

Hazardous reactions

Conditions to avoid	Prolonged, excessive heat
Materials to avoid	Strong oxidizing agents, reducing agents

SECTION 11 – TOXICOLOGICAL INFORMATION

Acute toxicity

Acute oral toxicity:	no data available
Acute inhalation toxicity:	no data available
Acute dermal toxicity:	no data available
Other routes of administration:	no data available
Aspiration toxicity:	no data available

Skin corrosion/irritation

Skin irritation:	no data available

Serious eye damage/eye irritation

Eye irritation:	no data available

Respiratory or skin sensitization

Sensitization:	no data available

Repeated dose toxicity

Repeated dose toxicity:	no data available

STOT

STOT - single exposure:	no data available
STOT - repeated exposure:	no data available

Carcinogenicity

Carcinogenicity:	no data available

Mutagenicity

Genotoxicity in vitro:	no data available
Genotoxicity in vivo:	no data available

Reproductive toxicity

Reproductive toxicity:	no data available

SECTION 12 – ECOLOGICAL INFORMATION

Ecotoxicity assessment

Ecotoxicity assessment:	no data available

Persistence and degradability

Biodegradability:	no data available

Other adverse effects

Environment assessment:	Not classified as dangerous for the environment according to EC criteria.

SECTION 13 – DISPOSAL CONSIDERATIONS

Product Disposal

Advice on Disposal:	Dispose of in accordance with local regulations.

SECTION 14 – TRANSPORTATION INFORMATION

ADR	not regulated
RID	not regulated
IMDG	not regulated
IATA	not regulated

Note: The above regulatory prescriptions are those valid on the date of publication of this sheet. Given the possible evolution of transport regulations for hazardous materials, it would be advisable to check their validity with your sales office.

SECTION 15 – REGULATORY INFORMATION

TSCA:	Not Listed
EU (REACH):	Not Listed
Philippines (PICCS):	Listed
(Asia-PAC):	Listed
China (IECSC):	Listed
New Zealand (NZIoC):	Listed

Follow all regulations in your country or region. Colonial Chemical, Inc is unable to confirm all regulatory information in regard to the substances in your country or region, and this information is subject to change without notice.

SECTION 16 – OTHER INFORMATION

Full text of P-Statements referred to under sections 2 and 3.

P264	Wash skin thoroughly after handling.
P273	Avoid release to the environment.
P280	Wear protective gloves/ eye protection/ face protection.
P302 + P352	IF ON SKIN: Wash with plenty of soap and water.
P305 + P351 + P338	IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing.
P310	Immediately call a POISON CENTER or doctor/ physician.
P332 + P313	If skin irritation occurs: Get medical advice/ attention.
P362	Take off contaminated clothing and wash before reuse.
P501	Dispose of contents/ container to an approved waste disposal plant.

HEALTH	**1**
FLAMMABILITY	**1**
REACTIVITY	**0**
PERSONAL PROTECTION	**B**

The information provided in this Safety Data Sheet is accurate to the best of Colonial Chemical, Inc.'s knowledge. No guarantees or liabilities are expressed or implied. Because users are most aware of the application of the product, they must ensure that proper personal protective equipment (PPE) is provided consistent with the information contained in the product SDS. This information is intended solely for the use of individuals trained in the particular hazard rating system. It does not release users from ensuring they are in conformity with all regulations linked to its activity.

Material Safety Data Sheet

TRADE NAME: PHOENATE GC-7

Date of Preparation/Revision: 10/2009

Section 1 - Chemical Product and Company Identification

Product Name: **PHOENATE GC-7**
Chemical Name: PEG-7 Glyceryl Cocoate
CAS Number: **68201-46-7**
Manufacturer: PHOENIX CHEMICAL, INC.
60 Fourth Street, Somerville, New Jersey 08876
Phone (908) 707-0232, Fax (908) 707-0186

CHEMTREC 24-HR EMERGENCY RESPONSE
NUMBER: 1-800-424-9300
INTERNATIONAL CALLS: COLLECT
1-703-527-3887
CHEMTREC should only be called in the event of chemical emergencies involving a spill, leak, fire, exposure, or accident involving chemicals.

Section 2 - Composition / Information on Ingredients

This product does not contain any active material considered hazardous as defined in 29 CFR 1910.120

Ingredient Name	CAS Number	% wt/vol
PEG-7 Glyceryl Cocoate	68201-46-7	100%

Trace Impurities:

	OSHA PEL		ACGIH TLV		NIOSH REL		NIOSH
Ingredient	**TWA**	**STEL**	**TWA**	**STEL**	**TWA**	**STEL**	**IDLH**
None Known	None Estab.	None Estab.	Not Estab.	Not Estab.	Not Estab.	Not Estab.	Not Estab

Section 3 - Hazards Identification

☆☆☆☆☆ Emergency Overview ☆☆☆☆☆

HMIS	
H	1
F	1
R	0
PPE	C

Potential Health Effects

There are no potential health effects expected from handling this material. Good manufacturing practices are always recommended when handling any chemical.
A knowledge of the available toxicology information and of the physical and chemical properties of the material suggests that overexposure is unlikely to aggravate existing medical conditions.
This material is registered with TSCA.
Exposure to small quantities is not expected to cause adverse health effects.
There are no significant laboratory data to suggest any specific hazard to humans.

Inhalation: Short-term harmful health effects are not expected from vapor-generated at ambient temperatures.
Eye Contact: May cause some moderate eye irritation.
Skin Contact: May cause some irritation or discomfort.
Ingestion: May cause abdominal discomfort, nausea, vomiting and diarrhea.
Carcinogenicity: IARC, NTP, and OSHA do not list this product as a carcinogen.

Section 4 - First Aid Measures

Inhalation: Short-term harmful health effects are not expected from vapor-generated at ambient temperatures. If first aid is required, move victim to fresh air.

Eye Contact: May cause some moderate eye irritation. Flush immediately with water for 15 to 20 minutes. Obtain medical attention if severe irritation occurs.

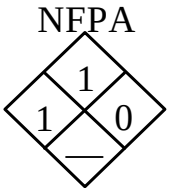
Skin Contact: May cause some irritation or discomfort. Remove contaminated clothing. Wash affected area with soap & water.

Ingestion: May cause abdominal discomfort, nausea, vomiting and diarrhea. Give two glasses of water. Do not induce vomiting. Obtain medical attention.

After first aid, get appropriate in-plant, paramedic, or community medical support.

Section 5 - Fire-Fighting Measures

Flash Point: >150^{O}C **Flash Point Method:** PMCC



Extinguishing Media: Use water spray, carbon dioxide, alcohol type or universal type foam applied in accordance with the manufacturer's instructions.

Fire-Fighting Instructions: Treat as an oil fire. Do not release runoff from fire control methods to sewers or waterways.

Fire-Fighting Equipment: Because fire may produce toxic thermal decomposition products, wear a self-contained breathing apparatus (SCBA) with a full facepiece operated in pressure-demand or positive-pressure mode.

Section 6 - Accidental Release Measures

Safeguards (Personnel): Review FIRE FIGHTING MEASURES and HANDLING (PERSONNEL) sections before proceeding with clean up. Use appropriate PERSONAL PROTECTIVE EQUIPMENT during clean up.

Spill /Leak Procedures: Collect for disposal in accordance with applicable Federal, State, or local regulations.

Containment: For large spills, dike far ahead of liquid spill for later disposal. Do not release into sewers or waterways.

Regulatory Requirements: Follow applicable OSHA regulations (29 CFR 1910.120).

Section 7 - Handling and Storage

Handling Precautions: (Personnel) Safety glasses and PVC gloves.

Storage Requirements: Keep container tightly closed.

Section 8 - Exposure Controls / Personal Protection

Engineering Controls: No special engineering controls are required under normal use.

Ventilation: Provide general or local exhaust ventilation systems to maintain airborne concentrations below OSHA PELs (Sec.2). Local exhaust ventilation is preferred because it prevents contaminant dispersion into the work area by controlling it at its source.

Administrative Controls:

Respiratory Protection: Seek professional advice prior to respirator selection and use. Follow OSHA respirator regulations (29 CFR 1910.134) and, if necessary, wear an MSHA/NIOSH-approved respirator. Select respirator based on its suitability to provide adequate worker protection for given working conditions, level of airborne contamination, and presence of sufficient oxygen. For emergency or non-routine operations (cleaning spills, reactor vessels, or storage tanks), wear a SCBA.

Warning! Air-purifying respirators do not protect workers in oxygen-deficient atmospheres. If respirators are used, OSHA requires a written respiratory protection program that includes at least: medical certification, training, fit testing, periodic environmental monitoring, maintenance, inspection, cleaning, and convenient, sanitary storage areas.

Protective Clothing/Equipment: Wear chemically protective gloves, boots, aprons, and gauntlets to prevent prolonged or repeated skin contact. Wear protective eyeglasses or chemical safety goggles, per OSHA eye- and face-protection regulations (29 CFR 1910.133). Contact lenses are **not** eye protective devices. Appropriate eye protection must be worn instead of, or in conjunction with contact lenses.

Safety Stations: Make emergency eyewash stations, safety/quick-drench showers, and washing facilities available in work area.

Contaminated Equipment: Separate contaminated work clothes from street clothes. Launder before reuse. Remove this material from your shoes and clean personal protective equipment.

Comments: Never eat, drink, or smoke in work areas. Practice good personal hygiene after using this material, especially before eating, drinking, smoking, using the toilet, or applying cosmetics.

Section 9 - Physical and Chemical Properties

Physical State: Liquid
Appearance and Odor: Yellow, mild odor
Vapor Pressure, mm Hg: <0.1 @ 20 ^{O}C
Vapor Density (Air=1): >1
Density: N/A
Specific Gravity (H_2O=1, @ 25^{o}C): approx. 0.94
pH: ~6

Water Solubility: Soluble
Boiling Point: >200 ^{O}C
Freezing/Melting Point: N/D
Viscosity: Moderate
Refractive Index: N/D
%Volatile: Nil
Evaporation Rate: N/A

Section 10 - Stability and Reactivity

Stability: Product is **STABLE** at room temperature in closed containers under normal storage and handling conditions.

Chemical Incompatibilities: Strong acids, alkalies and oxidizers..

Hazardous Thermal Decomposition Products: Oxides of Carbon.

Hazardous Polymerization: Will not occur.

Section 11- Toxicological Information

A knowledge of the available toxicology information and of the chemical properties of the material suggests that overexposure is unlikely to aggravate existing medical conditions.

Section 12 - Ecological Information

N/A

Section 13 - Disposal Considerations

Disposal: Contact a licensed contractor for detailed recommendations. Follow applicable Federal, State, and local regulations.

Section 14 - Transport Information

DOT Transportation Data (49 CFR 172.101):

DOT Proper Shipping Name: Not Regulated
DOT I.D. #: N/A
DOT Classification: N/A
UN Hazard Class: N/A

Section 15 - Regulatory Information

TSCA Inventory Status: **Listed**

EPA Regulations: SARA 311/312 Codes:

Acute:	None
Chronic:	None
Fire:	None
Reactivity:	None
Pressure:	None

State Regulations:

State	Component	CAS #	Wt.
NONE			

Section 16 - Other Information

Prepared by: PHOENIX CHEMICAL, INC., 60 Fourth Street, Somerville, NJ 08876, Phone: 908-707-0232

MAKINGCOSMETICS

Updated October 30, 2012

BEHENTRIMONIUM

Material Safety Data Sheet (MSDS)

1. PRODUCT IDENTIFICATION

Product Name: behentrimonium
INCI Name: behentrimonium chloride, ethyl alcohol
Chemical Name: docosyltrimethylammonium chlorid
CAS Number: 17301-53-0
EINECS Number: 241-327-0
Origin: synthetic

2. PHYSICAL & CHEMICAL PROPERTIES

Melting Point:	85°C (185°F)
Boiling Point:	not determined
Density:	0.9 g/cm^3 at 20°C
% Volatile by Volume:	15 (ethyl alcohol)
Specific Gravity:	not determined
Solubility in water:	partially soluble (soluble in isopropylene)
pH Value:	6 - 8 (2% solution)
Appearance & Odor:	white flakes, alcohol-like odor

3. STABILITY & REACTIVITY

Chemical Stability: stable under normal conditions
Incompatibility: strong oxidizing agents
Hazardous Decomposition: biodegradable; burning can produce carbon monoxide, carbon dioxide and oxides of nitrogen
Hazardous Polymerisation: will not occur

4. HANDLING & STORAGE

Avoid contact with eyes. Wash thoroughly after handling. As with all chemicals, good industrial hygiene practices should be followed when handling this material.
Avoid freezing or excessive heat. Do not handle or store near an open flame, heat or other sources of ignition. Keep the container tightly closed and in a cool, well-ventilated place.

5. ACCIDENTAL RELEASE MEASURES

Isolate spill area immediately. Keep unauthorized personnel away. Ventilate closed spaces before entering. Do not touch or walk through spilled material. Prevent entry into waterways, sewers, basements or confined areas. Surface may become slippery after spillage. Use vacuum or broom sweeping and remove to disposal container. If damp, flush with water.

6. EXPOSURE CONTROLS & PERSONAL PROTECTION

Respiratory Protection: Where exposure likely exceeds acceptable criteria, use NIOSH/OSHA-approved respiratory equipment.
Protective Clothing: Gloves recommended to prevent prolonged skin contact. Safety glasses, goggles, or face shield recommended for eye protection.
Other Protective Measures: Employees must practice good personal hygiene, washing exposed areas of skin several times daily and laundering contaminated clothing before re-use.

7. HAZARDS IDENTIFICATION

General: May cause irritation to skin, eyes and respiratory system.
Inhalation: Inhalation of vapor and mist may be irritating to the respiratory system and can cause dizziness.
Eye Contact: Eye irritant. Can cause serious damages to the eyes as blurred vision or permanent damage.
Skin Contact: can cause skin irritation upon prolonged or repeated exposure.
Ingestion: Do not ingest; may cause gastrointestinal irritation.

8. FIRST AID MEASURES

Eyes: Irrigate eyes with a heavy stream of water for at least 20 minutes. Seek medical attention if symptoms persist.
Skin: Wash exposed areas of the body with plenty of water.
Inhalation: Remove from area of exposure. If breathing is difficult, give oxygen. Seek medical attention if symptoms persist.
Ingestion: Drink water. Do not induce vomiting. If gastrointestinal symptoms develop, consult medical personnel.

9. FIRE FIGHTING MEASURES

Flash Point: not determined
Extinguishing Media: water spray, foam, carbon dioxide, dry powder
Fire Fighting Procedures: Firefighters should wear full fire-fighting turn-out gear (full Bunker gear) including NIOSH-approved self-contained breathing apparatus with full facepiece operated in the pressure demand or other positive pressure mode.

10. TOXICOLOGICAL INFORMATION

Acute LD50: >2000 mg/kg (rat, oral)
Dermal and Eye Irritation Test: irritant (source: CESIO)
Carcinogenicity, Mutagenicity: no data available
Environment: toxic to water organisms upon long-term exposure

11. DISPOSAL CONSIDERATIONS

Storage and disposal must be in accordance with applicable local, state & federal disposal regulations. Characterization and compliance with applicable laws are the responsibility solely of the generator.

12. TRANSPORT INFORMATION

General Information: flammable solid, organic, n.o.s, 4.1, UN1325, PG III
DOT Shipping Name: Refer to corresponding hazard class
ADR/RIC Code: Refer to corresponding hazard class
Sea Transport IMDG Code: Refer to corresponding hazard class
Air Transport IATA: Refer to corresponding hazard class

13. DISCLAIMER

This information relates only to the specific material designated and may not be valid for such material used in combination with any other materials or in any other process. Such information is to be the best of the company's knowledge and believed accurate and reliable as of the date indicated. However, no representation, warranty or guarantee of any kind, express or implied, is made as to its accuracy, reliability or completeness and we assume no responsibility for any loss, damage or expense, direct or consequential, arising out of use. It is the user's responsibility to satisfy himself as to the suitableness & completeness of such information for his own particular use.

ALL DATA HEREIN ARE ALL AS PER OUR SUPPLIER.

SAFETY DATA SHEET

MACKAMINE CE-2

1 IDENTIFICATION OF THE SUBSTANCE/PREPARATION AND OF THE COMPANY/UNDERTAKING

PRODUCT NAME	MACKAMINE CE-2
PRODUCT NO.	170013200
SUPPLIER	Rhodia UK Ltd Burrwood Way Holywell Green Halifax HX4 9BH England +441422312200 +441422312222 Chris Howard chris.howard@eu.rhodia.com
EMERGENCY TELEPHONE	+44(0)870 190 6777 (Carechem24)

2 HAZARDS IDENTIFICATION

Irritating to skin. Risk of serious damage to eyes. Very toxic to aquatic organisms.

CLASSIFICATION Xi;R38, R41. N;R50.

3 COMPOSITION/INFORMATION ON INGREDIENTS

Name	EC No.	CAS-No.	Content	Classification
WATER or AQUA	231-791-2	7732-18-5	>50%	-
DIHYDROXYETHYL COCAMINE OXIDE	263-180-1	61791-47-7	30-50%	Xi;R38,R41. N;R50.

The Full Text for all R-Phrases are Displayed in Section 16

EC No. 263-180-1

CAS-No. 61791-47-7

4 FIRST-AID MEASURES

INHALATION

Unlikely route of exposure as the product does not contain volatile substances.

INGESTION

NEVER MAKE AN UNCONSCIOUS PERSON VOMIT OR DRINK FLUIDS! Immediately rinse mouth and drink plenty of water (200-300 ml). Get medical attention if any discomfort continues.

SKIN CONTACT

Remove contaminated clothing. Wash the skin immediately with soap and water. Get medical attention if any discomfort continues.

EYE CONTACT

Immediately flush with plenty of water for up to 15 minutes. Remove any contact lenses and open eyelids widely. If irritation persists: Seek medical attention and bring along these instructions.

5 FIRE-FIGHTING MEASURES

EXTINGUISHING MEDIA

This product is not flammable. Use fire-extinguishing media appropriate for surrounding materials.

SPECIAL FIRE FIGHTING PROCEDURES

N/A.

UNUSUAL FIRE & EXPLOSION HAZARDS

N/A.

SPECIFIC HAZARDS

Fire creates: Oxides of: Carbon. Nitrogen.

PROTECTIVE MEASURES IN FIRE

Self contained breathing apparatus and full protective clothing must be worn in case of fire.

6 ACCIDENTAL RELEASE MEASURES

PERSONAL PRECAUTIONS

Wear protective clothing as described in Section 8 of this safety data sheet.

ENVIRONMENTAL PRECAUTIONS

Do not discharge into drains, water courses or onto the ground.

SPILL CLEAN UP METHODS

Absorb spillage with suitable absorbent material. Flush area clean with lots of water. Be aware of potential for surfaces to become slippery. Do not contaminate water sources or sewer.

7 HANDLING AND STORAGE

USAGE PRECAUTIONS

Avoid contact with skin and eyes.

STORAGE PRECAUTIONS

Store in tightly closed original container.

STORAGE CLASS

Chemical storage.

8 EXPOSURE CONTROLS/PERSONAL PROTECTION

INGREDIENT COMMENTS

WEL = Workplace Exposure Limits

PROTECTIVE EQUIPMENT

ENGINEERING MEASURES

No particular ventilation requirements.

RESPIRATORY EQUIPMENT

No specific recommendations.

HAND PROTECTION

For prolonged or repeated skin contact use suitable protective gloves.

EYE PROTECTION

Wear goggles/face shield.

OTHER PROTECTION

Wear suitable protective clothing as protection against splashing or contamination.

HYGIENE MEASURES

Promptly remove any clothing that becomes contaminated. No specific hygiene procedures noted, but good personal hygiene practices are always advisable, especially when working with chemicals.

9 PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE	Liquid
COLOUR	Light (or pale) Yellow
ODOUR	Mild
SOLUBILITY	Soluble in water.

MACKAMINE CE-2

MOL. WEIGHT	304	BOILING POINT (°C)	~ 100°C
RELATIVE DENSITY	~ 0.99 25°C	VAPOUR DENSITY (air=1)	> 1
pH-VALUE, DILUTED SOLUTION	~ 7 @ 10%	VISCOSITY	~ 350 cps 25°C
FLASH POINT (°C)	> 100°C CC (Closed cup).		

10 STABILITY AND REACTIVITY

STABILITY

Stable under normal temperature conditions.

CONDITIONS TO AVOID

Avoid excessive heat for prolonged periods of time.

MATERIALS TO AVOID

Strong oxidising substances.

HAZARDOUS DECOMPOSITION PRODUCTS

Fire creates: Oxides of: Carbon. Nitrogen.

11 TOXICOLOGICAL INFORMATION

TOXIC DOSE 1 - LD 50 > 2000 mg/kg (oral rat)

INHALATION

No specific health warnings noted.

INGESTION

No specific health warnings noted.

SKIN CONTACT

Irritating to skin.

EYE CONTACT

Risk of serious damage to eyes.

12 ECOLOGICAL INFORMATION

ECOTOXICITY

The product contains a substance which is very toxic to aquatic organisms.

DEGRADABILITY

This surfactant complies with the biodegradability criteria as laid down in Regulation (EC) No.648/2004 on detergents. Data to support this assertion are held at the disposal of the competent authorities of the Member States and will be made available to them, at their direct request or at the request of a detergent manufacturer.

13 DISPOSAL CONSIDERATIONS

DISPOSAL METHODS

Dispose of waste and residues in accordance with local authority requirements.

14 TRANSPORT INFORMATION

UK ROAD CLASS	9		
PROPER SHIPPING NAME	ENVIRONMENTALLY HAZARDOUS SUBSTANCE, LIQUID, N.O.S. (DIHYDROXYETHYL COCAMINE OXIDE)		
UN NO. ROAD	3082	UK ROAD PACK GR.	III
ADR CLASS NO.	9		

MACKAMINE CE-2

ADR CLASS	Class 9: Miscellaneous dangerous substances and articles.	ADR PACK GROUP	III
HAZARD No. (ADR)	90	ADR LABEL NO.	9
HAZCHEM CODE	3Z	CEFIC TEC(R) NO.	90GM6-III
RID CLASS NO.	9	RID PACK GROUP	III
UN NO. SEA	3082	IMDG CLASS	9
IMDG PACK GR.	III	EMS	F-A, S-F
MFAG	See Guide	MARINE POLLUTANT	No.
UN NO. AIR	3082	AIR CLASS	9
AIR PACK GR.	III		

15 REGULATORY INFORMATION

LABELLING

Irritant

Dangerous for the environment

RISK PHRASES

R38	Irritating to skin.
R41	Risk of serious damage to eyes.
R50	Very toxic to aquatic organisms.

SAFETY PHRASES

S24/25	Avoid contact with skin and eyes.
S26	In case of contact with eyes, rinse immediately with plenty of water and seek medical advice.
S37/39	Wear suitable gloves and eye/face protection.
S57	Use appropriate containment to avoid environmental contamination.
S60	This material and its container must be disposed of as hazardous waste.
S61	Avoid release to the environment. Refer to special instructions/safety data sheets.

STATUTORY INSTRUMENTS

Chemicals (Hazard Information and Packaging) Regulations.

APPROVED CODE OF PRACTICE

Classification and Labelling of Substances and Preparations Dangerous for Supply. Safety Data Sheets for Substances and Preparations.

GUIDANCE NOTES

Workplace Exposure Limits EH40. CHIP for everyone HSG(108).

16 OTHER INFORMATION

REVISION DATE	01/09/2006
REV. NO./REPL. SDS	2
GENERATED	

RISK PHRASES IN FULL

NC	Not classified.
R38	Irritating to skin.
R41	Risk of serious damage to eyes.
R50	Very toxic to aquatic organisms.

Appendix 4. Cytotoxicity (Elution Test) Test Report
NAMSA 15T_31655_04

GLP REPORT

TEST FACILITY

NAMSA
6750 Wales Road
Northwood, OH 43619
419.666.9455

SPONSOR

Mike Kalfus
Mammogrip
1130 Route 46 West
Parsippany, NJ 07054

CONFIDENTIAL

STUDY TITLE

Cytotoxicity Study Using the ISO Agarose Overlay Method

TEST ARTICLE NAME

MammoGRIP

TEST ARTICLE IDENTIFICATION

Lot #9976

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Summary

The test article, MammoGRIP, was evaluated to determine the potential for cytotoxicity. This study was conducted based on the requirements of ISO 10993-5: Biological evaluation of medical devices - Part 5: Tests for i*n vitro* cytotoxicity. Triplicate wells were dosed with 0.1 mL of the test article placed on a filter (test filter disc). Triplicate wells were dosed with 0.1 mL of 0.9% sodium chloride solution (SC) placed on a filter disc (filter disc control). Triplicate wells were dosed with a 1 cm length portion of high density polyethylene as a negative control. Triplicate wells were dosed with a 1 cm x 1 cm portion of latex as a positive control. Each was placed on an agarose surface directly overlaying a subconfluent monolayer of L-929 mouse fibroblast cells. After incubating at 37°C in the presence of 5% CO_2 for 24 to 26 hours, the cultures were examined macroscopically and microscopically for any abnormal cell morphology and cell lysis.

The test article showed evidence of causing severe cell lysis or toxicity. The test article did not meet the requirements of the test since the grade was greater than a grade 2 (mild reactivity).

Supervisory Personnel: Lisa A. Severhof, BA
Manager, In vivo Biocompatibility

Austin M. Zdawczyk, BS, MBA, ALAT
Manager, In vitro Biocompatibility

Study Director Approval:

Joshua M. Stowell, BS, LAT
Medical Research Manager

4/21/2015
Date

Statement of GLP Compliance

There were no deviations to the provisions of the FDA Good Laboratory Practice (GLP) Regulations (21 CFR, Part 58) noted during the course of the study.

Study Director: _____ 4/27/2015

Joshua M. Stowell, BS, LAT — Date

1. Introduction

1.1 Purpose

The purpose of this study was to determine the potential of a test article to cause cytotoxicity.

1.2 Testing Guidelines

This study was based on the requirements of the International Organization for Standardization 10993-5, Biological evaluation of medical devices - Part 5: Tests for *in vitro* cytotoxicity.

1.3 Dates

Test Article Received:	March 24, 2015
Cells Dosed:	April 21, 2015
Observations Concluded:	April 22, 2015

1.4 GLP Compliance

The study initiated by protocol signature on April 13, 2015 was conducted in accordance with the provisions of the FDA Good Laboratory Practice (GLP) Regulations, 21 CFR 58. A Statement of Quality Assurance Activities was issued with this report.

2. Identification of Test and Control Articles

The test article provided by the sponsor was identified and handled as described below:

Table 1: Test Article

Name:	MammoGRIP
Identification:	Lot #9976
Stability Testing:	Complete and on file with the sponsor (per sponsor)
Expiration Date:	12/2016 (per sponsor)
Strength, Purity and Composition:	Strength: Active ingredient - Benzalkonium chloride, .05; Purity: Active ingredient - Benzalkonium chloride, 50%; Composition: Benzalkonium chloride 0.1%, water, dihydroxypropyl PEG-5 linoleammonium chloride, glycereth-2 cocoate, behentrimonium chloride, and dihydroxyethyl cocamine oxide.
Physical Description of the Test Article	clear foam
Storage Conditions:	Ambient Temperature

Table 2: Filter Disc Control Article

Name:	0.9% Sodium Chloride (SC)
Stability Testing:	Marketed product, stability characterized by its labeling
Strength, Purity, Composition or Other Characteristics:	Purity: Meets requirements of USP Sodium Chloride for Irrigation and is certified as USP Grade; Composition: 0.9% NaCl ± 5.0% of label claim, balance is water; sodium chloride CAS No.: 7647-14-5/water CAS No.: 7732-18-5

Table 3: Negative Control Article

Name:	High density polyethylene (HDPE)
Stability Testing:	Marketed product, stability characterized by its labeling
Strength, Purity, Composition or Other Characteristics:	Purity: Meets USP <661> Polyethylene Containers, Multiple Internal Reflectance, Thermal Analysis, Heavy Metals, and Non-Volatile Residue; Composition: polyethylene

Table 4: Positive Control Article

Name:	Latex
Stability Testing:	Marketed product, stability characterized by its labeling
Strength, Purity, Composition or Other Characteristics:	Composition: natural rubber latex, zinc carbamate accelerators, zinc oxide, and titanium dioxide

Table 5: Ancillary Materials

Growth Media:	Single strength Minimum Essential Medium supplemented with 5% fetal bovine serum, 2% antibiotics (100 units/mL penicillin, 100 µg/mL streptomycin, and 2.5 µg/mL amphotericin B) and 1% (2 mM) L-glutamine (1X MEM) Double strength Minimum Essential Medium supplemented with 10% fetal bovine serum, 4% antibiotics (200 units/mL penicillin, 200 µg/mL streptomycin and 5.0 µg/mL amphotericin B) and 2% (4 mM) L-glutamine (2X MEM)

3. Test System

3.1 Test System and Justification of Test System

Mammalian cell culture monolayer consisting of L-929 mouse fibroblast cells (ECACC Cat #85103115, or equivalent source) was used. *In vitro* mammalian cell culture studies have been used historically to evaluate cytotoxicity of biomaterials and medical devices.

3.2 Test System Management

L-929 mouse fibroblast cells were propagated and maintained in flasks containing 1X MEM at 37°C with 5% carbon dioxide (CO_2). For this study, cells were seeded in 10 cm^2 cell culture wells, labeled with passage number and date, and incubated at 37°C in the presence of 5% CO_2 to obtain subconfluent monolayers of cells prior to use. Aseptic procedures were used in the handling of the cell cultures following approved NAMSA Standard Operating Procedures.

3.3 Preparation of Agarose Overlay

The culture wells were selected which contained a subconfluent cell monolayer. The agarose mixture was prepared with equal amounts of 2% agarose and 2X MEM supplemented with neutral red. The growth medium in each well was replaced with 2.0 mL of the agarose mixture. The agarose mixture was allowed to solidify over the cells to form the agarose overlay.

4. Method

4.1 Test Article Preparation

Triplicate wells were dosed with 0.1 mL of the test article placed on a filter (test filter disc).

Figure 1: Representative Photograph of the Test Article

Test Article

4.2 Control Article Preparation

Filter Disc Control: Triplicate wells were dosed with 0.1 mL of SC placed on a filter disc.

Negative Control: Triplicate wells were dosed with a 1 cm length portion of HDPE.

Positive Control: Triplicate wells were dosed with a 1 cm x 1 cm portion of latex.

4.3 Test Procedure

The test filter disc was placed on the solidified agarose surface in each of three cell culture wells. Similarly, the filter disc control, the negative control, and the positive control were each placed on the solidified agarose surface in three cell culture wells. The wells were labeled with the corresponding lab number and dosing date, and incubated at 37°C in the presence of 5% CO_2 for 24-26 hours.

Following incubation, the cells were examined macroscopically for cell decolorization around the test article and controls to determine the zone of cell lysis (if any). After macroscopic examination, the cell monolayers were examined microscopically (100X) to verify any decolorized zones and to determine cell morphology in proximity to the article. Scoring for cytotoxicity was based on the following criteria:

Table 6: Test Scoring

Grade	Reactivity	Condition of Cultures
0	None	No detectable zone around or under specimen
1	Slight	Some malformed or degenerated cells under specimen
2	Mild	Zone limited to area under specimen
3	Moderate	Zone extending specimen size up to 1.0 cm
4	Severe	Zone extending farther than 1.0 cm beyond specimen

For the suitability of the system to be confirmed, the negative control and filter disc control must have been a grade of 0 (reactivity none) and the positive control must have been a grade equal to or greater than a grade of 3 (reactivity moderate to severe). The test article passed the test if all three monolayers were less than or equal to a grade of 2 (reactivity mild).

All times and temperatures reported herein are approximate and are within ranges established by the external standards described in the References section of this report and/or NAMSA standard operating procedures.

5. Results

The scores obtained were as follows:

Table 7: Individual Scores

Articles		Zone of Lysis (mm)	Grade	Reactivity
Test Filter Disc	(1)	11*	4	Severe
	(2)	11*	4	Severe
	(3)	10*	3	Moderate
Filter Disc Control	(1)	0	0	None
	(2)	0	0	None
	(3)	0	0	None
Negative Control	(1)	0	0	None
	(2)	0	0	None
	(3)	0	0	None
Positive Control	(1)	8*	3	Moderate
	(2)	8*	3	Moderate
	(3)	8*	3	Moderate

*Complete cell lysis under the article.

Note: 1, 2, and 3 denote replicates.

6. Conclusion

The test article showed evidence of causing severe cell lysis or toxicity. The test article did not meet the requirements of the test since the grade was greater than a grade 2 (mild reactivity).

Results and conclusions apply only to the test article tested. Any extrapolation of these data to other articles is the sponsor's responsibility.

7. Quality Assurance

Inspections were conducted at intervals adequate to assure the integrity of the study in conformance with 21 CFR 58.35(b)(3). The final report was reviewed for conformance to Section 58.185, Subpart J, of the GLP Regulations. A Statement of Quality Assurance Activities was issued with the report.

8. Records

All raw data pertaining to this study and a copy of the final report are retained in designated NAMSA archive files in accordance with NAMSA SOPs.

9. ISO Compliance

All procedures were certified to ISO 13485 and accredited to ISO 17025.

10. References

Code of Federal Regulations (CFR), Title 21, Part 58, Good Laboratory Practice for Nonclinical Laboratory Studies.

International Organization for Standardization (ISO) 10993-1, Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process (2009/Technical Corrigendum 1 2010).

International Organization for Standardization (ISO) 10993-5, Biological evaluation of medical devices - Part 5: Tests for *in vitro* cytotoxicity (2009).

International Organization for Standardization (ISO) 10993-12, Biological evaluation of medical devices - Part 12: Sample preparation and reference materials (2012).

International Organization for Standardization (ISO) 13485, Medical devices - Quality management systems - Requirements for regulatory purposes (2003/Technical Corrigendum 1 2009).

International Organization for Standardization/International Electrotechnical Commission (ISO/IEC) 17025, General requirements for the competence of testing and calibration laboratories (2005/Technical Corrigendum 1 2006).

United States Pharmacopeia 37, National Formulary 32 (USP), General Chapter <87>, Biological Reactivity Tests, In Vitro (2014).

Statement of Quality Assurance Activities

Phase Inspected	Date Inspected	Study Director Notification Date	Management Notification Date
Scoring	April 22, 2015	April 22, 2015	April 22, 2015
Study Data Review	April 27, 2015	April 27, 2015	April 27, 2015
Final Report Review	April 27, 2015	April 27, 2015	April 27, 2015

Based on a review of this study, it has been concluded that this report accurately describes the methods and standard operating procedures, and that the reported results accurately reflect the raw data of the study. This study has been reviewed in accordance with the provisions of the FDA Good Laboratory Practice Regulations (21 CFR, Part 58).

QA Representative: Cherise M. McCoy

Cherise M. McCoy, B.S.
Auditor, Quality Assurance

April 27, 2015
Date

Joshua Stowell

From: NW Study Coordinators
Sent: Thursday, March 26, 2015 4:00 PM
To: Joshua Stowell
Subject: FW: Electronic Sample Submission 11110-1

15T_31655
40647_001 40647

15T_31655

From: esubmission@namsa.com [mailto:esubmission@namsa.com]
Sent: Thursday, March 26, 2015 10:05 AM
To: OH-Order-Processing; GLPPRO
Subject: Electronic Sample Submission 11110-1

T032615_032
UPS WM COOK

Overview

Submission ID: 11110
Revision #: 1
Date Created: Mar 26, 2015
Testing Location: Northwood
Proposal Number: 1_25370-L3N5N7
Purchase Order: MAM 3102
Quantity Submitted: 5 containers (1)

Billing and Shipping

Bill To: Mammogrip (40647)
1130 Route 46 West
Parsippany, NJ 07054
Ship To: Mammogrip (40647)
1130 Route 46 West
Parsippany, NJ 07054
Contact: Mike Kalfus (40647_001)
Mammogrip (40647)
mike@mammogrip.com

Test Article Information

Name: MammoGRIP
Batch Code / Lot Id: ~~pending~~ Lot #9976 (2)
Physical Description: clear foam
Type: Medical Device
Clinical Use: medical device for improved mammography
Sterility: Not Sterile
Can Be Cut: No
Special Instructions:

Ratio: ~~Weight, Irregularly shaped material or by request - ratio of 1 g :5mL~~ NA TMS1267 4/10/15
Contains Elastomer: No
Storage Conditions: Ambient Temperature (15-30 °C)
Disposition: Discard used and unused test article

(1) Received 3 containers TMS1267 4/10/15
(2) Per sample label TMS1267 4/10/15

GLP Information

Stability: Stability testing is complete and on file with sponsor.
Stability Expiration Date: ~~Mar 01, 2016~~ 12/2016 (see attached) NA TMS1267 4/13/15 TMS1267 4/13/2015
Analysis: Analysis is not necessary due to test article being a solid, powder, gel, or liquid being extracted or tested as received (mixture with a carrier not needed).
Has Active Ingredient: Yes
Active Ingredient: Benzalkonium Chloride
Strength: .05
Purity: ~~NA~~ 50% see attached. TMS1267 4/10/2015
Composition: ~~foam~~ see attached. TMS1267 4/10/2015

Testing Services

15T-31655

Test Code	Qty	Proposal	Grouping	STAT	Regulatory Scope	Comments	Purchase Order	Test Spec	Extracts
TI251-84S	1	1_25370-L3N5N7		No	GLP		~~MAM 3102~~		
V0014-130/s	1	1_25370-L3N5N7		No	GLP		MAM 3102		
TI261-306	1	1_25370-L3N5N7		No	GLP		MAM 3102		

NA see protocol. TMR 4/10/2015

Authorization

Electronically Signed By: mike@mammogrip.com **Date:** Mar 26, 2015

Reviewed By (NAMSA Associate Signature): _____ Date: 4/13/2015

GLP PROTOCOL

TEST FACILITY

NAMSA
6750 Wales Road
Northwood, OH 43619

SPONSOR

Mike Kalfus
Mammogrip
1130 Route 46 West
Parsippany, NJ 07054

STUDY TITLE

Cytotoxicity Study Using the ISO Agarose Overlay Method

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4. Method 5
5. Evaluation and Statistical Analysis 5
6. Protocol Changes 5
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Approvals

Sponsor Representative: Mike Kalfus

Date Approved: 4-7-15

Study Director (NAMSA):

Joshua M. Stowell, BS, LAT
Medical Research Manager

Date Initiated: 4/13/2015

1. Introduction

1.1 Purpose

The purpose of this study is to evaluate the cytotoxicity of a test article.

1.2 Testing Guidelines

This study will be conducted based on the requirements of the International Organization for Standardization 10993-5, Biological evaluation of medical devices - Part 5: Tests for *in vitro* cytotoxicity.

1.3 GLP Compliance

Good Laboratory Practice – This nonclinical laboratory study will be conducted in accordance with the United States Food and Drug Administration Good Laboratory Practice Regulations, 21 CFR Part 58.

2. Identification of Test and Control Articles

2.1 Test Article

The sponsor will submit the test article, MammoGRIP, to be evaluated. The sponsor provided detailed information about the test article to NAMSA on the sample submission form.

2.2 Control Articles

Negative Control: High density polyethylene, (approximate 1.0 cm length)

Filter Disc Control: Filter disc (12.7 mm) containing 0.1 mL of SC

Positive Control: Latex (approximate 1 cm x 1 cm section)

3. Test System

3.1 Test System and Justification

Mammalian cell culture monolayer consisting of L-929 mouse fibroblast cells (ECACC Catalog No. 85103115 or equivalent source) will be used. All stock cultures of cells will be tested to confirm the absence of mycoplasma contamination.

3.2 Test System Management

L-929 mouse fibroblast cells will be propagated and maintained in 1X MEM at 37°C with 5% carbon dioxide (CO_2). For this study, 10 cm^2 wells will be seeded, labeled with passage number and date, and incubated at 37°C in 5% CO_2 to obtain subconfluent monolayers of cells prior to use. Aseptic procedures will be used in the handling of the cell cultures following approved NAMSA Standard Operating Procedures.

3.3 Preparation of Agarose Overlay

The culture wells will be selected which contains a subconfluent cell monolayer. The growth medium in each well will be replaced with 2 mL of equal amounts of double strength Minimum Essential Medium supplemented with 10% fetal bovine serum, 4% antibiotics and 2% L-glutamine (2X MEM), supplemented with neutral red, and 2% agarose (final concentration 1% agarose, 1X MEM). The MEM-agarose mixture (2.0 mL) will be placed in the cell culture wells and allowed to solidify over the cells to form the agarose overlay.

4. Method

4.1 Test Article Preparation

The following information was completed based on the sponsor providing the information to NAMSA. Further instructions may be attached to the protocol.

The sample will be prepared as follows:

4.2 Preparation of Test Article

Liquid - paper filter disc (12.7 mm) containing 0.1 mL of test article. Requires the use of a filter disc control dosed with 0.9% Sodium Chloride Solution, USP (SC).

Note: The test article will be prepared in triplicate. Therefore, the amount of test article required is three times that indicated above.

4.3 Test Procedure

An appropriately prepared test article section (see Preparation of Test Article) will be placed on the solidified overlay surface in three separate cell culture wells. Similarly, the negative control, the filter disc control and the positive control sections will each be placed on the solidified overlay surface in three separate cell culture wells. The wells will be labeled with the corresponding lab number and dosing date and incubated at 37°C in 5% CO_2 for 24-26 hours.

Following incubation the cultures will be examined macroscopically for cell decolorization around the test article and controls and to determine the zone of cell lysis (if any). After macroscopic examination, the cell monolayers will be examined microscopically (100X) to verify any decolorized zones and to determine cell morphology in proximity to the articles.

5. Evaluation and Statistical Analysis

Scoring for cytotoxicity will be based on the following criteria:

Table 1: Test Scoring

Grade	Reactivity	Condition of Cultures
0	None	No detectable zone around or under specimen
1	Slight	Some malformed or degenerated cells under specimen
2	Mild	Zone limited to area under specimen
3	Moderate	Zone extending specimen size up to 1.0 cm
4	Severe	Zone extending farther than 1.0 cm beyond specimen

For the suitability of the system to be confirmed, the negative control and filter disc control must have a grade of 0 (reactivity none) and the positive control must have produced a zone of lysis (reactivity moderate to severe). The test article passes the test if none of the three monolayers exposed to the test article shows greater than a grade of 2 (reactivity mild). Repeat the test if the controls do not perform as anticipated.

6. Protocol Changes

Any necessary changes to the protocol after sponsor approval or study initiation will be documented and approved by the study director as protocol amendments. Copies will be distributed to the sponsor, the raw data file, and the NAMSA Quality Assurance department.

7. Report

The final report will include the test and control preparation, information on the cell line, the methods, the score for the test article and controls at 24 hours and any additional pertinent information.

8. Quality Assurance

Inspections will be conducted at intervals adequate to assure the integrity of the study in conformance with 21 CFR 58.35(b)(3). The final report will also be reviewed for conformance to Section 58.185, Subpart J, of the GLP Regulations. A Statement of Quality Assurance Activities will be provided with the final report.

9. Records

All raw data pertaining to this study and a copy of the final report will be retained in designated NAMSA archive files in accordance with NAMSA SOPs.

10. References

Code of Federal Regulations (CFR), Title 21, Part 58, Good Laboratory Practice for Nonclinical Laboratory Studies.

International Organization for Standardization (ISO) 10993-1, Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process (2009/Technical Corrigendum 1 2010).

International Organization for Standardization (ISO) 10993-5, Biological evaluation of medical devices - Part 5: Tests for *in vitro* cytotoxicity (2009).

International Organization for Standardization (ISO) 10993-12, Biological evaluation of medical devices - Part 12: Sample preparation and reference materials (2012).

International Organization for Standardization (ISO) 13485, Medical devices - Quality management systems - Requirements for regulatory purposes (2003/Technical Corrigendum 1 2009).

International Organization for Standardization/International Electrotechnical Commission (ISO/IEC) 17025, General requirements for the competence of testing and calibration laboratories (2005/Technical Corrigendum 1 2006).

United States Pharmacopeia 37, National Formulary 32 (USP), General Chapter <87>, Biological Reactivity Tests, In Vitro (2014).

Appendix 5. Intracutaneous Injection Test (Irritation) Test Report NAMSA 15T_31655_05

GLP REPORT

TEST FACILITY

NAMSA
6750 Wales Road
Northwood, OH 43619
419.666.9455

SPONSOR

Mike Kalfus
Mammogrip
1130 Route 46 West
Parsippany, NJ 07054

CONFIDENTIAL

STUDY TITLE

ISO Skin Irritation Study in Rabbits

TEST ARTICLE NAME

MammoGRIP

TEST ARTICLE IDENTIFICATION

Lot #9976

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Summary

The test article, MammoGRIP, was evaluated for primary skin irritation in rabbits. This study was conducted in accordance with the guidelines of ISO 10993-10, Biological evaluation of medical devices - Part 10: Tests for irritation and skin sensitization. Two 0.5 mL portions of the test article and control article were topically applied to the skin of each of three rabbits and left in place for a minimum of 23 hours and a maximum of 24 hours. The sites were graded for erythema and edema at 1, 24, 48 and 72 hours after removal of the single sample application.

There was very slight erythema and no edema observed on the skin of the animals treated with the test article. The Primary Irritation Index for the test article was calculated to be 0.8. The response of the test article was categorized as slight.

Supervisory Personnel: Lisa A. Severhof, BA
Manager, In vivo Biocompatibility

Study Director Approval: _____ 5/4/2015
Joshua M. Stowell, BS, LAT — Date
Medical Research Manager

Statement of GLP Compliance

There were no deviations to the provisions of the FDA Good Laboratory Practice (GLP) Regulations (21 CFR, Part 58) noted during the course of the study.

Study Director: _____ 5/4/2015

Joshua M. Stowell, BS, LAT — Date

1. Introduction

1.1 Purpose

The purpose of this study was to evaluate the test article for the potential to cause skin irritation in the rabbit.

1.2 Testing Guidelines

This study was conducted based on the International Organization for Standardization 10993-10, Biological evaluation of medical devices, Part 10: Tests for irritation and skin sensitization.

1.3 Dates

Test Article Received:	March 24, 2015
Treatment Started:	April 26, 2015
Observations Concluded:	April 30, 2015

1.4 GLP Compliance

The study initiated by protocol signature on April 13, 2015 was conducted in accordance with the provisions of the FDA Good Laboratory Practice (GLP) Regulations, 21 CFR 58. A Statement of Quality Assurance Activities was issued with this report.

1.5 Duplication of Experimental Work

By signature on the protocol, the sponsor confirmed that the conduct of this study did not unnecessarily duplicate previous experiments.

2. Identification of Test and Control Articles

The test article provided by the sponsor was identified and handled as described below:

Table 1: Test Article

Name:	MammoGRIP
Identification:	Lot #9976
Stability Testing:	Complete and on file with the sponsor (per sponsor)
Expiration Date:	12/2016 (per sponsor)
Strength, Purity and Composition:	Strength: Active ingredient - Benzalkonium chloride, .05; Purity: Active ingredient - Benzalkonium chloride, 50%; Composition: Benzalkonium chloride 0.1%, water, dihydroxypropyl PEG-5 linoleammonium chloride, glycereth-2 cocoate, behentrimonium chloride, and dihydroxyethyl cocamine oxide.
Physical Description of the Test Article	clear foam
Storage Conditions:	Ambient Temperature

Table 2: Control Article

Name:	Four-ply gauze, supplied by the test facility, was cut into 25 mm x 25 mm sections and moistened with 0.5 mL of saline per section.
Stability Testing:	Marketed product, stability characterized by its labeling
Strength, Purity, Composition or Other Characteristics:	Purity: FDA Quality System Requirements (QSR) as stipulated in 21 CFR Part 820; Composition: 20% rayon, 80% polyester blend

3. Test System

3.1 Test System

Species:	Rabbit (*Oryctolagus cuniculus*)
Breed:	New Zealand White
Source:	Robinson Services, Inc.
Sex:	Male
Body Weight Range:	2.1 kg to 2.2 kg at selection
Age:	Young adult
Acclimation Period:	Minimum 5 days
Number of Animals:	Three
Identification Method:	Ear tag

3.2 Justification of Test System

The rabbit (animal) is specified as an appropriate animal model for evaluating potential skin irritants by the current ISO testing standards. The rabbit is widely used for this purpose and relative ranking of irritant scores can be determined.

4. Animal Management

4.1 Husbandry, Housing and Environment

Conditions conformed to NAMSA Standard Operating Procedures that are based on the "*Guide for the Care and Use of Laboratory Animals.*" Animals were individually housed in stainless steel or plastic suspended cages identified by a card indicating the lab number, animal number, test code, sex, and date dosed.

The animal housing room temperature and relative humidity were monitored daily. The temperature for the room was set to 61-72°F and the relative humidity was set to 30-70%. There were no significant temperature or relative humidity excursions that adversely affected the health of the animals.

The light cycle was controlled using an automatic timer (12 hours light, 12 hours dark).

4.2 Food, Water and Contaminants

A commercially available rabbit feed, PROLAB Hi-Fiber Rabbit - 5P25, was provided daily. Potable water was provided *ad libitum* through species appropriate water containers or delivered through an automatic watering system.

No contaminants present in the feed and water impacted the results of this study.

4.3 Accreditation

NAMSA is an AAALAC International accredited facility and is registered with the United States Department of Agriculture. Additionally, NAMSA maintains an approved Animal

Welfare Assurance on file with the National Institutes of Health, Office for Laboratory Animal Welfare.

4.4 Personnel
Associates involved were appropriately qualified and trained.

4.5 Veterinary Care
Standard veterinary medical care was provided in this study.

4.6 IACUC
This procedure has been approved by the NAMSA Institutional Animal Care and Use Committee (IACUC), and is reviewed at least annually by the same committee.

4.7 Selection
Only healthy, previously unused, animals free from irritation or other dermatological lesions that could interfere with the test were selected.

5. Method

5.1 Test Article Preparation
0.5 mL portions of the test article were placed on 4-ply, 25 mm x 25 mm gauze pads, and applied to the skin of the rabbit.

Figure 1: Representative Photograph of the Test Article
Test Article

5.2 Test Procedure
The animals were weighed and the fur on the back of each animal was clipped with an electric clipper 4 to 24 hours prior to treatment. On the day of treatment, four sites, two on each side of the back and positioned cranially and caudally, were designated on each animal. The sites were free of blemishes that could interfere with the interpretation of results.

A 0.5 mL portion of the test article was applied to one cranial site on the left side and one caudal site on the right side (two sites per animal) by introduction under a 4 ply gauze layer to an area of skin approximately 25 mm x 25 mm square. The patches were covered with a nonreactive tape. The control was moistened with 0.5 mL of saline and similarly applied to the opposite cranial and caudal sites. The trunk of each animal was wrapped with an elastic binder to maintain the test patches in position. Animals were returned to their cages after treatment.

After a minimum of 23 hours and a maximum of 24 hours exposure, the binders, tape, and patches were removed. The perimeter of each site was marked with nontoxic ink. The sites were gently wiped with a gauze sponge dampened with deionized water in an attempt to remove any remaining residue.

5.2.1 Laboratory Observations

1. Animals were observed daily for general health.
2. Body weights were recorded for each animal at pretreatment.
3. Dermal observations for erythema and edema were recorded at 1, 24, 48 and 72 hours after patch removal in accordance with the criteria in Appendix 1.

All times and temperatures reported herein are approximate and are within ranges established by the external standards described in the References section of this report and/or NAMSA standard operating procedures.

6. Evaluation and Statistical Analysis

The Primary Irritation Index of the test was calculated following test completion for each animal. The erythema and edema scores obtained at the 24, 48 and 72 hour intervals were added together and divided by the total number of observations. The 1 hour score was not included in the calculation. This calculation was conducted separately for the test and control article for each animal. The score for the control was subtracted from the score for the test article to obtain the Primary Irritation Score. The Primary Irritation Score for each animal was added together to determine the Combined Primary Irritation Score. The Combined Primary Irritation Score was divided by the number of animals to obtain the Primary Irritation Index. The Primary Irritation Index was characterized based on the definitions outlined in Appendix 1.

7. Results

All animals were clinically normal throughout the study. Individual results of dermal scoring are presented in Appendix 2. Very slight erythema and no edema reactions resulted in an overall evaluation of slight irritation to the skin of the animals treated with the test article. The time of onset of the Maximum Irritation Response was at 1 hour and the time to Maximum response was 1 hour. The Primary Irritation Index of the test article was calculated to be 0.8. The irritation calculations are shown below:

Table 3: Irritation Calculations

Animal Number	Test Score Average	-	Control Score Average	Individual Primary Irritation Score	Combined Primary Irritation Score (CPIS)	Primary Irritation Index (CPIS ÷ 3)	Response Category
04030	0.8	-	0.0	0.8	2.3	0.8	Slight
04031	0.5	-	0.0	0.5			
04033	1.0	-	0.0	1.0			

8. Conclusion

There was very slight erythema and no edema observed on the skin of the animals treated with the test article. The Primary Irritation Index for the test article was calculated to be 0.8. The response of the test article was categorized as slight.

Results and conclusions apply only to the test article tested. Any extrapolation of these data to other articles is the sponsor's responsibility.

9. Quality Assurance

Inspections were conducted at intervals adequate to assure the integrity of the study in conformance with 21 CFR 58.35(b)(3). The final report was reviewed for conformance to Section 58.185, Subpart J, of the GLP Regulations. A Statement of Quality Assurance Activities was issued with the report.

10. Records

All raw data pertaining to this study and a copy of the final report are retained in designated NAMSA archive files in accordance with NAMSA SOPs.

11. ISO Compliance

All procedures were certified to ISO 13485 and accredited to ISO 17025.

12. References

Code of Federal Regulations (CFR), Title 9, Parts 1-4, Animal Welfare Act.

Code of Federal Regulations (CFR), Title 16, Part 1500, Federal Hazardous Substances Act (FHSA) Regulations (2008).

Code of Federal Regulations (CFR), Title 21, Part 58, Good Laboratory Practice for Nonclinical Laboratory Studies.

International Organization for Standardization (ISO) 10993-1, Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process (2009/Technical Corrigendum 1 2010).

International Organization for Standardization (ISO) 10993-2, Biological evaluation of medical devices - Part 2: Animal welfare requirements (2006).

International Organization for Standardization (ISO) 10993-10, Biological evaluation of medical devices - Part 10: Tests for irritation and skin sensitization (2010).

International Organization for Standardization (ISO) 10993-12, Biological evaluation of medical devices - Part 12: Sample preparation and reference materials (2012).

International Organization for Standardization (ISO) 13485, Medical devices - Quality management systems - Requirements for regulatory purposes (2003/Technical Corrigendum 1 2009).

International Organization for Standardization/International Electrotechnical Commission (ISO/IEC) 17025, General requirements for the competence of testing and calibration laboratories (2005/Technical Corrigendum 1 2006).

National Research Council, *Guide for the Care and Use of Laboratory Animals*, Washington, DC: National Academy Press, 2011.

Office of Laboratory Animal Welfare (OLAW), Public Health Service Policy on Humane Care and Use of Laboratory Animals.

Appendix 1 - Classification System For Skin Reaction

Reaction	Numerical Grading
Erythema and Eschar Formation	
No erythema	0
Very slight erythema (barely perceptible)	1
Well-defined erythema	2
Moderate erythema	3
Severe erythema (beet redness) to eschar formation preventing grading of erythema	4
Edema Formation	
No edema	0
Very slight edema (barely perceptible)	1
Well-defined 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 exposure area)	4
Total possible score for irritation	8

NOTE: Other adverse changes at the skin sites shall be recorded and reported

Irritation Response Categories in the Rabbit

Response Category	Mean Score
Negligible	0.0 to 0.4
Slight	0.5 to 1.9
Moderate	2.0 to 4.9
Severe	5.0 to 8.0

Appendix 2 - Dermal Observations

Animal Number/ Sex	Weight (kg)	Group	Observation	Interval (hours)							
				1		24		48		72	
				Left	Right	Left	Right	Left	Right	Left	Right
04030 Male	2.2	Test	Erythema	1	1	1	0	1	1	1	1
			Edema	0	0	0	0	0	0	0	0
		Control	Erythema	0	0	0	0	0	0	0	0
			Edema	0	0	0	0	0	0	0	0
04031 Male	2.2	Test	Erythema	1	0	1	0	1	0	1	0
			Edema	0	0	0	0	0	0	0	0
		Control	Erythema	0	0	0	0	0	0	0	0
			Edema	0	0	0	0	0	0	0	0
04033 Male	2.1	Test	Erythema	1	1	1	1	1	1	1	1
			Edema	0	0	0	0	0	0	0	0
		Control	Erythema	0	0	0	0	0	0	0	0
			Edema	0	0	0	0	0	0	0	0

Phase Inspected	Date Inspected	Study Director Notification Date	Management Notification Date
Scoring	April 29, 2015	April 29, 2015	April 29, 2015
Study Data Review	May 4, 2015	May 4, 2015	May 4, 2015
Final Report Review	May 4, 2015	May 4, 2015	May 4, 2015

Based on a review of this study, it has been concluded that this report accurately describes the methods and standard operating procedures, and that the reported results accurately reflect the raw data of the study. This study has been reviewed in accordance with the provisions of the FDA Good Laboratory Practice Regulations (21 CFR, Part 58).

QA Representative: Lauren M. Michaels, BSPS
Auditor, Quality Assurance

5-4-15
Date

Joshua Stowell

From: NW Study Coordinators
Sent: Thursday, March 26, 2015 4:00 PM
To: Joshua Stowell
Subject: FW: Electronic Sample Submission 11110-1

15T_31655
40647_001 40647

15T_31655

From: esubmission@namsa.com [mailto:esubmission@namsa.com]
Sent: Thursday, March 26, 2015 10:05 AM
To: OH-Order-Processing; GLPPRO
Subject: Electronic Sample Submission 11110-1

T032615_032 N/A TMS1267
UPS WM COOK 3/2/2015

Overview

Submission ID: 11110
Revision #: 1
Date Created: Mar 26, 2015
Testing Location: Northwood
Proposal Number: 1_25370-L3N5N7
Purchase Order: MAM 3102
Quantity Submitted: 5 containers (1)

Billing and Shipping

Bill To: Mammogrip (40647)
1130 Route 46 West
Parsippany, NJ 07054
Ship To: Mammogrip (40647)
1130 Route 46 West
Parsippany, NJ 07054
Contact: Mike Kalfas (40647_001)
Mammogrip (40647)
mike@mammogrip.com

Test Article Information

Name: MammoGRIP
Batch Code / Lot Id: ~~pending~~ Lot # 9976 (2)
Physical Description: clear foam
Type: Medical Device
Clinical Use: medical device for improved mammography
Sterility: Not Sterile
Can Be Cut: No
Special Instructions:

Ratio: N/A TMS1267 4/10/15 Weight, Irregularly shaped material or by request - ratio of 1 g :5mL
Contains Elastomer: No
Storage Conditions: Ambient Temperature (15-30 °C)
Disposition: Discard used and unused test article

(1) Received 3 containers TMS1267 4/10/15
(2) Re sample label TMS1267 4/10/15

GLP Information

Stability: Stability testing is complete and on file with sponsor.
Stability Expiration Date: ~~Mar 01, 2016~~ 12/2016 (see attached) N/A TMS1267 3/31/15 TMS1267 4/13/2015
Analysis: Analysis is not necessary due to test article being a solid, powder, gel, or liquid being extracted or tested as received (mixture with a carrier not needed).
Has Active Ingredient: Yes
Active Ingredient: Benzalkonium Chloride
Strength: .05
Purity: ~~N/A~~ 50% see attached. TMS1267 4/10/2015
Composition: ~~foam~~ see attached. TMS1267 4/10/2015

Testing Services

15T-31655

Test Code	Qty	Proposal	Grouping	STAT	Regulatory Scope	Comments	Purchase Order	Test Spec	Extracts
TI251-84S	1	1_25370-L3N5N7		No	GLP		~~MAM 3102~~		
V0014-130/s	1	1_25370-L3N5N7		No	GLP		MAM 3102		
TI261-306	1	1_25370-L3N5N7		No	GLP		MAM 3102		

NA see protocols. TMR 4/10/2015

Authorization

Electronically Signed By: mike@mammogrip.com **Date:** Mar 26, 2015

Reviewed By (NAMSA Associate Signature): _____ Date: 4/13/2015

GLP PROTOCOL

TEST FACILITY

NAMSA
6750 Wales Road
Northwood, OH 43619

SPONSOR

Mike Kalfus
Mammogrip
1130 Route 46 West
Parsippany, NJ 07054

STUDY TITLE

ISO Skin Irritation Study in Rabbits

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Approvals

Sponsor Representative: Mike Halfus

Date Approved: 4-6-15

Study Director (NAMSA): Joshua M. Stowell, BS, LAT
Medical Research Manager

Date Initiated: 4/13/2015

1. Introduction

1.1 Purpose

The purpose of this study is to determine whether a single topical application of a designated test article is irritating to the skin of the rabbit.

1.2 Testing Guidelines

This study will be conducted based on the International Organization for Standardization 10993-10, Biological evaluation of medical devices – Part 10: Tests for irritation and skin sensitization.

1.3 GLP Compliance

Good Laboratory Practice – This nonclinical laboratory study will be conducted in accordance with the United States Food and Drug Administration Good Laboratory Practice Regulations, 21 CFR Part 58.

1.4 Duplication of Experimental Work

By signature on this protocol, the sponsor confirms that the conduct of this study does not unnecessarily duplicate previous experiments.

2. Identification of Test and Control Articles

2.1 Test Article

The sponsor will submit the test article, MammoGRIP, to be evaluated. The sponsor provided detailed information about the test article to NAMSA on the sample submission form.

2.2 Control Article

It is recommended that a comparative material be used as a negative control. This material should physically resemble the test article and should be nonirritating.

3. Test System

3.1 Test System

Species:	Rabbit (*Oryctolagus cuniculus*)
Breed:	New Zealand White
Source:	Single USDA licensed supplier
Sex:	No particular sex is prescribed for this test; females will be nulliparous and nonpregnant
Body Weight Range:	Not less than 2.0 kg at selection
Age:	Young adults
Acclimation Period:	Minimum 5 days
Number of Animals:	Three
Identification Method:	Ear tag or marking

3.2 Justification of Test System

The rabbit (animal) is specified as an appropriate animal model for evaluating potential skin irritants by the current ISO testing standards. The rabbit is widely used for this purpose and relative ranking of irritant scores can be determined.

4. Animal Management

4.1 Husbandry, Housing and Environment

Conditions will conform to NAMSA Standard Operating Procedures that are based on the *"Guide for the Care and Use of Laboratory Animals."* Animals will be individually housed in stainless steel or plastic suspended cages identified by a card indicating the lab number, animal number, test code, sex and date dosed.

The animal housing room temperature and relative humidity will be monitored daily. The recommended temperature range for the room is 61-72°F. The recommended humidity range for the room is 30-70%.

The light cycle will be controlled using an automatic timer (12 hours light, 12 hours dark).

4.2 Food, Water and Contaminants

A commercially available rabbit feed will be provided daily. Potable water will be provided *ad libitum* through species appropriate water containers or delivered through an automatic watering system.

No contaminants present in the feed and water are expected to impact the results of this study.

4.3 Accreditation

NAMSA is an AAALAC International accredited facility and is registered with the United States Department of Agriculture. Additionally, NAMSA maintains an approved Animal Welfare Assurance on file with the National Institutes of Health, Office for Laboratory Animal Welfare.

4.4 Personnel

Associates involved in this study will be appropriately qualified and trained.

4.5 Sedation, Analgesia or Anesthesia

It has been determined that the use of sedation, analgesia or anesthesia will not be necessary during the routine course of this procedure.

4.6 Veterinary Care

All anesthetics, analgesics, and other medications may be given or altered at the discretion of the attending veterinarian in accordance with standard veterinary practice and the study objectives. This applies to specific medication, dose, and dosing intervals. In the unlikely event that an animal should become injured, ill, or moribund, care will be conducted in accordance with current veterinary medical practice. If warranted for humane reasons, euthanasia will be conducted in accordance with the current report of the American Veterinary Medical Association's Guidelines on Euthanasia. The objective of the study will be given due consideration in any decision and the study sponsor will be advised.

4.7 IACUC

This protocol has been approved by the NAMSA Institutional Animal Care and Use Committee (IACUC), and is reviewed at least annually by the same committee. Any significant changes to this protocol pertaining to the care and use of animals must be approved by the IACUC.

4.8 Selection

Only healthy animals with intact skin that is free from irritation or other dermatological lesions that could interfere with the test will be selected. To reduce the number of animals used for testing, and to comply with the directives of the NAMSA IACUC, animals on this study may have been used previously in an unrelated test model. Any previously evaluated test or control articles did not cause a response in the animals. Complete history of animal usage is traceable in laboratory records. Animals used for previous evaluations will be identified in the report.

5. Method

5.1 Test Article Preparation

The following information was completed based on the sponsor providing the information to NAMSA. The units of measure are per test site. Further instructions may be attached to the protocol.

The sample will be prepared as follows:

Liquid (will be placed on a 4 ply, 25 mm x 25 mm gauze pad):

0.5 mL

If the test article cannot be prepared as previously indicated (for example, odd shaped sample, sponsor requires a specific surface application), further instructions will be attached to the protocol.

5.2 Control Article Preparation

4 ply, 25 mm x 25 mm sections of gauze, moistened with 0.5 mL of 0.9 % sodium chloride USP solution, will be used as the control article.

5.3 Test Procedure

The animals will be weighed and each animal will be clipped free of fur from the back and both sides of the spinal column to allow a sufficient area for application of the materials 4 to 24 hours prior to treatment. On the day of treatment, the test sample, prepared as previously specified, will be topically applied to one cranial site and one caudal site on the back of each animal.

The samples will be secured with a nonreactive tape. The control sample will be similarly applied to the opposite cranial and caudal sites. The entire trunk of each animal will be wrapped with an elastic binder to maintain the patches in position.

After a minimum of 23 hours and a maximum of 24 hours of exposure, the binder, tape, and patches will be removed. Material residue will be gently removed with a gauze sponge, saturated with deionized water.

5.4 Laboratory Observations

1. Animals will be observed daily for general health.
2. Body weights will be recorded for each animal at pretreatment.
3. Dermal observations for erythema and edema will be conducted at 1, 24, 48, and 72 hours after patch removal. Skin reactions will be graded in accordance with the criteria outlined in Appendix 1. Other adverse changes at the skin sites will also be recorded.

After the test is completed, all animals will be handled in accordance with IACUC approved NAMSA procedures.

6. Evaluation and Statistical Analysis

For each animal, the erythema and edema scores obtained at the 24, 48, and 72 hour intervals will be added together and divided by the total number of observations (six, two at each time specified). The 1 hour score is not included in the calculation. This calculation will be conducted separately for the test and control article for each animal. The score for the control will be subtracted from the score for the test article to obtain the Primary Irritation Score. The Primary Irritation Score of each animal will be added together to determine the Combined Primary Irritation Score (CPIS). The CPIS will be divided by the total number of animals to determine the Primary Irritation Index (PII). The Primary Irritation Index will be categorized based on the definitions outlined in Appendix 1. If scores are present, the Maximum Irritation Response will be determined.

7. Protocol Changes

Any necessary changes to the protocol after sponsor approval or study initiation will be documented and approved by the study director as protocol amendments. Copies will be distributed to the sponsor, the raw data file, and the NAMSA Quality Assurance department.

8. Report

The final report will contain a description of the methods employed, a table of individual erythema and edema scores, the Primary Irritation Index, the Maximum Irritation Response, and a summary of findings.

9. Quality Assurance

Inspections will be conducted at intervals adequate to assure the integrity of the study in conformance with 21 CFR 58.35(b)(3). The final report will also be reviewed for conformance to Section 58.185, Subpart J, of the GLP Regulations. A Statement of Quality Assurance Activities will be provided with the final report.

10. Records

All raw data pertaining to this study and a copy of the final report will be retained in designated NAMSA archive files in accordance with NAMSA SOPs.

11. References

Code of Federal Regulations (CFR), Title 9, Parts 1-4, Animal Welfare Act.

Code of Federal Regulations (CFR), Title 16, Part 1500, Federal Hazardous Substances Act (FHSA) Regulations.

Code of Federal Regulations (CFR), Title 21, Part 58, Good Laboratory Practice for Nonclinical Laboratory Studies.

International Organization for Standardization (ISO) 10993-1, Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process (2009/Technical Corrigendum 1 2010).

International Organization for Standardization (ISO) 10993-2, Biological evaluation of medical devices - Part 2: Animal welfare requirements (2006).

International Organization for Standardization (ISO) 10993-10, Biological evaluation of medical devices - Part 10: Tests for irritation and skin sensitization (2010).

International Organization for Standardization (ISO) 10993-12, Biological evaluation of medical devices - Part 12: Sample preparation and reference materials (2012).

International Organization for Standardization (ISO) 13485, Medical devices - Quality management systems - Requirements for regulatory purposes (2003/Technical Corrigendum 1 2009).

International Organization for Standardization/International Electrotechnical Commission (ISO/IEC) 17025, General requirements for the competence of testing and calibration laboratories (2005/Technical Corrigendum 1 2006).

National Research Council, *Guide for the Care and Use of Laboratory Animals*, Washington, DC: National Academy Press, 2011.

Office of Laboratory Animal Welfare (OLAW), Public Health Service Policy on Humane Care and Use of Laboratory Animals.

Appendix 1 - Classification System For Skin Reaction

REACTION Erythema and Eschar Formation	NUMERICAL GRADING
No erythema	0
Very slight erythema (barely perceptible)	1
Well-defined erythema	2
Moderate erythema	3
Severe erythema (beet redness) to eschar formation preventing grading of erythema	4
Edema Formation	
No edema	0
Very slight edema (barely perceptible)	1
Well-defined 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 exposure area)	4
Total possible score for irritation	8

NOTE: Other adverse changes at the skin sites shall be recorded and reported

IRRITATION RESPONSE CATEGORIES IN THE RABBIT

RESPONSE CATEGORY	MEAN SCORE
Negligible	0.0 to 0.4
Slight	0.5 to 1.9
Moderate	2.0 to 4.9
Severe	5.0 to 8.0

Appendix 6. Kligman Maximization Test (Sensitivity) Test Report NAMSA15T_31655_06

GLP REPORT

TEST FACILITY

NAMSA
6750 Wales Road
Northwood, OH 43619
419.666.9455

SPONSOR

Mike Kalfus
Mammogrip
1130 Route 46 West
Parsippany, NJ 07054

CONFIDENTIAL

STUDY TITLE

ISO Closed Patch Sensitization Study in Guinea Pigs

TEST ARTICLE NAME

MammoGRIP

TEST ARTICLE IDENTIFICATION

Lot #9976

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Summary

The test article, MammoGRIP, was evaluated for the potential to elicit delayed dermal contact sensitization in the guinea pig. This study was conducted based on the requirements of ISO 10993-10, Biological evaluation of medical devices, Part 10: Tests for irritation and skin sensitization.

The test article was occlusively patched to the intact skin of ten animals for 6 hours (±30 minutes), three times a week, over a 3 week period. The control article was similarly patched to five animals. Following a 2-week recovery period, the ten test and five control animals were occlusively patched with the test article and the control article. All sites were observed for evidence of dermal reactions at 24 and 48 hours after patch removal.

The test article showed no evidence of causing delayed dermal contact sensitization in the guinea pig.

Supervisory Personnel: Lisa A. Severhof, BA
Manager, In vivo Biocompatibility

Study Director Approval:

Joshua M. Stowell, BS, LAT
Medical Research Manager

6/8/2015
Date

Statement of GLP Compliance

There were no deviations to the provisions of the FDA Good Laboratory Practice (GLP) Regulations (21 CFR, Part 58) noted during the course of the study.

Study Director: _____ 6/18/2015

Joshua M. Stowell, BS, LAT — Date

1. Introduction

1.1 Purpose

The purpose of this study was to evaluate the potential of the test article to cause delayed dermal contact sensitization following repeated occlusive patching in the guinea pig.

1.2 Testing Guidelines

This study was conducted based on the International Organization for Standardization 10993-10, Biological evaluation of medical devices, Part 10: Tests for irritation and skin sensitization.

1.3 Dates

Test Article Received:	March 24, 2015
Treatment Started:	April 22, 2015
Observations Concluded:	May 27, 2015

1.4 GLP Compliance

The study initiated by protocol signature on April 13, 2015 was conducted in accordance with the provisions of the FDA Good Laboratory Practice (GLP) Regulations, 21 CFR 58. A Statement of Quality Assurance Activities was issued with this report.

1.5 Duplication of Experimental Work

By signature on the protocol, the sponsor confirmed that the conduct of this study did not unnecessarily duplicate previous experiments.

2. Identification of Test and Control Articles

The test article provided by the sponsor was identified and handled as described below:

Table 1: Test Article

Name:	MammoGRIP
Identification:	Lot #9976
Stability Testing:	Complete and on file with the sponsor (per sponsor)
Expiration Date:	12/2016 (per sponsor)
Strength, Purity and Composition:	Strength: Active ingredient - Benzalkonium chloride, .05; Purity: Active ingredient - Benzalkonium chloride, 50%; Composition: Benzalkonium chloride 0.1%, water, dihydroxypropyl PEG-5 linoleammonium chloride, glycereth-2 cocoate, behentrimonium chloride, and dihydroxyethyl cocamine oxide.
Physical Description of the Test Article	clear foam
Storage Conditions:	Ambient Temperature

Table 2: Control Article

Name:	0.9% Sodium chloride (SC) was used as the diluent applied to a Hill Top Chamber®.
Stability Testing:	SC: Marketed product; stability characterized by its labeling Hill Top Chamber: Stable for intended use based on components of the article
Strength, Purity, Composition or Other Characteristics:	SC: Purity: Meets requirements of USP Sodium Chloride for Injection and is certified as USP Grade; Composition: 0.9% NaCl ± 5.0% of label claim, balance is water; sodium chloride CAS No.: 7647-14-5/water CAS No.: 7732-18-5 Hill Top Chamber: Composition: The Hill Top Chamber is manufactured using Kraton® G-2705, a product of the Shell Oil Company. Kraton meets or exceeds the current USP requirements for physico-chemical and biological tests for Class VI polymers. The chamber is soft and flexible, thus providing cohesion between the test article and the skin sites. The Kraton material has been approved for use by the FDA

3. Test System

3.1 Test System

Species:	Guinea pig (*Cavia porcellus*)
Strain:	Hartley
Source:	Elm Hill Labs
Sex:	Female; females were nulliparous and nonpregnant
Body Weight Range:	336 grams to 452 grams at study initiation
Age:	Young adult
Acclimation Period:	Minimum 5 days
Number of Animals:	Fifteen
Identification Method:	Ear tag

3.2 Justification of Test System

The Hartley albino guinea pig (animal) has been used historically for sensitization studies. Repeated patching of the test article to fur-clipped intact skin was employed. Topical applications are related to the human exposure route and permit the evaluation of dermal contact and/or absorption of potential sensitizers during induction and challenge phases. Reactions directly under the topical application site can be observed. The susceptibility of the Hartley guinea pig strain to a known sensitizing agent, 1-chloro-2,4-dinitrobenzene (DNCB), has been substantiated at NAMSA with this method under lab number 15T_27117_01 completed on April 23, 2015.

4. Animal Management

4.1 Husbandry, Housing and Environment

Conditions conformed to NAMSA Standard Operating Procedures that are based on the "*Guide for the Care and Use of Laboratory Animals.*" Animals were housed in groups in stainless steel or plastic suspended cages identified by a card indicating the lab number, animal numbers, test code, sex, and first treatment date.

The animal housing room temperature and relative humidity were monitored daily. The temperature for the room was set to 68-79°F and the relative humidity was set to 30-70%.

There were no significant temperature or relative humidity excursions that adversely affected the health of the animals.

The light cycle was controlled using an automatic timer (12 hours light, 12 hours dark).

4.2 Food, Water and Contaminants

A commercially available guinea pig feed, PROLAB Guinea Pig - 5P18, was provided daily. Potable water was provided *ad libitum* through species appropriate water containers or delivered through an automatic watering system.

No contaminants present in the feed and water impacted the results of this study.

4.3 Accreditation

NAMSA is an AAALAC International accredited facility and is registered with the United States Department of Agriculture. Additionally, NAMSA maintains an approved Animal Welfare Assurance on file with the National Institutes of Health, Office for Laboratory Animal Welfare.

4.4 Personnel

Associates involved in this study were appropriately qualified and trained.

4.5 Veterinary Care

Standard veterinary medical care was provided in this study.

4.6 IACUC

This procedure has been approved by the NAMSA Institutional Animal Care and Use Committee (IACUC), and is reviewed at least annually by the same committee.

4.7 Selection

Only healthy, previously unused animals were selected.

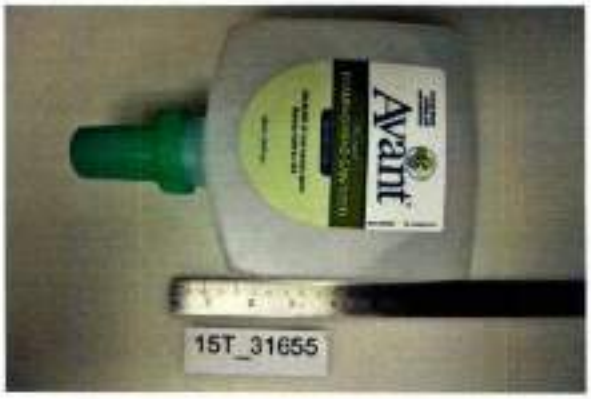
5. Method

5.1 Test Article Preparation

A 0.3 mL aliquot of the test article was applied to a nonwoven cotton disk contained inside a Hilltop Chamber and then applied to the skin of the guinea pig.

Figure 1: Representative Photograph of the Test Article

Test Article



5.2 Test Procedure

On the day of first induction treatment, each animal was weighed. The hair was removed with an electric clipper from the left flank of ten guinea pigs designated as test animals and five guinea pigs designated as control animals.

5.2.1 Induction

A nonwoven cotton disk contained inside a Hill Top Chamber® was saturated with 0.3 mL of the test or control article and applied to the appropriate animal. The chamber was then secured with hypoallergenic tape to the intact skin. The trunk of each animal was wrapped with an elastic band to maintain the occluded patch in position.

After 6 hours (±30 minutes), the wraps and patches were removed. The sites were wiped with dry gauze to remove any residue.

The application procedure was repeated three times each week (e.g., Monday-Wednesday-Friday) for 3 consecutive weeks until nine applications were made to the left flank of the animals. The hair was removed with an electric clipper as necessary to provide a clear site.

5.2.2 Challenge

At 14 days after the final induction patch, the hair of each animal was removed with an electric clipper from the right flank area. A nonwoven cotton disk inside a Hill Top Chamber® was saturated with 0.3 mL of the test article and topically secured with hypoallergenic tape to the intact skin on the ventral flank of each test and control animal. The control article was similarly patched to the dorsal flank of each test and control animal. The trunk of each animal was wrapped with an elastic band to hold the occluded patches in place.

After 6 hours (±30 minutes), the wraps and patches were removed. The sites were wiped with dry gauze to remove any residue. At 24 hours after patch removal, the challenged sites and surrounding area were shaved.

5.2.3 Laboratory Observations

1. Animals were observed daily for general health.
2. Body weights were recorded for each animal at pretreatment.
3. Dermal observations for erythema were recorded at 2-4 hours following shaving of the animals. Scoring was also conducted at 48 hours after challenge patch removal. Sites were wiped with 35% isopropyl alcohol saturated gauze before scoring at each interval. Evaluations for the challenge phase were based on dermal reactions which were scored as outlined below:

Table 3: Test Scoring

Patch Test Reaction	Grading Scale
No visible change	0
Discrete or patchy erythema	1
Moderate and confluent erythema	2
Intense erythema and swelling	3

All times and temperatures reported herein are approximate and are within ranges established by the external standards described in the References section of this report and/or NAMSA standard operating procedures.

6. Evaluation

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

Occasionally, the test group will have a greater number of animals showing a response than the control group, although the intensity of the reaction is not greater than that exhibited by the control group. In these instances, a rechallenge may be necessary to define the response clearly.

A true sensitization reaction can be confirmed by rechallenge. Absence of dermal responses at rechallenge may nullify earlier findings. Recurring observations in at least one of the same animals verify findings of the primary challenge.

7. Results

7.1 Body Weights and Clinical Observations

Individual body weights and clinical observations are presented in Appendix 1. All animals were clinically normal throughout the study.

7.2 Dermal Observations

Individual results of dermal scoring for the challenge phase are presented in Appendix 2. No evidence of sensitization was observed.

8. Conclusion

The test article showed no evidence of causing delayed dermal contact sensitization in the guinea pig.

Results and conclusions apply only to the test article tested. Any extrapolation of these data to other articles is the sponsor's responsibility.

9. Quality Assurance

Inspections were conducted at intervals adequate to assure the integrity of the study in conformance with 21 CFR 58.35(b)(3). The final report was reviewed for conformance to Section 58.185, Subpart J, of the GLP Regulations. A Statement of Quality Assurance Activities was issued with the report.

10. Records

All raw data, test and control articles pertaining to this study and a copy of the final report are retained in designated NAMSA archive files in accordance with NAMSA SOPs.

11. ISO Compliance

All procedures were certified to ISO 13485 and accredited to ISO 17025.

12. References

Code of Federal Regulations (CFR), Title 9, Parts 1-4, Animal Welfare Act.

Code of Federal Regulations (CFR), Title 21, Part 58, Good Laboratory Practice for Nonclinical Laboratory Studies.

International Organization for Standardization (ISO) 10993-1, Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process (2009/Technical Corrigendum 1 2010).

International Organization for Standardization (ISO) 10993-2, Biological evaluation of medical devices - Part 2: Animal welfare requirements (2006).

International Organization for Standardization (ISO) 10993-10, Biological evaluation of medical devices - Part 10: Tests for irritation and skin sensitization (2010).

International Organization for Standardization (ISO) 10993-12, Biological evaluation of medical devices - Part 12: Sample preparation and reference materials (2012).

International Organization for Standardization (ISO) 13485, Medical devices - Quality management systems - Requirements for regulatory purposes (2003/Technical Corrigendum 1 2009).

International Organization for Standardization/International Electrotechnical Commission (ISO/IEC) 17025, General requirements for the competence of testing and calibration laboratories (2005/Technical Corrigendum 1 2006).

National Research Council, *Guide for the Care and Use of Laboratory Animals*, Washington, DC: National Academy Press, 2011.

Office of Laboratory Animal Welfare (OLAW), Public Health Service Policy on Humane Care and Use of Laboratory Animals.

Appendix 1 - Individual Body Weights and Clinical Observations

Group	Animal Number	Individual Observation	
		Pretreatment Body Weight (g)	Clinical Observations
Test	6975	366	No findings
	6976	393	No findings
	6977	373	No findings
	6978	361	No findings
	6979	408	No findings
	6980	367	No findings
	6981	401	No findings
	6982	336	No findings
	6983	365	No findings
	6984	452	No findings
Control	6985	379	No findings
	6986	352	No findings
	6987	407	No findings
	6988	398	No findings
	6989	372	No findings

Appendix 2 - Dermal Reactions - Challenge

Group	Animal Number	Hours Following Patch Removal			
		24 Hour Score		48 Hour Score	
		Control	Test Article	Control	Test Article
Test	6975	0	0	0	0
	6976	0	0	0	0
	6977	0	0	0	0
	6978	0	0	0	0
	6979	0	0	0	0
	6980	0	0	0	0
	6981	0	0	0	0
	6982	0	0	0	0
	6983	0	0	0	0
	6984	0	0	0	0
Control	6985	0	0	0	0
	6986	0	0	0	0
	6987	0	0	0	0
	6988	0	0	0	0
	6989	0	0	0	0

Appendix 3 - Periodic Positive Control Study for the Closed Patch Sensitization Test

What was tested

1-chloro-2,4-dinitrobenzene (DNCB)

Dates

Treatment Started: March 11, 2015 under NAMSA Lab Number: 15T_27117_01
Observations Concluded: April 10, 2015

Purpose

A periodic positive control study was conducted for the ISO Closed Patch Sensitization Study in Guinea Pigs to meet the following objectives: 1) the methodology in the International Organization for Standardization 10993-10, Biological Evaluation of Medical Devices, Part 10: Tests for Irritation and Skin Sensitization was confirmed, 2) the potential of DNCB to cause delayed contact sensitization following repeated occlusive application was substantiated, 3) proper training of the technologists/technicians performing these studies was verified, and 4) the susceptibility of the Hartley guinea pig strain to sensitization was substantiated.

Methods

The test utilized young adult, nulliparous and not pregnant, female Hartley albino guinea pigs supplied by Elm Hill Labs. The weight at study initiation ranged from 319 grams to 425 grams. A 0.1% (w/v) concentration of DNCB in IPA was occlusively patched for 6 hours (±30 minutes) to the intact skin of ten guinea pigs, once a week, for a total of three induction treatments over a 3 week period. The 70% IPA was similarly patched to five control guinea pigs. Following a recovery period, the ten test and five control animals received a challenge patch of a 0.1% (w/v) concentration of DNCB in acetone and the acetone control article. All sites were scored at 24 and 48 hours after patch removal. The patch sites were graded using the scale:

Patch Test Reaction	Grading Scale
No visible change	0
Discrete or patchy erythema	1
Moderate and confluent erythema	2
Intense erythema and swelling	3

Results

All of the ten test animals demonstrated a positive sensitization response to the known sensitizer, DNCB. None of the control animals demonstrated a sensitization response. The results are shown below:

Treatment Group	Animal Number	Dermal Reactions				Result (+) or (-)
		24 Hour Score		48 Hour Score		
		Control	Test Article	Control	Test Article	
Test	3961	0	1	0	1	+
	3962	0	2	0	2	+
	3963	0	1	0	1	+
	3964	0	1	0	2	+
	3965	0	2	0	2	+
	3966	0	1	0	1	+
	3967	0	1	0	1	+
	3968	0	1	0	1	+
	3969	0	1	0	1	+
	3970	0	1	0	1	+
Control	3971	0	0	0	0	-
	3972	0	0	0	0	-
	3973	0	0	0	0	-
	3974	0	0	0	0	-
	3975	0	0	0	0	-

Conclusion

The known sensitizer DNCB did produce significant evidence of causing delayed dermal contact sensitization in the Hartley strain of guinea pig. Therefore, the following objectives were met: 1) the methodology in the International Organization for Standardization 10993-10, Biological Evaluation of Medical Devices, Part 10: Tests for Irritation and Skin Sensitization was confirmed, 2) the potential of DNCB to cause delayed contact sensitization following repeated occlusive application was substantiated, 3) proper training of the technologists/technicians performing these studies was verified, and 4) the susceptibility of the Hartley guinea pig strain to sensitization was substantiated.

Phase Inspected	Date Inspected	Study Director Notification Date	Management Notification Date
Test Article Application	May 6, 2015	May 6, 2015	May 6, 2015
Study Data Review	June 8, 2015	June 8, 2015	June 8, 2015
Final Report Review	June 8, 2015	June 8, 2015	June 8, 2015

Based on a review of this study, it has been concluded that this report accurately describes the methods and standard operating procedures, and that the reported results accurately reflect the raw data of the study. This study has been reviewed in accordance with the provisions of the FDA Good Laboratory Practice Regulations (21 CFR, Part 58).

QA Representative: Debra S. Dunn 6-8-15

Debra S. Dunn
Auditor, Quality Assurance

Date

Joshua Stowell

From: NW Study Coordinators
Sent: Thursday, March 26, 2015 4:00 PM
To: Joshua Stowell
Subject: FW: Electronic Sample Submission 11110-1

15T_31655
40647_001 40647
T032415-032 JMS1267 6/4/2015
T032615_032
UPS NA ~~WMCOOK~~
JMS1267 6/4/2015

15T_31655

From: esubmission@namsa.com [mailto:esubmission@namsa.com]
Sent: Thursday, March 26, 2015 10:05 AM
To: OH-Order-Processing; GLPPRO
Subject: Electronic Sample Submission 11110-1

Overview

Submission ID: 11110
Revision #: 1
Date Created: Mar 26, 2015
Testing Location: Northwood
Proposal Number: 1_25370-L3N5N7
Purchase Order: MAM 3102
Quantity Submitted: 5 containers (1)

Billing and Shipping

Bill To: Mammogrip (40647)
1130 Route 46 West
Parsippany, NJ 07054
Ship To: Mammogrip (40647)
1130 Route 46 West
Parsippany, NJ 07054
Contact: Mike Kalfus (40647_001)
Mammogrip (40647)
mike@mammogrip.com

Test Article Information

Name: MammoGRIP
Batch Code / Lot Id: ~~pending~~ Lot #9976 (6)
Physical Description: clear foam
Type: Medical Device
Clinical Use: medical device for improved mammography
Sterility: Not Sterile
Can Be Cut: No
Special Instructions:

Ratio: ~~Weight, Irregularly shaped material or by request - ratio of 1 g :5mL~~ NA JMS1267 4/10/15
Contains Elastomer: No
Storage Conditions: Ambient Temperature (15-30 °C)
Disposition: Discard used and unused test article

(1) Received 3 containers JMS1267 4/10/15
(2) Re sample label JMS1267 4/10/15

GLP Information

Stability: Stability testing is complete and on file with sponsor.
Stability Expiration Date: Mar 01, 2016 12/2016 (see attached) JMS1267 4/13/2015
Analysis: Analysis is not necessary due to test article being a solid, powder, gel, or liquid being extracted or tested as received (mixture with a carrier not needed).
Has Active Ingredient: Yes
Active Ingredient: Benzalkonium Chloride
Strength: .05
Purity: ~~NA~~ 50% see attached. JMS1267 4/10/2015
Composition: ~~foam~~ see attached. JMS1267 4/10/2015

Testing Services

15T-31655

Test Code	Qty	Proposal	Grouping	STAT	Regulatory Scope	Comments	Purchase Order	Test Spec	Extracts
TI251-84S	1	1_25370-L3N5N7		No	GLP		~~MAM 3102~~		
V0014-130's	1	1_25370-L3N5N7		No	GLP		MAM 3102		
TI261-306	1	1_25370-L3N5N7		No	GLP		MAM 3102		

NA see protocols. TMR 4/10/2015

Authorization

Electronically Signed By: mike@mammogrip.com **Date:** Mar 26, 2015

Reviewed By (NAMSA Associate Signature): _____ Date: 4/13/2015

GLP PROTOCOL

TEST FACILITY

NAMSA
6750 Wales Road
Northwood, OH 43619

SPONSOR

Mike Kalfus
Mammogrip
1130 Route 46 West
Parsippany, NJ 07054

STUDY TITLE

ISO Closed Patch Sensitization Study in Guinea Pigs

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15T-31655 06

Approvals

Sponsor Representative: Mike Kalfus

Date Approved: 4-6-15

Study Director (NAMSA): Joshua M. Stowell, BS, LAT
Medical Research Manager

Date Initiated: 9/13/2015

1. Introduction

1.1 Purpose

The purpose of this study is to evaluate the potential for the test article to produce delayed dermal sensitization following repeated occlusive application in the guinea pig. The Buehler method has proven effective in identifying a variety of chemical allergens.

1.2 Testing Guidelines

This study will be conducted based on the International Organization for Standardization 10993-10, Biological evaluation of medical devices – Part 10: Tests for irritation and skin sensitization.

1.3 GLP Compliance

Good Laboratory Practice – This nonclinical laboratory study will be conducted in accordance with the United States Food and Drug Administration Good Laboratory Practice Regulations, 21 CFR Part 58.

1.4 Duplication of Experimental Work

By signature on this protocol, the sponsor confirms that the conduct of this study does not unnecessarily duplicate previous experiments.

2. Identification of Test and Control Articles

2.1 Test Article

The sponsor will submit the test article, MammoGRIP, to be evaluated. The sponsor provided detailed information about the test article to NAMSA on the sample submission form.

2.2 Control Article

Any diluent or vehicle used in this study will serve as the control measure.

3. Test System

3.1 Test System

Species:	Guinea pig (*Cavia porcellus*)
Strain:	Hartley
Source:	NAMSA approved supplier
Sex:	No particular sex is prescribed for this test; females will be nulliparous and nonpregnant
Body Weight Range:	300-500 grams at study initiation
Age:	Young adults
Acclimation Period:	Minimum 5 days
Number of Animals:	Minimum of fifteen
Identification Method:	Ear tag

3.2 Justification of Test System

The Hartley albino guinea pig (animal) has been used historically for sensitization studies. Repeated patching of the test article to fur-clipped intact skin will be employed. Topical applications are related to the human exposure route and permit the evaluation of dermal contact and/or absorption of potential sensitizers during induction and challenge phases. Reactions directly under the topical application site can be observed. The susceptibility of the Hartley strain to a known sensitizing agent, 1-chloro-2,4-dinitrobenzene (DNCB) has been substantiated at NAMSA with this method.

4. Animal Management

4.1 Husbandry, Housing and Environment

Conditions will conform to NAMSA Standard Operating Procedures that are based on the "*Guide for the Care and Use of Laboratory Animals*." Animals will be housed in groups in stainless steel or plastic suspended cages identified by a card indicating the lab number, animal numbers, test code, sex, and first treatment date.

The animal housing room temperature and relative humidity will be monitored daily. The recommended temperature range for the room is 68-79°F. The recommended humidity range for the room is 30-70%.

The light cycle will be controlled using an automatic timer (12 hours light, 12 hours dark).

4.2 Food, Water and Contaminants

A commercially available guinea pig feed will be provided daily. Potable water will be provided *ad libitum* through species appropriate water containers or delivered through an automatic watering system.

No contaminants present in the feed and water are expected to impact the results of this study.

4.3 Accreditation

NAMSA is an AAALAC International accredited facility and is registered with the United States Department of Agriculture. Additionally, NAMSA maintains an approved Animal Welfare Assurance on file with the National Institutes of Health, Office for Laboratory Animal Welfare.

4.4 Personnel

Associates involved in this study will be appropriately qualified and trained.

4.5 Sedation, Analgesia or Anesthesia

It has been determined that the use of sedation, analgesia or anesthesia will not be necessary during the routine course of this procedure.

4.6 Veterinary Care

All anesthetics, analgesics, and other medications may be given or altered at the discretion of the attending veterinarian in accordance with standard veterinary practice and the study objectives. This applies to specific medication, dose, and dosing intervals. In the unlikely event that an animal should become injured, ill, or moribund, care will be conducted in accordance with current veterinary medical practice. If warranted for humane reasons, euthanasia will be conducted in accordance with the current report of the American Veterinary Medical Association's Guidelines on Euthanasia. The objective of the study will be given due consideration in any decision and the study sponsor will be advised.

4.7 IACUC

This protocol has been approved by the NAMSA Institutional Animal Care and Use Committee (IACUC), and is reviewed at least annually by the same committee. Any significant changes to this protocol pertaining to the care and use of animals must be approved by the IACUC.

4.8 Selection

Only healthy, previously unused animals will be selected.

5. Method

5.1 Test Article Preparation

The following information was completed based on the sponsor providing the information to NAMSA. Further instructions may be attached to the protocol.

The units of measure shown below are per application; a minimum of 105 application units are necessary for the study. The sample will be prepared as follows:

Test Article Form:

Liquid - 0.3 mL

A 0.3 mL aliquot of the test article will be placed on an application pad contained in a Hill Top Chamber®.

5.2 Control Article Preparation

A 0.3 mL aliquot of 0.9% sodium chloride USP solution (SC) will be placed on an application pad contained in a Hill Top Chamber®.

5.3 Test Procedure

On the day of first induction treatment, fifteen animals will be weighed (ten test, five irritant control). The fur of each animal will be clipped from the left flank area.

5.3.1 Induction

The animals will be treated three times per week for 3 consecutive weeks (e.g., Monday, Wednesday, Friday). An appropriate sample will be applied to the fur-clipped left flank area of each of the animals. The application unit will be backed by hypoallergenic tape to ensure good contact of material to the skin and to retard evaporation. The trunk of the animal will then be wrapped with an elastic band to hold the occluded patches in place. Five irritant control animals will be treated similarly.

After 6 hours (±30 minutes) exposure, all wraps and patches will be removed. The sites will be wiped with dry gauze to remove any residue. Should three or more test sites show significant (≥2 score) reactions, the concentration of the preparation may be reduced in a suitable diluent for subsequent exposures or a virgin site may be used for subsequent exposures.

This procedure will be repeated until nine induction patches have been applied to the animals. The fur will be reclipped as necessary to provide a clear site.

5.3.2 Challenge

At 14 days (±1 day) after the last (ninth) induction application, the animals will be clipped free of fur over the right flank and dorsum. The test article or solution will be applied to the right flank of each animal. In addition, the vehicle or diluent (as applicable) on the application units or approximate 25 mm x 25 mm sections of 4-ply gauze will be applied as a separate patch to the right flank. The trunk of each animal will be wrapped as before.

After 6 hours (±30 minutes) exposure, all wraps and patches will be removed. The sites were wiped with dry gauze to remove any residue. At 24 hours after patch removal, the challenged sites and surrounding area will be shaved.

5.3.3 Laboratory Observations

1. Animals will be observed daily for general health.
2. Body weights will be recorded for each animal at pretreatment.
3. Observations for any signs of irritation or sensitization reaction will be made at a minimum of 2 hours and a maximum of 4 hours following shaving of the animals. Scoring will be repeated at 48 hours after removal of the challenge patches. Prior to scoring, each site will be wiped gently with a 35% isopropyl alcohol gauze sponge. Dermal sensitization results will be compared between the test and control animals in accordance with the criteria shown below:

Table 1: Grading Scale

Patch Test Reaction	Grading Scale
No visible change	0
Discrete or patchy erythema	1
Moderate and confluent erythema	2
Intense erythema and swelling	3

5.3.4 Rechallenge

Should the original challenge results prove to be equivocal, the animals may be rechallenged approximately 1 to 2 weeks after the first challenge application. The rechallenge will be conducted in the same manner as the primary challenge but at virgin sites (e.g., dorsum). After the test is completed, all animals will be handled in accordance with IACUC approved NAMSA procedures.

6. Evaluation and Statistical Analysis

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

Occasionally, the test group has a greater number of animals showing a response than the control group, although the intensity of the reaction is not greater than that exhibited by the control group. In these instances, a rechallenge may be necessary to define the response clearly.

A true sensitization reaction can be confirmed by rechallenge. Absence of dermal responses at rechallenge may nullify earlier findings. Recurring observations in at least one of the same animals verify findings of the primary challenge.

7. Protocol Changes

Any necessary changes to the protocol after sponsor approval or study initiation will be documented and approved by the study director as protocol amendments. Copies will be distributed to the sponsor, the raw data file, and the NAMSA Quality Assurance department.

8. Report

The final report will include a description of the methods employed, individual dermal observations and conclusions regarding potential sensitization caused by the test article.

9. Quality Assurance

Inspections will be conducted at intervals adequate to assure the integrity of the study in conformance with 21 CFR 58.35(b)(3). The final report will also be reviewed for conformance to Section 58.185, Subpart J, of the GLP Regulations. A Statement of Quality Assurance Activities will be provided with the final report.

10. Records

All raw data, test and control articles pertaining to this study and a copy of the final report will be retained in designated NAMSA archive files in accordance with NAMSA SOPs.

11. References

Code of Federal Regulations (CFR), Title 9, Parts 1-4, Animal Welfare Act.

Code of Federal Regulations (CFR), Title 21, Part 58, Good Laboratory Practice for Nonclinical Laboratory Studies.

International Organization for Standardization (ISO) 10993-1, Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process (2009/Technical Corrigendum 1 2010).

International Organization for Standardization (ISO) 10993-2, Biological evaluation of medical devices - Part 2: Animal welfare requirements (2006).

International Organization for Standardization (ISO) 10993-10, Biological evaluation of medical devices - Part 10: Tests for irritation and skin sensitization (2010).

International Organization for Standardization (ISO) 10993-12, Biological evaluation of medical devices - Part 12: Sample preparation and reference materials (2012).

International Organization for Standardization (ISO) 13485, Medical devices - Quality management systems - Requirements for regulatory purposes (2003/Technical Corrigendum 1 2009).

International Organization for Standardization/International Electrotechnical Commission (ISO/IEC) 17025, General requirements for the competence of testing and calibration laboratories (2005/Technical Corrigendum 1 2006).

National Research Council, *Guide for the Care and Use of Laboratory Animals*, Washington, DC: National Academy Press, 2011.

Office of Laboratory Animal Welfare (OLAW), Public Health Service Policy on Humane Care and Use of Laboratory Animals.

Appendix 7. Biological Risk Assessment
NAMSA Project 154356

PROJECT

SUMMARY REPORT,
BIOLOGICAL RISK ASSESSMENT

Women's Imaging Solutions Enterprises, LLC

MammoGrip™

CONSULTING OFFICE

NAMSA
Product Safety and Validation
4050 Olson Memorial Hwy, Suite 450
Minneapolis, MN 55422

SPONSOR

Nancy DeRobertis, Chief Executive Officer
Women's Imaging Solutions, LLC
1130 Route 46 West
Parsippany, NJ 07054

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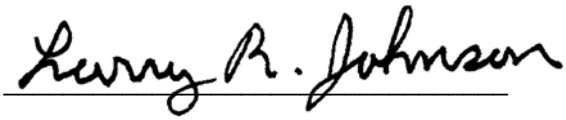
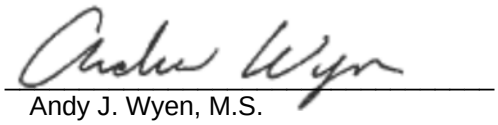
Prepared by: 

Larry R. Johnson, D.V.M., Ph.D., DABT
Principal Medical Research Scientist
NAMSA

Reviewed by: 

Andy J. Wyen, M.S.
Medical Research Manager
NAMSA

Date: July 16, 2015

1.0 Executive Summary

A biological risk assessment of the Women's Imaging Solutions Enterprises, LLC, MammoGrip™, hereafter referred to as MG has been performed. This assessment focused on meeting the requirements of ISO 10993-1:2009 - *Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process*, EN ISO 14971:2012 - *Medical devices – Application of risk management to medical devices*, FDA General Program Memorandum #G95-1, *Use of International Standard ISO-10993, Biological Evaluation of Medical Devices Part 1: Evaluation and Testing*, and the European Union Medical Device Directive 93/42/EEC.[1,2,3,4] This assessment considered the toxicological and related information on the MG ingredients in the literature, biocompatibility test data on MG as well as individual MG ingredients, and the history of safe and effective use of these ingredients in humans.

MG is a non-medicated skin adhesive solution to be placed on the mammogram technologist's hands prior to the imaging session. When used as intended MG facilitates the positioning of the breast tissue onto the image. MG will contact the patient's intact skin for a limited period (i.e. <24 hr). MG is therefore classified according to ISO 10993-1 as: a surface, limited contact (< 24 hr) with skin device.

The purpose of this report is to use applicable regulatory guidance and information reviewed to assess patient risk associated with MG use.

To evaluate the biological safety of MG, consideration was given to the type of patient contact, the potential hazards associated with MG ingredients, *in vivo & in vitro* test results for MG and its ingredients, the history of clinical use of the ingredients, and other information available in the literature.

Based upon this evaluation, MG has met the requirements of ISO 10993-1:2009, EN ISO 14971:2012, FDA General Program Memorandum #G95-1, and the European Union Medical Device Directive 93/42/EEC for a surface device with limited skin contact (<24 hr). MG can be considered safe for the intended use.

2.0 Device Description

MG is a 0.1% benzalkonium chloride foam product, and its formulation is currently marketed over-the-counter as Avant® Alcohol-Free Instant Foaming Hand Sanitizer. MG is a non-medicated and non-fragranced skin adhesive solution used when conducting mammograms to enable the technologist to obtain more breast tissue into an image. The MG is to be applied (i.e. approximately 0.7 ml) on the technologist's hands prior to each imaging segment with a maximum of 4 imaging segments per patient mammography session. When MG is applied to the technician's hands, it imparts a slightly tacky or sticky surface which allows a better grip of the breast tissue, thereby allowing more tissue to be pulled into the field of view.

2.1 MG Ingredients

The ingredients of MG are reported to be primarily water and 0.1% benzalkonium chloride. MG ingredients are summarized in Table 1; however, only the concentration of benzalkonium chloride use was disclosed, while the exact proportions of use for the other ingredients in MG have been held confidential by the manufacturer.

Table 1. MG Ingredients

MG Ingredient	Ingredient Purpose	CAS	Concentration (% Weight Ingredient/Weight Solution)
Water	Diluent	7732-18-5	99, Estimated
Benzalkonium chloride	Active Ingredient for Avant	8001-54-5	0.1, Disclosed by Manufacture
Dihydroxypropyl PEG-5 linoleammonium chloride	Foaming surfactant	168677-75-6	0.01 to 0.9, Estimated
Glycereth-2 cocoate	Foaming and moisturizing	68201-46-7	0.01 to 0.9, Estimated
Behentrimonium chloride	Preservative	17301-53-0	0.01 to 0.9, Estimated
Dihydroxyethyl cocamine oxide	Not Available	61791-47-1	0.01 to 0.9, Estimated

3.0 Device Classification

When MG is used as intended to enable the mammogram technologist to position breast tissue onto the image it will contact the patient's intact skin for a limited period (i.e. <24 hr). MG is therefore classified according to ISO 10993-1 as: surface, limited contact (< 24 hr) with skin.

Because the MG intended use includes the application of a surface device which has limited contact with skin, consideration must be given to all relevant endpoints defined by ISO 10993-1:2009 and FDA Blue Book Memorandum #G95-1, that is: cytotoxicity, sensitization, and irritation (Table 2).

Table 2. MG ISO 10993 and FDA Blue Book Biological Endpoints for Consideration

Biological Endpoint	Applicable ISO 10993 Standard	
Cytotoxicity	ISO 10993-5:	Tests for Cytotoxicity – *In Vitro* methods
Sensitization	ISO 10993-10:	Tests for Sensitization and Irritation
Irritation	ISO 10993-10:	Tests for Sensitization and Irritation

It is important to note that while all of the endpoints listed above must be considered, they can be addressed in a number of different ways including biocompatibility testing or written justification/risk assessment.

4.0 Purpose

The purpose of this report is to use applicable regulatory guidance and information reviewed to assess the patient risk associated with MG use.

To evaluate the biological safety of MG, consideration was given to the type of patient contact with the device, the potential hazards associated with MG ingredients, *in vivo & in vitro* test results for MG and its ingredients, the history of clinical use of the ingredients, and other information available in the literature.

5.0 Safety Assessment Approach Used

This document assesses the risk posed to the patients on whom MG will be used. The International Standards Organization 10993-1:2009: *Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process*, describes the principles governing the biological evaluation of medical devices. ISO 10993-1 applies to the non-clinical testing of the MG device. It should be noted that clause 4.5 states: "*All known possible biological hazards shall be taken into account for every material and final product, but this does not imply that testing for all possible hazards will be necessary or practical*." Clause 4.1 of this standard specifies: "*Evaluation may include both a study of relevant preclinical and clinical experience and actual testing. Such an evaluation might result in the conclusion that no testing is needed if the material has a demonstrable safe history of use in a specified role and physical form that is equivalent to that of the device under design*."

EN ISO 14971:2012, Medical devices – *Application of risk management to medical devices* states that toxicological risk assessment shall be based on:

- The physical and chemical characteristics of the device components and materials;
- Any history of clinical use or human exposure data;
- Any existing toxicology and other biological safety data on the product components and materials;
- Test procedures and results.

Collectively, knowledge of the composition of a medical device, including additives and processing aids, prior use of the relevant material(s) in a predicate device or similar device, and biological safety tests should provide predictive evidence of potential hazards to users of the device.

Evaluation of the chemical nature of the material can take the form of experimental data and/or information on the chemistry of the materials/components involved. Literature studies conducted on the materials help evaluate the biological response and are useful in assessing a finished medical device for its intended use/intended purpose. Some

factors that affect the biocompatibility of the material include the identity, concentration, availability, and toxicity of all constituents such as additives, processing aids, and monomers.

To evaluate prior use of materials, information on previous uses of the device/materials or intended additives, and any adverse reactions encountered, should be reviewed. Account should be taken of the intended use, the concentration of the ingredients, and current toxicological information. Biological safety should be considered giving special attention to the ISO 10993 series for a particular application. The need for testing should be reviewed on a case-by-case basis.

The amount of data required on a material, and the depth of the investigation, is dependent upon the intended use in manufacturing of devices and the function and duration of patient contact. Knowledge of a material's composition and potential leachable compounds, combined with results from biological safety testing, should provide predictive evidence of any potential toxicological risk to patients.

Medical devices must be designed and manufactured in such a way as to reduce to a minimum the risks posed by substances leaching from the device. Special attention shall be given to substances which are carcinogenic, mutagenic, or toxic to reproduction, in accordance with Annex I to Council Directive 67/548/EEC of 27 June 1967 on the approximation of laws, regulations and administrative provisions relating to the classification, packaging and labeling of dangerous substances.[5]

6.0 Biological Risk Estimation

This section reviews the ISO 10993-1:2009 standard and available biological testing data on the component materials of the MG device to provide a risk estimation of its biological safety. The available ISO 10993-1:2009 biocompatibility data in the literature were reviewed to identify the key elements of the individual assays and how this testing relates to the intended use of the device.

6.1 Requirements of ISO 10993-1

International Standards Organization 10993-1:2009: Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process was reviewed. This included the recommended biological testing and the principles governing the biological evaluation of medical devices. ISO 10993-1:2009 applies to the non-clinical or pre-clinical testing of devices. It should be noted that clause 4.5 states:

> "*All known possible biological hazards shall be taken into account for every material and final product, but this does not imply that testing for all possible hazards will be necessary or practical*."

Clause 4.1 of this standard specifies:

> "*Evaluation may include both a study of relevant preclinical and clinical experience and actual testing. Such an evaluation might result in the conclusion that no testing is needed if the material has a demonstrable safe history of use in a specified role and physical form that is equivalent to that of the device under design*."

ISO 10993-1 contains many other clauses that allow for exceptions and exemptions from pre-clinical biological testing. Notable examples are:

> Clause 6.2.1.b: *The choice of test procedures shall take into account*:
>
> > Clause 6.2.1.b.4: *certain tests…may not be applicable where the presence of leachable chemicals has been excluded, or where chemicals have a known and acceptable toxicity profile*;
> >
> > Clause 6.2.1.b.6: *the existing information based on the literature, previous experience, and non-clinical tests*;
> >
> > Clause 6.2.1.b.8: *the protection of humans is the primary goal of this part of ISO 10993; a secondary goal is to ensure animal welfare and to minimize the number and exposure of the test animals*.
>
> The Introduction to ISO 10993-1:2009 states: *It is not intended that ISO 10993 provide a rigid set of test methods, including pass/fail criteria, as this might result in either an unnecessary constraint on the development and use of novel medical devices, or a false sense of security in the general use of medical*

devices. Where a particular application warrants it, experts in the product or in the area of application concerned can choose to establish specific tests and criteria, described in a product-specific vertical standard.

This part of ISO 10993 is intended for use by professionals, appropriately qualified by training and experience, who are able to interpret its requirements and judge the outcome of the evaluation for each medical device, taking into consideration all the factors relevant to the device, its intended use and the current knowledge of the medical device provided by review of the scientific literature and previous clinical experience.

Annex A states: *Table A.1 is a framework for the development of an assessment program and is not a checklist (see Clause 6). For particular medical devices, different sets of tests may be necessary, including either more or less testing than is indicated in Table A.1*.

6.2 Risk Analysis of Device Materials

This section focuses on the evaluation of the known toxicological properties and history of use for the key MG device ingredients which could present a risk to the patient.

6.2.1 Exposure Assessment and Target Health Based Endpoints

In risk assessment for human health, the normal procedure is to compare exposure levels to a population that is exposed or likely to be exposed with those levels at which no toxic effects are expected to occur. This is normally performed by comparing the exposure level, obtained from the exposure assessment, with the No Observed Adverse Effect Level (NOAEL) or some other derived limit, such as Tolerable Daily Intake (TDI) or Tolerable Exposure (TE). When a NOAEL is not obtainable, the Lowest Observed Adverse Effect Level (LOAEL) or No Observed Effect Level (NOEL) can be used.

ISO 10993-17[6] provides guidance on establishing Tolerable Intake (TI), Tolerable Exposure (TE), and Allowable Limits (AL) using health based endpoints such as NOAEL. A definition of these terms as well as guidance on how to calculate these endpoints is provided by ISO 10993-17 and is summarized below.

6.2.2 Tolerable Intake (TI): An estimate of the average daily intake of a substance over a specified time period, expressed on a body weight basis that is considered to be without appreciable adverse health effects. Normally expressed as mg/kg/day, the TI is calculated by using the following formula:

$$TI = \frac{NOAEL, LOAEL,}{MF}$$

Where MF = Modifying Factor composed of UF1, UF2, and UF3

These UF (Uncertainty Factors) are defined as follows:

UF1 = Inter-individual variation among humans (generally = 10)

UF2 = Extrapolation of data derived in species other than human (generally = 10)

UF3 = Uncertainty around quality and relevance of experimental data (generally 1-10)

6.2.3 Tolerable Exposure (TE): A product of the Tolerable Intake, the body mass, and the utilization factor.

From the TI value, a TE can be calculated considering body mass and a Utilization Factor. The following formula is used:

$$TE = TI \times m_B \times UTF$$

Where m_B= the body mass (70 kg for adult or 10 kg for child)

UTF = Utilization Factor (default is 0.2 when absolute exposure is unknown or 1.0 if less than 5 devices are used at one time; ISO 10993-17, part 6.3.2)

6.2.4 Margin of Safety (MOS): The MOS is determined by calculating the ratio of the TE expressed in mg compared with the level to which an adult human may be exposed. The MOS is calculated as follows:

$$MOS = \frac{TE\ (mg)}{Exposure\ (mg)}$$

A MOS value greater than 1 is typically judged by risk assessors and regulatory bodies to be unlikely to cause harm.[7] If a margin greater than an acceptable level exists after considering uncertainties associated with both effects and exposure estimation, the risk may be considered low and no further action is indicated.

6.2.5 Benzalkonium Chloride (BAC), *N*-Alkyl-*N*-benzyl-*N*,*N*-dimethylammonium chloride (CAS No. 8001-54-5)

Benzalkonium Chloride (CAS 8001-54-5, BAC), (Figure 1) is classified as a quaternary ammonium compound. Benzalkonium chloride has the following basic structure with specific compounds possessing varying, even-numbered alkyl chain lengths. These compounds are also known as alkyl dimethylbenzyl ammonium chloride (ADBAC).

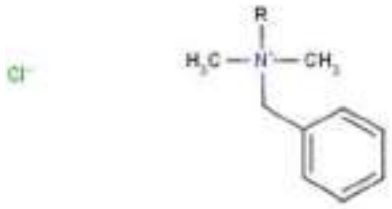


Figure 1. Chemical Structure Benzalkonium Chloride, BAC

Benzalkonium chloride (BAC) is a commonly used bactericidal preservative in albuterol and metaproterenol nebulizer solutions in the United States and in beclomethasone and ipratropium bromide nebulizer solutions in other countries. It is also commonly used as a preservative in many ophthalmic, otic and nasal formulations. Benzalkonium chloride topical gel can be used in the treatment of superficial minor skin infections and as a skin disinfectant gel, especially for individuals that may be allergic to ingredients contained in commercially available skin disinfectant products.[8] BAC is commonly used in pharmaceutical formulations as an antimicrobial preservative, ophthalmic preparations as a preservative at concentrations ranging from 0.002 to 0.02 %.[10]

The following toxicological property information is provided for Benzalkonium Chloride:

- Acute Toxicity: BAC has demonstrated the ability to be acutely toxic by various routes of exposure in multiple lab animal species. The acute toxicity tests results for BAC are summarized in Table 3 below.[9]

Table 3. Summary of Benzalkonium Chloride Acute Toxicity

Species	Route	LD_{50} (mg/kg)
Rat	Oral	240
Rat	Dermal	704
Rat	Intraperitoneal	14.5
Rat	Intravenous	13.9
Rat	Subcutaneous	400
Mouse	Intraperitoneal	10
Mouse	Intravenous	10
Mouse	Subcutaneous	62
Guinea Pig	Oral	200

- Repeat Dose Toxicity: A 12 week oral rat gavage study was conducted on BAC. A total of 40 rats were used in the study with 10 animals of each sex used per dose group. The rats received 0, 50 or 100 mg/kg/bw daily doses of BAC. Reduced body weights were observe in the 100 mg/kg/bw dose group and thus the NOAEL was determined to be 50 mg/kg/bw where no adverse BAC related effects were observed. There were no clinical signs of toxicity observed and no gross or microscopic pathology findings.[10]

- Carcinogenicity/Mutagenicity/Reproductive Toxicity: The tumorigenicity of Benzalkonium Chloride was evaluated in a dermal study involving 100 Swiss mice (female) and 10 New Zealand rabbits (8 weeks old, both sexes). Half of the mice and rabbits were treated with 8.5% Benzalkonium Chloride, and the remaining half with 17.0% Benzalkonium Chloride. The solvent for both solutions of Benzalkonium Chloride was either acetone or methanol. The solutions were applied (volume = 0.2 mL) to the backs of mice and to the left ear of each rabbit twice per week. None of the animals survived 80 weeks (mice) and 90 weeks (rabbits) of treatment. The untreated control groups consisted of 100 mice and 19 rabbits. Positive control groups were treated with 0.1% (40 mice) and 1.0% 9,10-dimethyl-benz(a)anthracene (15 rabbits). Tumors and lesions were recorded weekly and a complete necropsy was performed on each animal. Skin samples, grossly observed tumors, the lungs, liver, kidneys, and other organs were studied microscopically. A significant decrease in the survival rates of mice and rabbits that was directly attributable to Benzalkonium Chloride was not observed. Benzalkonium Chloride induced ulceration and inflammation in mice and rabbits, but no tumors.[10]

  The mutagenic potential of Benzalkonium Chloride was evaluated in the standard plate incorporation assay and the E. coli DNA polymerase A- assay. Salmonella typhimurium strains TA 98, TA1538, TA1537, and TA100 were tested in the plate incorporation assay. Each strain was incubated with the test substance for 48 hr (37 deg C) Benzalkonium Chloride (10-100 ug/plate) did not induce mutagenicity in any of the strains in the presence or absence of metabolic activation. The E. coli DNA polymerase assay was used because it detects repairable DNA damage and complements the Ames assay. Strains W3110 (pol A+) (wild-type) and p 3478 (pol A-) of E. coli were each incubated with 20 uL of Benzalkonium Chloride for 24 hr (37 deg C), either in the dark, or illuminated. Benzalkonium Chloride induced repairable DNA damage. Its genetic toxicity was also enhanced in the presence of visible light.[10]

  Both reversion and rec-assays were used to evaluate the mutagenic potential of Benzalkonium Chloride in another study. In the reversion assays, two tryptophan-requiring strains of Escherichia coli (B/r try WP2 and WP2 try hcr) and four strains of Salmonella typhimurium requiring histidine and biotin (TA1535, TA 1536, TA 1537, and TA 1538) were used. Benzalkonium Chloride was not found to be mutagenic.[10]

  The mutagenic potential of Benzalkonium Chloride was evaluated in microbial test systems using the rec-assay in combination with reverse mutation systems. The rec-assay is a simple method capable of detecting DNA-damaging capacity by analyzing differences in growth sensitivities of Rec+ and Recmutant cells of Bacillus subtilis. The bacterial strains used in the reverse mutation systems were TA1535, 1536, 1537, and 1538 (Salmonella typhimurium), and two tryptophan-requiring mutants of E. coli (B/r WP2 hcr+ and WP2 hcr). Benzalkonium Chloride was not mutagenic in this test system.[10]

- Developmental and Reproductive: Developmental or Reproductive Toxicity/ Single doses (0, 25, 50, 100, and 200 mg/kg) of aqueous Benzalkonium Chloride solutions were instilled (1 mL/kg) into the vaginas of adult, nulliparous female Wistar rats (169-203 g; groups of 6-8 rats). Dams were killed on day 21 of gestation. The fetuses were examined for viability and external malformations. A significant reduction in maternal body weight gain was noted on day 6 of pregnancy in dams receiving the 200 mg/kg dose. On days 15 and 20, maternal body weights, when compared to controls, were markedly reduced in groups receiving 100 and 200 mg/kg doses. Reductions in body weight were attributed to small litter sizes and decreased litter weights, since postcesarean body weights, without uterine contents, were similar to those of the control group. Also, vaginas of all necropsied rats given the 100 and 200 mg/kg doses were inflamed. Statistically significant, dosage-related reductions in the mean numbers of live fetuses and litter weights were noted in groups dosed with 50, 100, or 200 mg/kg solutions. No visceral anomalies were observed in Benzalkonium Chloride-exposed fetuses; however, sternal defects (absent, or nonaligned sternebrae, or retarded ossification) were more frequent in the fetuses of 100 and 200 mg/kg-treated dams. There was also a reduction in the number of implantations in treated animals. The mean number of implantations in dams treated with the 200 mg/kg solution was

significantly reduced in comparison with the control group (5.4 +/- 1.1 vs. 10.8 +/- 0.5; $p < 0.05$). The rat intravaginal developmental/reproductive toxicity NOAEL established by this study for BAC is 25 mg/kg/bw/day.[10] Incidental oral ingestion for short and intermediate contact NOAEL is 10 mg/kg/day derived from a developmental toxicity study in the rat with decreased body weight and food consumption. The acute oral toxicity of a moisturizing cream containing 0.13% Benzalkonium Chloride was evaluated using 10 young adult Sprague Dawley rats (5 males, 5 females). Each animal was dosed at a level of 5 mL/kg of the cream via oral gavage. No toxic effects were observed following 14 days following administration.[10]

- Irritation: Multiple primary skin irritation studies have been conducted in laboratory animals and man on formulations containing BAC. These studies indicate that formulations which contain ≥ 0.1% BAC have the potential to cause skin irritation.[10,11] Multiple eye irritation tests have been conducted in laboratory animals with formulations that contain BAC. These studies indicate that BAC has the potential to cause eye irritation at very low concentrations of exposure. [10,12]

- Sensitization: A review of over 40,000 human sensitization responses to topical drugs, ophthalmics and disinfectants which contained 0.1% BAC provided only very weak evidence at best that BAC has the potential to cause dermal sensitization.[10] Reports of laboratory animal sensitization testing on BAC could not be found.

The no observed effect level NOEL value of 50 mg/kg/day from the 12 week repeat dose oral gavage rat sub-chronic systemic toxicity study was judged to be the most applicable study to evaluate the possible risk from BAC in the MG device and it has been used to derive a BAC Tolerable Intake (TI) value.

$$TI = \frac{50 \text{ mg/kg/day}}{100} = 0.50 \text{ mg/kg/day}$$

Uncertainty Factors:

UF1 = Inter-individual variation among humans (10)

UF2 = Extrapolation of data derived in species other than human (10)

UF3 = Uncertainty around quality and relevance of experimental data (1 selected since MG dermal exposure would reduce BAC adsorption as compared to the oral route of administration)

$TE = TI \times m_B \times UTF = 0.50 \text{ mg/kg/day} \times 58 \text{ kg} \times 1 = 29 \text{ mg/day}$

The above calculation was made using 58 kg as the average adult female mass and an UTF value of 1 (as less than 5 devices are used at one time; ISO 10993-17, part 6.3.2).

MG contains 0.1% BAC by weight and the MG has a specific gravity of 1 (i.e. 1 g/mL) since it is predominantly water. Making the assumption that all of the MG applied to the mammography technologist hands are transferred to the patient (i.e. 0.7 ml MG x 4 applications = 2.8 ml = 2.8 grams). The 2.8 grams of MG that could possibly be applied to the patient contains 2.8 mg of BAC, (i.e. 2.8 g x 0.1% = 0.0028 g = 2.8 mg).

$$MOS = \frac{TE \text{ (mg)}}{\text{Exposure (mg)}}$$

$$MOS = \frac{29 \text{ mg/day}}{2.8 \text{ mg/day}}$$

$$= 10$$

With a MOS = 10, the margin of safety supports the conclusion that the patient risk of systemic toxicity from the presence of BAC in MG is negligible. The MG only contains 0.1% BAC by weight and at this very low concentration the patient risk of potential BAC irritation and reproductive toxicity predicted by lab animal hazard testing is negligible. As presented in a later section of this assessment (i.e. section 7.1) MG did produce cytotoxicity when tested but only a slight degree of skin irritation when tested in the rabbit primary skin irritation study. The large and highly charged BAC

molecule is not expected to readily penetrate the skin of the patient so the hazards identified in the rat intravaginal reproductive/developmental toxicity study are unlikely to present a risk to the MG patient.

6.2.6 Dihydroxypropyl PEG-5 linoleammonium chloride (CAS No. 168677-75-6), Glycereth-2 cocoate (CAS No. 68201-46-7), Benentrimonium chloride (CAS No. 17301-53-0) and Dihydroxyethyl cocamine oxide (CAS No. 61791-47-1)

In order to identify relevant toxicity data on these remaining disclosed MG ingredients, multiple sources were searched for data. These sources included on-line databases such as: ExPub which indexes dozens of relevant toxicity databases such as RTECS, FDA's Select Committee on GRAS Substances (SCOGS) Reports database, European Chemicals Agency database, ATSDR reports database), ChemIDplus (which indexes databases such as HSDB, DART, EMIC, CCRIS, IRIS, Medline, and Toxline), TSCATS (which catalogs toxicity studies submitted to EPA under TSCA), and ChemFinder. In addition, the World Wide Web was searched using Google. No useful toxicology property data was found during this search that would enable the estimates of tolerable exposure levels and respective margins of safety related to the use of these ingredients in MG.

The TTC concept developed in recent years extends the TI methodology to address substances that have very limited or no toxicity data, but for which reasonable exposure estimates can be made. The Threshold of Toxicological Concern (TTC) is a pragmatic risk assessment tool for assessing substances of unknown toxicity. It is based on the principle of establishing a human exposure threshold value for all chemicals, below which there is very low probability of an appreciable risk to human health.[13]

The TTC concept was the scientific basis of the U.S. Food and Drug Administration (FDA) guideline for indirect food additives (U.S. FDA "Redbook I" 1982 and FDA "Redbook II" in 1993). The TTC concept has also been adopted by the Joint FAO/WHO Expert committee on food Additives and the International Life Sciences Institute (ILSI) Europe Expert Group and is currently being evaluated as a tool for medical devices and materials within a working group of the ISO 10993 series of standards.[14,15]

A notable use of the TTC concept was in the 1996 report issued by the Pharmaceutical Quality Research Institute (PQRI) working group on leachables and extractables in orally inhaled and nasal drug products (OINDPs).[16] This approach has also been embraced by groups concerned with regulatory issues as well as toxicological safety.[17] Dolan *et al*. argue that "acceptable daily intakes (ADIs), based on the 'thresholds of toxicological concern' (TTC) concept should be used to support manufacturing quality operations, with specific application to cleaning validation and the resolution of atypical extraneous matter investigations for relatively unstudied compounds in active pharmaceutical ingredients and finished pharmaceutical products when limited or no toxicity data are available."

A significant driving force for approaching toxicological risk assessments from the TTC perspective has been the increasing sensitivity of analytical methods used to detect and measure impurities, as well as ever more powerful techniques to obtain structural information on unknown compounds. The commercial development of mass spectrometers (MS) of numerous types, but especially those attached as detectors to gas chromatography (GC/MS) and high-performance liquid chromatography (HPLC/MS) instruments makes possible the identification, or partial or tentative identification, of many of these trace substances. Once such trace-level extractables and leachables can be detected and identified, it becomes feasible to analyze the risk that they might pose. However, the effort and cost required to perform a risk assessment on extractable chemicals are dramatically increased as the number of chemicals requiring assessment increases, even if the concentrations of the chemicals are extremely low.

The "decision tree" procedure of Cramer *et al.* is a method of chemical classification which relies on chemical structure, and estimates of total human intake, to assess toxic hazard and to establish priorities for appropriate testing. The procedure utilizes recognized pathways of metabolic deactivation and activation, data on toxicity, and the presence of the substance as a component of traditional chemicals, and as an endogenous metabolite. Cramer first validated this approach in 1978 with 82 chemicals.[18]

The first step in the decision tree approach is the identification and evaluation of possible structural alerts for genotoxicity and high potency carcinogenicity. This step excludes aflatoxin-like compounds, N-nitroso-compounds, and azoxy-compounds that are genotoxic. The next step is to categorize substances into structural classes I, II, and III. According to Cramer, the structural classes are defined as follows:

Class I – Substances with simple chemical structures and for which efficient modes of metabolism exist, suggesting a low order of toxicity.

Class II – Substances possessing structures that are less innocuous than Class I substances, but do not contain structural features suggestive of toxicity like those in Class III.

Class III – Substances with chemical structures that permit no strong initial presumption of safety or many even suggest significant toxicity or have reactive functional groups.

The TTC levels for Class I, II, and III are 30, 9, and 1.5 µg/kg body weight/day, respectively. For a 58 kg person, the levels become:

Class I: 30 µg/kg × 58 kg = 1,740 µg/day

Class II: 9 µg/kg × 58 kg = 522 µg/day

Class III: 1.5 µg/kg × 58 kg = 87 µg/day

The MG Dihydroxypropyl PEG-5 linoleammonium chloride (CAS No. 168677-75-6), Glycereth-2 cocoate (CAS No. 68201-46-7), Benentrimonium chloride (CAS No. 17301-53-0) and Dihydroxyethyl cocamine oxide (CAS No. 61791-47-1) ingredients all have structures that do not raise concerns for extreme genotoxicity potential and structures that fit well into Cramer Class II. The average adult female can be safely exposed to 522 µg/day of a Cramer Class II chemical. MG is estimated to contain up to 0.9% by weight of any one of these ingredients and the MG has a specific gravity of 1 (i.e. 1 g/mL) since it is predominantly water. Making the worst case assumption that all of the MG applied to the mammography technologist's hands is transferred to the patient, the total MG mass applied per application is 2.8 g, (i.e. 0.7 ml MG x 4 applications = 2.8 ml = 2.8 grams). The 2.8 grams of MG that could possibly be applied to the patient is estimated to contain at most 25 mg of any one of these ingredients, (i.e. 2.8 g x 0.9% = 0.025 g = 25 mg). Since the worst case estimate of MG patient exposure to anyone of these ingredients of 25 mg per day is greater than the TTC Cramer Class II predicted safe dose of 0.522 mg/day, patient safety can't be concluded based upon this conservative risk assessment approach. However; at a qualitative level the MG patient risk associated with these MG ingredients is judged to be negligible for the following reasons:

- Each of these ingredients are large chemicals that are highly charged so they are unlikely to readily penetrate the patient's skin at a high rate or in a high quantity.
- It is very unlikely that all of the MG applied to the mammography technologist's hands will transfer to the patient since the MG product is partially dry at the time of contact with the patient.
- The 0.9% by weight estimate of each of the ingredients is most likely more than the amount actually being used since these ingredients have a safe history of being used for their disclosed purposes at lower concentrations, (i.e. ≤ 0.1%).

7.0 Biological Endpoints Evaluated for MG

Biological safety testing is a non-clinical requisite for a medical device that is intended to be marketed in the premier medical device markets of the world. Use of biocompatible materials and sub-components is the cornerstone to the fabrication of a biocompatible device. The combination of biocompatible materials of construction and sub-components into a medical device should not increase the risk of adverse biological effects. This must be verified and validated, during new device development.

When MG is used as intended, it will contact the patient's intact skin for a limited period (i.e. <24 hr). MG is therefore classified according to ISO 10993-1 as: surface, limited contact (< 24 hr) with skin.

Because the MG intended use includes the application of a surface device which has limited contact with skin, consideration must be given to all relevant endpoints defined by ISO 10993-1:2009 and the FDA Blue Book Memorandum #G95-1, that is: cytotoxicity, sensitization, and irritation.

7.1 Biological Safety Testing

Based upon the MG device classification selected biocompatibility tests were completed to provide further evidence of its safety for its intended use. The results for these tests are summarized and addressed below.

Cytotoxicity: The test article, MG, was evaluated to determine the potential for cytotoxicity. This study was conducted based on the requirements of ISO 10993-5: Biological evaluation of medical devices - Part 5: Tests for in vitro cytotoxicity. Triplicate wells were dosed with 0.1 mL of the test article placed on a filter (test filter disc). Triplicate wells were dosed with 0.1 mL of 0.9% sodium chloride solution (SC) placed on a filter disc (filter disc control). Triplicate wells were dosed with a 1 cm length portion of high density polyethylene as a negative control. Triplicate wells were dosed with a 1 cm x 1 cm portion of latex as a positive control. Each was placed on an agarose surface directly overlaying a subconfluent monolayer of L-929 mouse fibroblast cells. After incubating at 37°C in the presence of 5% CO2 for 24 to 26 hours, the cultures were examined macroscopically and microscopically for any abnormal cell morphology and cell lysis.

The test article showed evidence of causing severe cell lysis or toxicity. The test article did not meet the requirements of the test since the cellular reactivity grade was greater than a grade 2 (mild reactivity).

Skin Irritation: The test article, MG, was evaluated for primary skin irritation in rabbits. This study was conducted in accordance with the guidelines of ISO 10993-10, Biological evaluation of medical devices - Part 10: Tests for irritation and skin sensitization. Two 0.5 mL portions of the test article and control article were topically applied to the skin of each of three rabbits and left in place for a minimum of 23 hours and a maximum of 24 hours. The sites were graded for erythema and edema at 1, 24, 48 and 72 hours after removal of the single sample application. There was very slight erythema and no edema observed on the skin of the animals treated with the test article. The Primary Irritation Index for the test article was calculated to be 0.8. The response of the test article was categorized as slight.

Guinea Pig Closed Patch Sensitization: The test article, MG, was evaluated for the potential to elicit delayed dermal contact sensitization in the guinea pig. This study was conducted based on the requirements of ISO 10993-10, Biological evaluation of medical devices, Part 10: Tests for irritation and skin sensitization. The test article was occlusively patched to the intact skin of ten animals for 6 hours (±30 minutes), three times a week, over a 3 week period. The control article was similarly patched to five animals. Following a 2-week recovery period, the ten test and five control animals were occlusively patched with the test article and the control article. All sites were observed for evidence of dermal reactions at 24 and 48 hours after patch removal. The test article showed no evidence of causing delayed dermal contact sensitization in the guinea pig.

All of the biological safety tests performed for MG were successfully performed and the results are summarized below.

Table 4. Summary of Biocompatibility Testing on MG

ISO Standard	Biological Effect	Test Method	Result	NAMSA Lab Number(s)
10993-5	Cytotoxicity	Cytotoxicity Study Using the ISO Agarose Overlay Method	Cytotoxic	15T_31655_04
10993-10	Irritation	ISO Intracutaneous Study in Rabbits - saline and sesame oil extracts	Slight Irritant	15T_31655_05
10993-10	Sensitization	ISO Closed Patch Sensitization Study in Guinea Pigs	Non-sensitizer	15T_31655_06

MG showed evidence of causing severe cell lysis or toxicity. MG did not meet the requirements of the cytotoxicity test since the cellular reactivity grade was greater than a grade 2 (mild reactivity). ISO 10993-5:2009 indicates in clause 10 that the results of cytotoxicity test shall be evaluated considering the classification of the device. It goes on to indicate that any cytotoxicity result can be of a concern, but indicates that it is the *potential* for *in vivo* toxicity that is the primary concern and a device cannot be determined unsuitable for a given application based solely on *in vitro* cytotoxicity data. It would be an inaccurate decision, and an incomplete evaluation, to identify a device as not biocompatible based solely on the result of an *in vitro* test alone without some correlation to an identified *in vivo* effect. Without this correlation, materials commonly used in medical devices such as silver, latex, copper, and acetal resins which commonly produce a positive cytotoxic response would be deemed as unfit for device applications. Through further *in vivo* evaluation of devices containing these materials, one can conclude that they are suitable for medical

device applications. This also demonstrates that cytotoxicity studies do not provide a perfect correlation to the clinical condition.

Cytotoxicity testing, due to the unprotected nature of the cell line *in vitro*, is often used to screen materials intended for use in the body. Cytotoxicity results typically provide good correlation to the potential response of the tissue near the site of use to a material. It can be concluded that materials can be regarded as potentially biologically safe if they have successfully passed *in vitro* cytotoxicity testing.[19]

However, because these *in vitro* tests only expose a single layer of cells in a culture, these results cannot always be directly related to effects on a complex biological system such as living tissue. Hanks *et al*. investigated why conclusions from tissue culture are sometimes different from those obtained from *in vivo* biocompatibility studies.[20] It was concluded that in many cases the *in vitro* tests were too sensitive resulting in many materials being rejected due to *in vitro* test results. Some studies have shown that candidate materials that display moderate *in vitro* cytotoxicity have excellent biocompatibility *in vivo*.[21] Rosengren *et al*. studied this phenomenon further and concluded that there is not a definite negative implication to using a biomaterial exhibiting *in vitro* cytotoxicity.[21] Some clinically effective and widely used materials as noted above have been cytotoxic in *in vitro* cytotoxicity tests but have proven to be successful in long-term clinical implantation. Mimicking a complex biological system in a single *in vitro* experiment is not always straightforward.

Considering the results of the cytotoxicity test and the guidance provided by the ISO 10993-5:2009 regarding the evaluation of cytotoxicity results, it is appropriate to focus on the results of the more clinically relevant and definitive *in vivo* studies conducted on MG that are summarized above. In addition, MG contains the active ingredient Bezalkonium Chloride which is used as an anti-microbial so the cytotoxicity of individual cells used in the cytotoxicity biocompatibility screening assay was expected. Other clinically safe anti-microbial agents (i.e. silver, BZT, isopropyl alcohol and ethyl alcohol) show similar results. MG was subjected to *in vivo* sensitization and irritation assays. MG demonstrated no potential to cause sensitization and only a very slight ability to cause skin irritation. From these results it can be determined that the *in vitro* cell cytotoxicity results do not correspond to the *in vivo* results and can be considered an anomaly.

The very slight irritation observed in the rabbit primary skin irritation study is not considered to be clinically significant. The MG device has been commercially marketed and used for years as a hand sanitizer without issue and thus its possible indirect application to the intact skin covering breast tissue would not be expected to cause irritation. In addition, the MG coated technologist's hands will only contact the breast tissue for a very short period of time while the very sensitive skin of the young rabbits used in the primary skin irritation testing was directly exposed to MG under an occlusive patch for 24 hours.

8.0 Summary of Risk Assessment and Biocompatibility Testing

A toxicology based risk assessment was performed on the MG ingredients. The quantitative risk assessment completed on the fully disclosed Benzalkonium Chloride ingredient concluded that MG patient risk associated with its use in the product is negligible. A similar quantitative risk assessment could not be completed on the remaining MG ingredients since there was no available data on their toxicological properties to the enable the implementation of a quantitative risk assessment. A qualitative risk assessment was completed on these remaining MG ingredients and concluded that their use in MG presents a negligible level of risk to the MG patient.

The biocompatibility testing to be considered for this type of medical device was performed. MG was found to be cytotoxic; however, the more definitive *in vivo* primary skin irritation and sensitization tests also performed indicate that MG will not cause MG patient irritation or sensitization responses.

This risk assessment and evaluation of the MG biocompatibility testing results indicates that the likelihood of a toxic effect from MG use is negligible and that the product should be considered safe for use as intended.

9.0 Conclusion

To evaluate the biological safety of MG, consideration was given to the type of patient contact, the potential hazards associated with MG ingredients, *in vivo & in vitro* test results for MG and its ingredients, the history of clinical use of the ingredients, and other information available in the literature.

Based upon this evaluation MG has met the requirements of ISO 10993-1:2009, EN ISO 14971:2012, FDA General Program Memorandum #G95-1, and the European Union Medical Device Directive 93/42/EEC for a surface device with limited skin contact (<24 hr). MG can be considered safe for the patient when placed on the mammogram technologist's hands to enable them to position breast tissue onto the image.

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