**510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION**
**DECISION SUMMARY**

**A. 510(k) Number:**

K171498

**B. Purpose for Submission:**

New device and instrument

**C. Measurand:**

C-reactive protein (CRP)

**D. Type of Test:**

Sandwich immunoassay employing electroluminescence (ECL), Quantitative

**E. Applicant:**

Meso Scale Diagnostic, LLC

**F. Proprietary and Established Names:**

MSD® CRP Assay Kit
MESO® SECTOR S 700 Instrument

**G. Regulatory Information:**

1. Regulation section:

   21 CFR §866.5270—C-Reactive Protein Immunological Test System

2. Classification:

   Class II

3. Product code:

   DCK—C-Reactive Protein, Antigen, Antiserum and Control
   DCN— System, Test, C-reactive protein

4. Panel:

   Immunology (82)

## H. Intended Use:

1. Intended use:

   The MSD CRP Kit is intended for in vitro diagnostic use in the quantitative determination of C-reactive protein (CRP) in human serum using the MESO SECTOR S 700 instrument. Measurement of CRP aids in the evaluation of infection, tissue injury, and inflammatory disorders. This test will be performed in a hospital or clinical laboratory setting by trained laboratory personnel. The target patient population for the MSD CRP Assay is symptomatic adults. Clinicians should utilize the results of the MSD CRP Assay for diagnosis of inflammatory diseases in conjunction with other clinical and laboratory findings.

2. Indication for use:

   Same as Intended Use above

3. Special conditions for use statement:

   Fore prescription use only

4. Special instrument requirements:

   MESO® SECTOR S 700 Instrument

## I. Device Description:

The MSD CRP Assay Kit is a quantitative in-vitro diagnostic assay for conventional measurement of C-reactive protein in human serum. The CRP Assay Kit is designed for use with the MESO SECTOR® S 700 Instrument. The kit components include the 96-well CRP assay plate, CRP calibrator, CRP detection antibody, CRP diluent and CRP read buffer. The assay in the MSD CRP Kit is a sandwich immunoassay employing electrochemiluminescence (ECL) detection. In the instrument, a voltage is applied to the plate electrodes causing the captured labels to emit light. The instrument measures the intensity of emitted light from each spot to provide a quantitative measure of analyte in the sample.

## J. Substantial Equivalence Information:

1. Predicate device name:

   Roche Diagnostics C-Reactive Protein (Latex) Assay and Roche Diagnostics Cobas Integra 800 Analyzer

2. Predicate 510(k) number:

   K073277

3. Comparison with predicate:

| Similarities | | |
|---|---|---|
| Item | Device<br>MSD CRP Assay Kit and MESO<br>SECTOR S 700 Instrument | Predicate<br>Roche Diagnostics C-Reactive Protein<br>(Latex) Assay and Roche Diagnostics<br>Cobas Integra 800 Analyzer<br>(K073277) |
| Intend Use/Indications for Use | The MSD CRP Kit is intended for in vitro diagnostic use in the quantitative determination of C-reactive protein (CRP) in human serum using the MESO SECTOR S 700 instrument. Measurement of CRP aids in the evaluation of infection, tissue injury, and inflammatory disorders. This test will be performed in a hospital or clinical laboratory setting by trained laboratory personnel. The target patient population for the MSD CRP Assay is symptomatic adults. Clinicians should utilize the results of the MSD CRP Assay for diagnosis of inflammatory diseases in conjunction with other | In vitro test for the quantitative immunological determination of C-reactive protein in human serum and plasma on COBAS INTEGRA systems.<br><br>In vitro test for the quantitative determination of C-reactive protein in human serum and plasma on Roche/Hitachi cobas c systems. |

| Similarities | | |
|---|---|---|
| Item | Device<br>MSD CRP Assay Kit and MESO<br>SECTOR S 700 Instrument | Predicate<br>Roche Diagnostics C-Reactive Protein (Latex) Assay and Roche Diagnostics<br>Cobas Integra 800 Analyzer (K073277) |
| | clinical and laboratory findings. | |
| Assay Analyte | CRP | Same |
| Controls | None provided | Same |
| Antibody | Mouse monoclonal anti-human CRP antibodies | Same |
| Measurement | Quantitative | Same |

| Differences | | |
|---|---|---|
| Item | Device<br>MSD CRP Assay Kit and MESO<br>SECTOR S 700 Instrument | Predicate<br>Roche Diagnostics C-Reactive Protein (Latex) Assay and Roche Diagnostics<br>Cobas Integra 800 Analyzer (K073277) |
| Technology Type | Sandwich-type electrochemiluminescence immunoassay | Particle-enhanced turbidimetric assay |
| Reference interval | 3.0 – 160 mg/L | 1.0 – 200 mg/L |
| Limit of detection | 0.05 mg/L | 1.0 mg/L |
| Calibration | MSD CRP Calibrator | Cfas Proteins (K012393) |
| Traceability | Traceable to the ERM®-DA 474 reference material | Traceable to CRM 470 |
| Specimen Type | Serum | Serum and Plasma |
| Assay Storage Conditions | CRP Plate, CRP Detection Antibody:<br>2–8°C<br>CRP Calibrator: ≤ -70°C<br>CRP Diluent: ≤ -10°C<br>CRP Read Buffer: 15–30°C | 2–8°C |

## K. Standard/Guidance Document Referenced (if applicable):

- CLSI EP05-A3:2014, Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline - Third Edition

- CLSI EP06-A:2003, Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline
- CLSI EP07-A2:2005, Interference Testing in Clinical Chemistry; Approved Guideline - Second Edition
- CLSI EP09-A3:2013, Measurement Procedure Comparison and Bias Estimation Using Patient Samples; Approved Guideline - Third Edition
- CLSI EP17-A2:2012, Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline - Second Edition
- CLSI EP25-A:2009, Evaluation of Stability of In Vitro Diagnostic Reagents; Approved Guideline
- CLSI EP28-A3c:2010, Defining, Establishing, and Verifying Reference Intervals in The Clinical Laboratory; Approved Guideline - Third Edition
- Review Criteria for Assessment of C-Reactive Protein (CRP), High Sensitivity C-Reactive Protein (hsCRP) and Cardiac C-Reactive Protein (cCRP) Assays, Guidance for Industry and FDA Staff, Issued on September 22, 2005

## L. Test Principle:

The assay in the MSD CRP Kit is a sandwich immunoassay employing electrochemiluminescence (ECL) detection. This assay is carried out in a 96-well plate that has integrated carbon ink electrodes screen-printed on the bottom of each well. The plate is provided pre-coated with capture antibody on a single, well-defined region of the electrode surface. The user adds the calibrator or sample and a solution containing detection antibody conjugated with electrochemiluminescent labels over the course of two incubation periods. Analyte in the sample binds to the capture antibodies immobilized on the electrode surface; recruitment of the detection antibodies by the bound analyte completes the sandwich. The user adds a buffer that creates the appropriate chemical environment for the electrochemiluminescent signal and loads the plate into an MSD MESO SECTOR S 700 instrument. In the instrument, a voltage is applied to the plate electrodes causing the captured labels to emit light. The instrument measures the intensity of emitted light to provide a quantitative measure of analyte in the sample.

## M. Performance Characteristics (if/when applicable):

1. Analytical performance: All results presented below were within the sponsor's pre-determined acceptance criteria for each study.

   *a. Precision/Reproducibility:*

   The precision and reproducibility of the MSD CRP assay was evaluated by testing five serum samples containing various concentrations of CRP, per CLSI EP05-A3. This study was performed at three different sites, using three different instruments, with a different operator at each site. Each sample was run in duplicate, with two runs per day, over a period of 20 days, with one lot of reagents. (N=240 data points per sample). The results are summarized in the table below.

| Sample | Mean (mg/L) | Within-Run | | Between-Run | | Between-Day | | Between-Instrument | | Total | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | SD | CV (%) | SD | CV (%) | SD | CV (%) | SD | CV (%) | SD | CV (%) |
| 1 | 4.49 | 0.45 | 10.1 | 0.14 | 3.2 | 0.09 | 2.1 | 0.29 | 6.4 | 0.56 | 12.6 |
| 2 | 8.47 | 0.25 | 2.9 | 0.18 | 2.1 | 0.22 | 2.6 | 0.59 | 6.9 | 0.70 | 8.2 |
| 3 | 10.80 | 0.31 | 2.8 | 0.26 | 2.4 | 0.26 | 2.4 | 0.62 | 5.7 | 0.78 | 7.3 |
| 4 | 57.18 | 1.83 | 3.2 | 1.24 | 2.2 | 1.29 | 2.3 | 3.23 | 5.7 | 4.12 | 7.2 |
| 5 | 214.11 | 7.10 | 3.3 | 21.32 | 10.0 | 0.00 | 0.00 | 11.36 | 5.3 | 25.18 | 11.8 |

The lot-to-lot reproducibility of the assay was evaluated by testing five serum samples containing various concentrations of CRP. Each sample was run in five replicates per run, two runs per day, over five days of testing (N=50 data points per sample). The results are summarized in the table below.

| Sample | Mean (mg/L) | Within-Run | | Between-Run | | Between-Day | | Between-Lot | | Total | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | SD | CV (%) | SD | CV (%) | SD | CV (%) | SD | CV (%) | SD | CV (%) |
| 1 | 4.09 | 0.09 | 2.1 | 0.08 | 2.1 | 0.03 | 0.7 | 0.03 | 0.07 | 0.13 | 3.1 |
| 2 | 8.04 | 0.16 | 2.0 | 0.16 | 2.0 | 0.03 | 0.4 | 0.00 | 0.00 | 0.23 | 2.8 |
| 3 | 10.51 | 0.23 | 2.2 | 0.22 | 2.1 | 0.00 | 0.0 | 0.11 | 1.00 | 0.34 | 3.2 |
| 4 | 57.23 | 1.10 | 1.9 | 1.80 | 3.1 | 0.55 | 1.0 | 1.16 | 2.00 | 2.47 | 4.3 |
| 5 | 213.65 | 4.38 | 2.0 | 7.83 | 3.7 | 0.00 | 0.0 | 6.94 | 3.20 | 11.34 | 5.3 |

*b. Linearity/assay reportable range:*

Linearity: The linearity across the measuring range of the assay was evaluated by a study according to CLSI EP6-A. Eleven serially diluted sampels were prepared by mixing "low" (0.6 mg/L CRP) and "high" (214 mg/L CRP) pooled serum samples. Each dilution sample was tested in a single replicate per plate. A total of four plates/replicate were tested. Each plate was run using three lots of MSD CRP Assay kits. This yielded a total of twelve runs. Linear regression results of this analysis are as follows:

| Test Range (mg/L) | Slope (95% CI) | Intercept (95% CI) | $R^2$ | % Recovery |
|---|---|---|---|---|
| 0.627–201 | 0.942 (0.926–0.958) | 0.0296 (-0.04 – 0.98) | 0.997 | -8.9% – 0.0% |

The manufacturer is reporting that the assay is linear from 3 to 160 mg/L.

Hook effect (antigen excess):

The assay was tested for prozone or hook effect up to a CRP concentration of 800 mg/L. No prozone effect was observed.

c. *Traceability, Stability, Expected values (controls, calibrators, or methods):*

Traceability:

The calibrators used to calibrate the MSD CRP test are traceable to the ERM®-DA 474 reference material.

Value assignment: A reference lot is created by diluting bulk calibration material. It is assigned using four dilutions across the quantitation range; CRM474 is utilized as the calibration standard. Production lots of kit calibrator are created by diluting the bulk calibration material in CRP Diluent to the nominal highest calibration level used in the assay. The concentration of each lot of kit calibrator is assigned using four dilutions across the quantitation range, using the reference lot as the calibration standard.

Controls:

The manufacturer recommends that at least two controls be run to verify the performance of the assay method. A control in the mid to upper end of the normal range, and a control in the mid-region of the assay curve are recommended for the day to day evaluation of the performance of the assay. The manufacturer recommends that at least two CRP controls at two different levels be used for quality control. The manufacturer recommends Bio-Rad's Liquichek™ Cardiac Markers Plus Controls, Liquichek™ Elevated CRP Controls or equivalent.

Stability:

*Kit stability/Shelf Life:*

All kit components are one-time use only, and therefore open-vial stability testing is not required. A total of three kits were utilized for stability testing. Real-time stability testing was conducted at baseline, three months, six months, seven months, nine months and 12 months. Six replicates were run per plate, three total runs per kit, three kits, and six time intervals for a total of 108 data points. The provided data support the kit stability claim of 7 months. The real-time stability study is ongoing.

Data provided for the calibrator stability testing after thawing support the stability of the calibrators for 2 hours after thawing.

*d. Detection limit:*

All three studies below were conducted based on CLSI EP17-A2.

The Limit of Blank (LoB) was determined by assaying 24 replicates of the blank sample (assay diluent) over five working days on three different lots of MSD CRP assay kits. A total of 120 data points per lot were generated. LoB was determined to be 0.02 mg/L for all three assay lots.

Limit of Detection (LoD) was determined by testing 20 replicates of six low-level CRP pools that were prepared by mixing the MSD CRP Calibrator and the MSD CRP Diluent in varying propritions. This resulted in 120 data points per lot, and three different lots were tested. The measured LoD values for the three assay kits used for this testing were 0.039 mg/L, 0.049 mg/L and 0.048 mg/L. The overall LoD for the test system is equal to the highest LoD calculated for any of the 3 assay lots used for testing. Therefore, the overall test system LoD = 0.049 mg/L.

Limit of Quantitation (LoQ) was determined by further testing six low-level CRP pools that were prepared by mixing the MSD CRP Calibrator and the MSD CRP Diluent in varying proportions. Each sample was tested in eight replicates in a single run, and one run was conducted per day for a total of five closely grouped working days. Three los were tested. A total of 48 data points were acquired per lot. The LoQ for the MSD CRP Assay Kit and MESO SECTOR S 700 Instrument was determined to be 0.597 mg/L, and the Sponsor is claiming an\ LoQ of 3 mg/L.

*e. Analytical specificity:*

Interference study was performed according to CLSI EP7-A2 using pooled human serum or CRP Diluent samples with CRP concentrations ranging from 10 mg/L to 40 mg/L. Each sample was tested in five replicates across three different lots of reagents. The following putative interferents were tested by spiking in pooled human serum samples with the CLSI EP7-A2-recommended concentrations (control samples were spiked with the same volume of the sample diluent): unconjugated bilirubin (32 mg/dL), conjugated bilirubin (5.4 mg/dL), hemoglobin (22,200 mg/dL), triglyceride-rich lipoproteins (633 mg/dL), rheumatoid factor (4000 IU/mL), human anti-mouse antibodies (500 ng/mL), acetaminophen (1324 mM), acetylsalicylic acid (3.62 mM), ibuprofen (2425 mM), salicylic acid (4.34 mM), methotrexate (2 mM). No interferences from the tested substances were observed at the concentrations tested.

*f. Assay cut-off:*

See the reference range/expected value.

2. Comparison studies:

   a. *Method comparison with predicate device:*

   *Method comparison with Roche Diagnostics C-Reactive Protein (Latex) Assay and Roche Diagnostics Cobas Integra 800 Analyzer*: Human serum samples with varying varying levels of CRP were obtained from biorepositories from different geographical locations within the United States. A total of 120 samples were used for this study. 13/120 (10.8%) of samples were contrived, i.e., pooled or spiked with CRP. For each of the 120 samples, one aliquot was tested at MSD using the MSD system and the other was tested by a commercial laboratory using the predicate device. This testing yielded a total of 120 matched-pair data points for comparison. The results are summarized below:

| **N** | **Range (mg/L)** | **Slope (95% CI)** | **Intercept (95% CI)** | **R-squared** |
|---|---|---|---|---|
| 120 | 3.7-179.0 | 1.094 (1.077-1.120) | 0.088 (-0.548-0.736) | 0.988 |

   b. *Matrix comparison:*

   Not applicable

3. Clinical studies:

   a. *Clinical Sensitivity:*

   Not applicable

   b. *Clinical specificity:*

   Not applicable

   c. *Other clinical supportive data (when a. and b. are not applicable):*

   Not applicable

4. Clinical cut-off:

   Not applicable

5. Expected values/Reference range:

   The reference range in the normal population was established per CLSI EP28-A3c by testing 120 apparently healthy individuals. Samples reflected a representative adult U.S. population with respect to race, age, and gender. The results showed a median CRP value of 1.01 mg/L; the central 95% interval was 0.100 – 12.9 mg/L.

**N. Instrument Name:**

MESO SECTOR S 700 Instrument

**O. System Descriptions:**

1. Modes of Operation:

   Does the applicant's device contain the ability to transmit data to a computer, webserver, or mobile device?

   Yes _____ or No ___X_____

   Does the applicant's device transmit data to a computer, webserver, or mobile device using wireless transmission?

   Yes _____ or No ___X_____

2. Software:

   FDA has reviewed applicant's Hazard Analysis and software development processes for this line of product types:

   Yes ____X____ or No _____

3. Specimen Identification:

   Samples are identified by a barcode reader that reads barcodes on 96-well plates. Sample IDs on the plate can be entered manually or 96-well plate sample layout can be imported from an external .csv file.

4. Specimen Sampling and Handling:

   The assay is carried out in a 96-well plate consumable that has integrated carbon ink electrodes screen-printed on the bottom of each well. The plate is provided pre-coated with capture antibody on a single, well-defined region of electrode surface. The user adds the calibrator or samples and a solution containing detection antibody conjugated with electrochemiluminescent labels over the course of two incubaton periods. Serum samples

are diluted per instructions for use by first adding 790 uL of CRP diluent to 10 µL of sample, generating an 80-fold dilution. Then, 10 µL of 80-fold diluted sample is added into 990uL of CRP diluent, to generate a final 8000-fold dilution. Finally, 50 µl of diluted sample, calibrator or control is added to a well on the 96-well plate, the plate is sealed with an adhesive plate seal and incubated, with subsequent washes and additions of detection antibody solution. At the end of the two incubation periods, read buffer is added to the plate and the plate is placed on the MESO SECTOR S 700 instrument for analysis by employing electrochemiluminescence (ECL) detection to assess the CRP concentrations in each well.

5. Calibration:

   MSD supplies a calibrator for the MSD CRP kit at the concentration of the highest standard. The highest standard calibrator is diluted using the CRP diluent to generate a total of 7 calibrators. Calibrators are run on each 96-well plate, by running two replicates at each calibrator level.

6. Quality Control:

   The manufacturer recommends that at least two CRP controls at two different levels be used for quality control. The manufacturer recommends Bio-Rad's Liquichek™ Cardiac Markers Plus Controls, Liquichek™ Elevated CRP Controls or equivalent.

## P. Other Supportive Instrument Performance Characteristics Data Not Covered In The "Performance Characteristics" Section above:

N/A

## Q. Proposed Labeling:

The labeling is sufficient and it satisfies the requirements of 21 CFR Part 809.10.

## R. Conclusion:

The submitted information in this premarket notification is complete and supports substantial equivalence decision.