GLP REPORT

TEST FACILITY

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STUDY TITLE

C3a Complement Activation Assay

TEST ARTICLE NAME

Occlusin 505 Artificial Embolization Device

TEST ARTICLE IDENTIFICATION

FL288

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Summary

The test article, Occlusin 505 Artificial Embolization Device, FL288, was evaluated for the potential to activate the complement system. The clinical significance of the results should be evaluated with respect to the use of the medical device and its likely potential for activation of the complement system in clinical use. This study was conducted *in vitro* by incubating the test article in normal human serum (NHS) and detecting the presence of C3a in the exposed serum by an enzyme immunoassay method. The C3a concentration from the test article sample was compared statistically to activated NHS and negative (low density polyethylene) controls. The results for the inactivated NHS control did not meet the acceptance criteria for a valid study. A repeat study was conducted.

Under the conditions of this assay, the C3a concentration of the test article sample was 14,323 ± 2,288 ng/mL (mean ± S.D.). The concentration of C3a in the test sample was not statistically higher than the activated NHS control and was not statistically higher than the negative control. As a result, the test article was not considered to be a potential activator of the complement system.

Supervisory Personnel:

Don R. Pohl, B.S.
Manager, Technical Sales and Services

Todd A. Festerling, B.S., M.S.
Manager, In Vitro Toxicology

Approved by:

Lesia M. Wasio, B.S.
Study Director

November 10, 2009
Date Completed

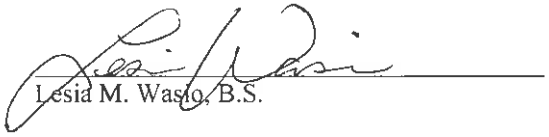
Statement of GLP Compliance

This study was conducted in accordance with the provisions of the FDA Good Laboratory Practice (GLP) Regulations (21 CFR, Part 58).

There were no deviations from the protocol, standard operating procedures or the GLP Regulations which were judged to have had any significant impact on the validity or interpretation of the data.

All laboratory data have been accurately recorded and verified, as indicated by the signature below.

Study Director:



Lesia M. Waslo, B.S.

November 16, 2009
Date

1. Introduction

Purpose
The test article identified below was evaluated for the ability to activate the complement system. The activation of the complement system can be clinically significant. This study was conducted *in vitro* by incubating the test article in normal human serum and detecting the presence of C3a in the exposed serum by an enzyme immunoassay (EIA) method. Formation of C3a from C3 occurs in both the classical and alternative pathways of complement activation.

Dates
Test Article Receipt: October 2, 2009
Test Conducted Date: October 21, 2009
Retest Conducted Date: November 5, 2009

GLP Compliance
The study initiated by protocol signature on October 8, 2009, 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 the report.

2. Materials

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

Test Article Name: Occlusin 505 Artificial Embolization Device

Test Article Identification: FL288

Pre-Preparation

Post-Preparation

Stability Testing: In progress

Expiration Date: Stable for duration of intended testing

Strength, Purity and Composition: Strength: Not applicable because no active ingredients are used to formulate a concentration; Purity: Not applicable because the test article is a multi-component device; Composition: Polylactide-co-glycolide and bovine collagen

Physical Description of the Test Article: Microspheres supplied as a dry powder in sterile sealed glass vials/ 400mg/vial

Storage Conditions: Refrigerated

Complement Source: Normal Human Serum (NHS), certified as negative for HIV (I and II) and Hepatitis B and C, was purchased from an outside source.

Test Article Preparation:	A 0.001 g portion of the sample (surface area, per sponsor: 6.436 cm^2) was included in each preparation. Based on the USP ratio of 120 cm^2:20 mL, a 6.4 cm^2 portion of the test article was covered with 1.1 mL of NHS for the original and repeat studies. Triplicate preparations were incubated at 37°C for 60 minutes.
Positive Control:	Cobra Venom Factor (CVF) was used to confirm maximal activation of complement. Ten units of CVF were added to a 0.5 mL aliquot of NHS. Triplicate preparations were incubated at 37°C for 60 minutes.
Stability Testing:	Marketed product, stability characterized by its labeling.
Strength, Purity and Composition:	Strength and Purity: ≥95%; Composition: Cobra venom factor, water.
Low Control:	An aliquot of reconstituted human plasma (supplied with the EIA kit) with a C3a content less than 200 ng/mL served as an additional control measure.
Activated NHS Control:	Triplicate aliquots of NHS were incubated at 37°C for 60 minutes to serve as the activated baseline control.
Positive Biomaterial Reference Control:	Latex examination gloves were used as the positive biomaterial reference control. Based on the USP ratio of 120 cm^2:20 mL, a 3.0 cm^2 portion of the control material was covered with 0.5 mL of NHS. Triplicate preparations were incubated at 37°C for 60 minutes.
Stability Testing:	Marketed product, stability characterized by its labeling.
Strength, Purity and Composition:	Strength: Not more than 50 µg of total water extractable latex protein/gram; Purity: Not more than 50 µg of total water extractable latex protein/gram, balance is the natural rubber latex, zinc carbamate accelerators, zinc oxide, and titanium dioxide; Composition: Natural rubber latex, zinc carbamate accelerators, zinc oxide, and titanium dioxide.
Negative Control:	Low density polyethylene (LDPE), a biomaterial with a low ability to activate complement, was used as a negative control. Based on the USP ratio of 60 cm^2:20 mL, a 1.4 cm^2 portion of the control material was covered with 0.5 mL of NHS. Triplicate preparations were incubated at 37°C for 60 minutes.
Stability Testing:	Marketed product, stability characterized by its labeling.
Strength, Purity and Composition:	Strength: Not applicable, no active components in the formulation; Purity: Meets FDA 21 CFR 177.1520; Composition: Low density polyethylene.
Inactivated NHS Control:	An aliquot of NHS was placed on ice for 60 minutes to verify the background C3a concentration.

3. Test System

Test System and Justification

The Quidel C3a Enzyme Immunoassay (EIA) kit was purchased from Quidel Corporation, San Diego, CA. This system uses enzyme immunoassay technology to measure the C3a fragment formed during activation of the complement system. Activation of either the classical or alternative pathways results in the assembly of C3 convertases which cleave C3 into two fragments, C3a and C3b. The anaphylatoxin C3a is very short-lived. When formed, it is immediately cleaved into the more stable C3a-desArg. The C3a EIA kit quantitates C3a-desArg and allows reliable conclusions about the level of complement activation in the test samples.

Sample Preparation

Each prepared test article, positive biomaterial reference control, and negative control were placed into separate, labeled polypropylene tubes and covered with the appropriate aliquots of NHS. The positive control (CVF) and NHS control were also prepared in polypropylene tubes. All test article(s) and controls except the inactivated NHS control were incubated for 60 minutes in a 37°C water bath. The inactivated NHS control was placed on ice for 60 minutes. The samples were agitated immediately before and immediately following incubation. Following incubation, the NHS was removed from the test article and controls and placed into cryogenic storage vials. To perform the assay, the NHS was appropriately diluted with sample buffer. The standards, low control, NHS controls, negative control, positive control and positive biomaterial reference control were prepared and diluted as appropriate.

4. Method

The Quidel C3a Enzyme Immunoassay for the quantification of C3a in human serum is a three-step procedure using a microassay plate coated with monoclonal anti-human C3a, a horseradish peroxidase (HRP)-conjugated rabbit anti-C3a in phosphate buffered saline, and a chromogenic substrate. The Quidel test kit provided the C3a standard, a lyophilized human plasma containing 1100 ng/mL of C3a. Serial dilutions of the reconstituted standard were prepared to obtain concentrations of 550, 275, and 137.5 ng/mL.

Prepared standards, controls, and test article sample dilutions were transferred to the wells of the microassay plate precoated with anti-C3a monoclonal antibody. The anti-C3a monoclonal antibody is specific for C3a and will not bind to C3, C3b or any other complement fragment. The C3a present in the standards, controls, or test article sample dilutions bound to the immobilized anti-C3a. After 1 hour of incubation, a wash cycle was performed to remove unbound material. HRP-conjugated rabbit anti-C3a was added to each well. In this step, the enzyme conjugated anti-C3a bound to C3a which was captured by the monoclonal anti-C3a on the surface of the microassay wells.

After 1 hour of incubation, a wash cycle was conducted to remove unbound, excess conjugate. A chromogenic enzyme substrate was added to each well of the microassay plate. The bound HRP-conjugate reacted with the substrate. After 15 minutes of incubation, the enzyme reaction was chemically stopped by the addition of 1N H_2SO_4.

The optical density was measured spectrophotometrically for each well at 450 nm using a plate reader. The color intensity of the reaction mixture was proportional to the concentration of C3a present in the test samples, standards, and controls.

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. Evaluation and Statistical Analysis

A standard curve was prepared by plotting the net absorbance values obtained for the standards and blank on the y-axis against the respective C3a concentration on the x-axis. The C3a concentrations of the test samples and controls were determined from the standard curve. The concentrations of C3a produced by the test article, negative control, positive control, activated NHS control, and positive biomaterial reference control were reported in ng/mL. The concentrations of C3a in the positive control and test article sample were compared statistically with the activated NHS and negative control using t-tests. A p value of < 0.05 was considered statistically significant. The test article extract was considered to have no effect on complement activation if the C3a concentration of the test article sample was not statistically higher than both the activated NHS and negative control.

The study was considered valid since the following criteria were met:

- The correlation coefficient for the standard curve was above 0.95.
- The buffer blank was less than 0.2 A_{450} units.
- The most concentrated standard was greater than 0.5 A_{450} units.
- The C3a concentration of the low control was less than 200 ng/mL.
- The C3a concentration of the positive control was statistically higher than the activated NHS and negative control.
- The C3a concentration of the inactivated NHS control was less than three fold the C3a value stated on the certificate of analysis for the NHS lot.

Currently, there is no regulatory guidance for evaluation of complement activation by medical devices. Interpretation of the results should be based on the clinical use of the device, which takes into account the degree of blood exposure. For example, medical devices such as dialyzers and by-pass circuits have a large surface area and prolonged blood exposure, and thereby pose a greater concern for complement activation. In contrast, devices such as catheters and guidewires with much smaller surface areas and blood exposure pose significantly less concern for complement activation. As a result, the results from complement assay should be evaluated with respect to the medical device's clinical use and its likely potential for complement activation under such clinical use.

6. Results

The inactivated NHS control did not perform as anticipated in the initial test and a repeat study was conducted. The absolute C3a concentrations obtained for the test article and each control are presented in the following tables. Data generated from the initial test are found in Table 1 and were not used in the final evaluation. Results from the repeat assay are found in Table 2. The controls performed as anticipated in the repeat study.

Table 1 - C3a Concentrations

	C3a Concentration of Sample 1 (ng/mL)	C3a Concentration of Sample 2 (ng/mL)	C3a Concentration of Sample 3 (ng/mL)	C3a Concentration ng/mL (mean ± S.D.)
Test Article	16,980	15,077	18,376	16,811 ± 1,656
Positive Control	147,841	157,490	169,594	158,308 ± 10,900[ab]
Activated NHS Control	14,988	15,980	16,971	15,980 ± 991.5
Positive Biomaterial Reference Control	38,655	35,746	34,586	36,329 ± 2,096
Negative Control	14,261	15,650	18,585	16,165 ± 2,208
Inactivated NHS Control*	10,322	Not Applicable	Not Applicable	Not Applicable
Low Control	<137.5	Not Applicable	Not Applicable	Not Applicable

[a] = The C3a concentration of the positive control was statistically higher than the activated NHS control (p value < 0.05)
[b] = The C3a concentration of the positive control was statistically higher than the negative control (p value < 0.05)

*C3a concentration was not less than 3 fold the C3a value stated on the certificate of analysis for the NHS lot. Result does not meet criteria for a valid study.

Table 2 - C3a Concentrations (Repeat Study)

	C3a Concentration of Sample 1 (ng/mL)	C3a Concentration of Sample 2 (ng/mL)	C3a Concentration of Sample 3 (ng/mL)	C3a Concentration ng/mL (mean ± S.D.)
Test Article	13,319	12,709	16,942	14,323 ± 2,288
Positive Control	122,774	124,748	137,085	128,202 ± 7,756[ab]
Activated NHS Control	9,877	11,896	11,149	10,974 ± 1,021
Positive Biomaterial Reference Control	26,197	29,541	28,137	27,958 ± 1,679
Negative Control	12,072	10,010	13,975	12,019 ± 1,983
Inactivated NHS Control	2,580	Not Applicable	Not Applicable	Not Applicable
Low Control	<137.5	Not Applicable	Not Applicable	Not Applicable

[a] = The C3a concentration of the positive control was statistically higher than the activated NHS control (p value < 0.05)
[b] = The C3a concentration of the positive control was statistically higher than the negative control (p value < 0.05)

7. Conclusion

Under the conditions of this assay, the C3a concentration of the test article sample was 14,323 ± 2,288 ng/mL (mean ± S.D.). The concentration of C3a in the test sample was not statistically higher than the activated NHS control and was not statistically higher than the negative control. As a result, the test article was not considered to be a potential activator of the complement system.

Results and conclusions apply only to the test article tested. Any extrapolation of these data to other articles is the sponsor's responsibility. All procedures were conducted in conformance with good manufacturing practices and certified to ISO 13485:2003.

8. 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.

9. Records

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

10. References

Code of Federal Regulations (CFR), Title 21, Part 58, Good Laboratory Practice for Nonclinical Laboratory Studies (2008).

Quidel C3a Enzyme Immunoassay Kit package insert, Quidel Corporation, San Diego, CA.

NAMSA Validation: Lab No. 02T 14130 00.

Statement of Quality Assurance Activities

Phase Inspected	Date Inspected	Date Reported to Study Director	Date Reported to Management
Spectrophotometer Readings	October 21, 2009	October 21, 2009	October 21, 2009
Activation	November 5, 2009	November 5, 2009	November 5, 2009
Study Data Review	October 22, 2009	October 22, 2009	October 22, 2009
Study Data Review	November 10, 2009	November 10, 2009	November 10, 2009
Final Report Review	November 10, 2009	November 10, 2009	November 10, 2009

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: Erica K. Kujawa — 11-10-09

Erica G. Kujawa, B.S.
Auditor, Quality Assurance

Date

GLP PROTOCOL

TEST FACILITY:

NAMSA
6750 Wales Road
Northwood, OH 43619

SPONSOR:

NAMSA Ohio
6750 Wales Road
Northwood, OH 43619

STUDY TITLE:

C3a Complement Activation Assay

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Approvals

Sponsor Representative (Sponsor): _____

Date Approved: _____

Study Director (NAMSA): _____

Date Initiated: _____

1. Introduction

Purpose
The purpose of this study is to determine the complement activation potential of a biomaterial or a medical device using an *in vitro* test system. The activation of the complement system can be clinically significant. This study will be conducted *in vitro* by incubating the test article in normal human serum and detecting the presence of C3a in the exposed serum by an enzyme immunoassay (EIA) method. Formation of C3a from C3 occurs in both the classical and alternative pathways of complement activation.

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. Materials

Test Article
The sponsor will submit the test article to be evaluated. Detailed information about the test article was provided to NAMSA by the sponsor and is listed below:

Test Article Name:	Occlusion 505 Artificial Embolization Device
Test Article Identification:	FL288
Test Article Physical Description:	Microspheres supplied as a dry powder in sterile sealed glass vials/ 400mg/vial
Test Article Intended Clinical Use:	Embolotherapy
Test Article Stability:	Stability testing is in progress and sponsor affirms that test article is stable for duration of intended testing.
Test Article Strength:	Strength is not applicable because no active ingredients are used to formulate a concentration.
Test Article Purity:	Purity is not applicable because the test article is a multi-component device.
Test Article Composition:	The test article is composed of the following materials: polylactide – co-glycolide and bovine collagen
Test Article Mixture Analysis:	Analysis is not necessary because test article is a solid, powder, gel, or liquid being extracted or being tested as received (will not be mixed with a carrier).
Test Article Disposition:	Discard unused test article.

Only insoluble or solid materials can be tested. Gels and liquids cannot be analyzed. If the material is composed of multiple parts, each part must be supplied and tested separately.

USP guidelines for extraction will be used to determine the amount of test article per unit volume of normal human serum (NHS). The NHS employed in this test is not an extraction vehicle but rather the complement source. NHS that has been tested negative for HIV I & II, and Hepatitis B and C surface antigen will be purchased from Quidel Corporation.

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:

Ratio of test article to NHS
Material thickness less than 0.5 mm - ratio of 3.0 cm^2:0.5 mL (based on the USP ratio 120 cm^2:20 mL)

NOTE: Due to testing constraints, the volume of NHS used for incubation will be limited to 0.5 mL. If a volume greater than 0.5 mL of NHS is needed, the price will be adjusted.

Test Article Preparation Instructions
Prepare based on the following: Use 0.001g of sample. 0.001g of sample has a surface area of 6.4375cm^2.

Special Laboratory Instructions
Following the extraction procedure, it is acceptable to centrifuge the extract with the sample in it to be able to remove enough extract for testing.

Control Article
Positive Biomaterial Reference Control: Latex examination gloves, a biomaterial with a high capacity to activate complement, will be prepared using a ratio of 3.0 cm^2:0.5 mL.

Negative Control: Low density polyethylene, a biomaterial with a low ability to activate complement, will be prepared using a ratio of 1.5 cm^2:0.5 mL.

Positive Control: 10 units of Cobra Venom Factor (CVF) will be used to confirm maximal complement activation. CVF has been shown to be a strong activator of the complement system.

Low Control: Reconstituted human plasma (supplied with the EIA kit) with a C3a content less than 200 ng/mL will be used as an additional control measure.

Activated NHS Control: NHS incubated at 37°C for 60 minutes will serve as the activated baseline control.

Inactivated NHS Control: NHS incubated on ice for 60 minutes will serve as the inactivated baseline control.

The lot number and expiration date for the materials and control articles will be recorded.

3. Test System

Test System and Justification
Some biomaterials have the potential to activate the complement system via the alternative pathway when they come in contact with blood, producing undesirable results. Thus, for blood contacting medical devices, it is important to evaluate their potential for activating the complement system.

The Quidel C3a Enzyme Immunoassay (EIA) kit will be purchased from Quidel Corporation, San Diego, CA. The system uses enzyme immunoassay technology to measure the C3a fragment formed during activation of the complement system. Activation of either the classical or alternative pathways results in the assembly of C3 convertases which cleave C3 into two fragments, C3a and C3b. The anaphylatoxin C3a is very short-lived. When formed, it is immediately cleaved into the more stable C3a-desArg. The C3a EIA kit quantitates C3a-desArg and allows reliable conclusions about the level of complement activation in the test samples.

4. Preparation

Each test article, positive biomaterial reference control, activated NHS control, positive control and negative control will be prepared in triplicate in order to be compared statistically. The low control and inactivated NHS control will be prepared as a single sample and will only be used for quality control of the system. All test article(s) and controls will be covered with the appropriate amount of NHS and incubated for 60 minutes in a 37°C water bath with the exception of the inactivated NHS control. The inactivated NHS control will be placed on ice for 60 minutes. The activated NHS control provides a baseline value to evaluate production of the C3a complement fragment by the positive control and test article. The samples will be agitated immediately before and immediately following incubation.

Following the 60 minute incubation, the tubes will be placed on ice to hinder further activation of complement. The serum will be withdrawn from all controls and test articles, and placed into labeled polypropylene tubes. The test article sera and controls will be diluted, as needed, with sample buffer. All serum samples and dilutions will be kept on ice to hinder further activation of complement. Each prepared dilution will be tested using the complement activation kit according to the manufacturer's directions.

5. Method

Manufacturer's Instructions
The Quidel C3a Enzyme Immunoassay for the quantification of C3a in human serum is a three-step procedure using a microassay plate coated with monoclonal anti-human C3a, a horseradish peroxidase (HRP)-conjugated rabbit anti-C3a in Phosphate Buffered Saline, and a chromogenic substrate. The Quidel test kit will provide the C3a standard, a lyophilized human plasma containing 1100 ng/mL of C3a. Serial dilutions of the reconstituted standard will be prepared to attain concentrations (ng/mL) of 550, 275, and 137.5.

Prepared standard series, blank, low control and inactivated control will be added to duplicate microassay wells precoated with anti-C3a monoclonal antibody. All triplicate samples (positive biomaterial reference control, negative control, positive control, activated NHS control and test article) will be added to single wells precoated with anti-C3a monoclonal antibody. The anti-C3a monoclonal antibody is specific for C3a and will not bind to C3, C3b nor any other complement fragment. The C3a present in

the standards, controls, or test article dilutions will bind to the immobilized anti-C3a. After 1 hour of incubation, a wash cycle will be used to remove unbound material.

HRP-conjugated rabbit anti-C3a will be added to each well. In this step, the enzyme conjugated anti-C3a will bind to C3a which was captured by the monoclonal anti-C3a on the surface of the microassay wells. After 1 hour of incubation, a wash cycle will be used to remove unbound, excess conjugate.

A chromogenic enzyme substrate will be added to each microassay well. The bound HRP-conjugate will react with the substrate forming a blue color. After 15 minutes of incubation, the enzyme reaction will be chemically stopped by the addition of 1N H_2SO_4, and the color intensity will be measured spectrophotometrically at 450 nm. The color intensity of the reaction mixture will be proportional to the concentration of C3a present in the test specimens, standards, and controls.

6. Evaluation and Statistical Analysis

A standard curve will be prepared by plotting the net absorbance values obtained for the standards and blank on the y-axis against the respective C3a concentration on the x-axis. The concentration of C3a in the test samples and controls will be calculated from the standard curve and reported in ng/mL. The concentration of C3a in the positive control and test article samples will be compared statistically with the activated NHS and negative control using t-tests. A p value of < 0.05 will be considered statistically significant.

The study will be considered valid if the following criteria are met:

a. The correlation coefficient for the standard curve must be above 0.95.
b. The buffer blank must be less than 0.2 A_{450} units.
c. The most concentrated standard must be greater than 0.5 A_{450} units.
d. The concentration of C3a in the positive control must be statistically higher than the activated NHS and negative controls.
e. The low control should demonstrate a C3a content of less than 200 ng/mL.
f. The C3a concentration in the inactivated NHS control should be less than 3 fold the C3a value stated on the certificate of analysis for the NHS lot.

For evaluation of the test sample results, the following criteria will be considered:

- If the C3a concentration of the test sample is statistically higher than both the activated NHS and negative controls, then the test article is considered a potential activator of the complement system. The data will be reviewed by the appropriate scientific personnel.
- If a positive response (statistically higher as compared to both the activated NHS control and negative control) is noted for the test sample, then the C3a concentration of the test sample will be compared with the C3a concentration of the positive biomaterial reference control based on the following formula:

$$\frac{(\overline{X}\ \text{C3a Concentration of Test Article} - \overline{X}\ \text{C3a Concentration of Activated NHS Control})}{(\overline{X}\ \text{C3a Concentration of Positive Biomaterial Reference Control} - \overline{X}\ \text{C3a Concentration of Activated NHS Control})} \ X\ 100$$

If a positive response is noted for the test article, the C3a concentration of the test article will be compared to the historical range of the activated NHS and negative controls to determine biological relevance. If the C3a concentration for the test article is within the mean ± 1 standard deviation of both the activated NHS and negative historical controls, then the article will be considered a “low potential activator” of the complement system.

Currently, there is no regulatory guidance for evaluation of complement activation by medical devices. Interpretation of the results should be based on the clinical use of the device, which takes into account the degree of blood exposure. For example, medical devices such as dialyzers and by-pass circuits have a large surface area and prolonged blood exposure, and thereby pose a greater concern for complement activation. In contrast, devices such as catheters and guidewires with much smaller surface areas and blood exposure pose significantly less concern for complement activation. As a result, the results from the complement assay should be evaluated with respect to the medical device’s clinical use and its likely potential for complement activation under such clinical use. Other data and/or information may be utilized in reaching a final conclusion regarding the results of this assay.

7. Report

The final report will include a detailed description of the methods employed, acceptability of controls and a table listing C3a concentrations of triplicate samples as well as the mean concentration and standard deviation for the test article, positive control, activated NHS control, negative control, positive biomaterial reference control and the C3a concentration of the inactivated NHS control and the low control.

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. Proposed Dates

The study dates will be finalized by the study director following receipt of the sponsor-approved protocol and appropriate material for the study. Initiation of the study will be the date on which the study director signs the GLP protocol. Projected dates for starting the study (first treatment) and for the completion of the study (final report release) will be provided to the sponsor (or representative of the sponsor).

10. Records

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

11. References

Code of Federal Regulations (CFR), Title 21, Part 58, Good Laboratory Practice for Nonclinical Laboratory Studies (2008).

Quidel C3a Enzyme Immunoassay Kit package insert, Quidel Corporation, San Diego, CA.

NAMSA Validation; Lab No. 02T 14130 00.

12. 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.