

**510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY TEMPLATE**

A. 510(k) Number:

k081731

B. Purpose for Submission:

New device

C. Measurand:

Creatine kinase, Creatine kinase MB isoenzyme

D. Type of Test:

Quantitative

E. Applicant:

Siemens Healthcare Diagnostics Inc.

F. Proprietary and Established Names:

Dimension® (CKI) Flex® reagent cartridge

Dimension® (MBI) Flex® Reagent Cartridge

CKI/MBI Calibrator

G. Regulatory Information:

1. Regulation section:

21 CFR 862.1215 Creatine phosphokinase/creatinase or isoenzymes test system

21 CFR 862.1150 Calibrator, multi-analyte mixture

2. Classification:

Class II

3. Product code:

CGS

JHS

JIX

4. Panel:

75 Chemistry

H. Intended Use:

1. Intended use(s):

See Indications for use below

2. Indication(s) for use:

Dimension® (CKI) Flex® Reagent Cartridge (DF38)

The CKI method is an *in vitro* diagnostic test for the quantitative measurement of creatine kinase in human serum and plasma on the Dimension® clinical chemistry system. Measurements of creatine phosphokinase and its isoenzymes are used in the diagnosis and treatment of myocardial infarction and muscle diseases such as progressive, Duchenne-type muscular dystrophy.

Dimension® (MBI) Flex® Reagent Cartridge (DF32)

The creatine kinase MB (MBI) method is an *in vitro* diagnostic test for the quantitative measurement of creatine kinase MB isoenzyme activity in human serum and plasma on the Dimension® clinical chemistry system. Measurements of creatine phosphokinase and its isoenzymes are used in the diagnosis and treatment of myocardial infarction and muscle diseases such as progressive, Duchenne-type muscular dystrophy.

CKI/MBI Calibrator (DC32)

The CKI/MBI CAL is an *in vitro* diagnostic product for the calibration of the Creatine Kinase (CKI) and Creatine Kinase MB (MBI) methods on the Dimension® clinical chemistry system.

3. Special conditions for use statement(s):

For prescription use only

4. Special instrument requirements:

Dimension ® clinical chemistry system

I. Device Description:

The Dimension® CKI Flex® reagent cartridge is a prepackaged in-vitro diagnostic test method that is specifically designed to be used on the Dimension® clinical chemistry systems. There are six wells per reagent. Reagents contained in the Dimension® CKI Flex® reagent cartridge are: Hexokinase (yeast), G-6-PDH (bacterial), ADP, AMP, EDTA, Mg Acetate, Diadenosine Pentaphosphate, NADP, N-acetylcysteine, Imidazole Buffer, Creatine Phosphate, Glucose, EDTA, and CAPSO Buffer.

The Dimension® MBI Flex® reagent cartridge is a prepackaged in-vitro diagnostic test method that is specifically designed to be used on the Dimension® Clinical Chemistry Systems. The reagents contained in the Dimension® MBI Flex® reagent cartridge are: NADP, ADP, AMP, Diadenosine Pentaphosphate, N-Acetyl Cysteine, Hexokinase (yeast), G-6-PDH (bacterial), EDTA, Mg Acetate, Imidazole Buffer, Glucose, Creatine Phosphate, Anti CK-M Antibody (mouse), Mg Acetate, and CAPSO Buffer.

CKI/MBI CAL is a liquid, multi-analyte, human serum albumin based product containing creatine kinase (human source) and creatine kinase MB (porcine source). The kit consists of four vials, two vials per level (2 and 3) with 2.0 mL per vial. Level 1 calibrator for CKI/MBI is not included in the CKI/MBI CAL carton. Purified Water Diluent or reagent grade water is required for use as Calibrator Level 1. This product contains human source material. Each donor unit used in the preparation of this product was tested by FDA-approved methods for the presence of antibodies to Human Immunodeficiency Virus Type 1 (HIV-1) and Type 2 (HIV-2), as well as for Hepatitis B Surface Antigen (HBSAg) and antibody to Hepatitis C Virus (HCV), and found to be negative.

J. Substantial Equivalence Information:

1. Predicate device name(s):

Roche Diagnostic Systems Inc. CK-NAC Reagent, Roche Diagnostic Systems Inc. CK-MB Reagent, Roche Diagnostic Systems Inc. Calibrator for Automated Systems, Roche Diagnostic Systems Inc. Calibrator for Automated Systems, CKMB

2. Predicate K number(s):

k834502, k003158, k990460

3. Comparison with predicate:

| Similarities | | |
|--|--|--|
| Item | Device | Predicate |
| Dimension® (CKI) Flex® Reagent Cartridge | | |
| Intended use | The CKI method is an <i>in vitro</i> diagnostic test for the quantitative measurement of creatine kinase in human serum and plasma on the Dimension® clinical chemistry system. | In vitro assay for the quantitative determination of creatine kinase (CK) in human serum and plasma on Roche automated clinical chemistry analyzers. |
| Dimension® (MBI) Flex® Reagent Cartridge | | |
| Intended use | The creatine kinase MB (MBI) method is an <i>in vitro</i> diagnostic test for the quantitative measurement of creatine kinase MB isoenzyme activity in human serum and plasma on the Dimension® clinical chemistry system. | Immuno-inhibition assay for the quantitative <i>in vitro</i> determination of the MB isoenzyme of creatine kinase in human serum and plasma on Roche automated clinical chemistry analyzers. |
| Analytic sensitivity | 3 U/L | 3 U/L |
| CKI/MBI Calibrator | | |
| Intended use | The CKI/MBI CAL is an <i>in vitro</i> diagnostic product for the calibration of the Creatine Kinase (CKI) and Creatine Kinase MB (MBI) methods on the Dimension® clinical chemistry system. | Calibrator for automated systems (C.f.a.s.) is for use in the calibration of quantitative Roche methods on Roche clinical chemistry analyzers as specified in the value sheet. |

| Differences | | |
|--|---------------------|-------------|
| Item | Device | Predicate |
| Dimension® (CKI) Flex® Reagent Cartridge | | |
| Measuring range | 7-1000 U/L | 3-2300 U/L |
| Dimension® (MBI) Flex® Reagent Cartridge | | |
| Measuring range | 3-125 U/L | 3-2300 U/L |
| CKI/MBI Calibrator | | |
| Matrix | Human serum albumin | Human serum |
| Form | Liquid | lyophilized |

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

CLSI/NCCLS EP17-A, Protocols for Determination of Limits of Detection and Limits of Quantitation; CLSI EP5-A2, Evaluation of Precision Performance of Clinical Chemistry Devices; CLSI EP6-A Evaluation of the Linearity of Quantitative Measurement; CLSI EP9-A2 Method Comparison and Bias Estimation Using Patient Samples; CLSI C28-A2, How to Define and Determine Reference Intervals in the Clinical Laboratory

L. Test Principle:

Dimension® (CKI) Flex® Reagent Cartridge

In a coupled enzyme reaction, the creatine kinase in patient samples catalyzes the transphosphorylation of phosphate from creatine phosphate to adenosine-diphosphate (ADP) producing adenosine-triphosphate (ATP). Hexokinase (HK) uses ATP to phosphorylate glucose. The resulting glucose-6-phosphate is oxidized by glucose-6-phosphate dehydrogenase (G-6-PDH) with the simultaneous reduction of nicotinamide adenine dinucleotide phosphate (NADP). The rate of formation of NADPH is directly proportional to the CK activity in the sample and is measured bichromatically at 340 and 540 nm.

Dimension® (MBI) Flex® Reagent Cartridge

The activity of the CK-MM isoenzyme is inhibited by an antibody specific for the CK-M subunit. The activity of the B subunit of creatine kinase MB isoenzyme is not inhibited, and it is on this basis that CK-MB can be measured.

In an enzyme coupled reaction, creatine kinase in patient samples catalyzes the transphosphorylation of creatine phosphate to adenosine-diphosphate (ADP), producing adenosine-triphosphate (ATP). Hexokinase (HK) uses the ATP to phosphorylate glucose. The resulting glucose-6-phosphate is oxidized by glucose-6-phosphate dehydrogenase (G-6-PDH) with the simultaneous reduction of nicotinamide adenine dinucleotide phosphate (NADP) to NADPH. The rate of formation of NADPH is measured bichromatically at 340, 540 nm and is directly proportional to CK-MB activity in the sample.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. *Precision/Reproducibility:*

To determine imprecision of the CKI Flex® reagent cartridge, CLSI EP5-A2, Evaluation of Precision Performance of Clinical Chemistry Devices, was followed. During each day of testing, two separate runs, with two test samples, for each test material, were analyzed for 20 days on the Dimension RxL analyzer (n = 80 for each sample).

For the CKI Flex® reagent cartridge, the results are shown in the table below:

| Material | Mean (U/L) | Repeatability | | Within-lab | |
|-----------------|------------|---------------|-----|------------|-----|
| | | SD | %CV | SD | %CV |
| Serum pool 1 | 46 | 0.7 | 1.4 | 1.3 | 2.8 |
| Serum pool 2 | 166 | 1.4 | 0.8 | 3.5 | 2.1 |
| Control level 1 | 108 | 1.1 | 1.0 | 3.5 | 3.3 |
| Control level 3 | 788 | 3.3 | 3.3 | 13.4 | 1.7 |

To determine imprecision of the MBI Flex® reagent cartridge, CLSI EP5-A2, Evaluation of Precision Performance of Clinical Chemistry Devices, was followed. During each day of testing, two separate runs, with two test samples, for each test material, were analyzed for 20 days on the Dimension RxL analyzer (n = 80 for each sample).

For the MBI Flex® reagent cartridge, the results are shown in the table below:

| Material | Mean (U/L) | Repeatability | | Within-lab | |
|-----------------|------------|---------------|-----|------------|------|
| | | SD | %CV | SD | %CV |
| Serum pool 1 | 26 | 1.0 | 3.9 | 1.3 | 5.0 |
| Control level 2 | 15 | 1.5 | 9.8 | 1.7 | 11.5 |
| Control level 3 | 92 | 3.1 | 3.4 | 3.4 | 3.7 |

b. *Linearity/assay reportable range:*

The sponsor conducted a linearity study based on CLSI EP6-A Evaluation of the Linearity of Quantitative Measurement. For both the CKI and MBI assays, a high pool sample was serially diluted with a low pool sample to cover the sponsor's claimed measuring range (7-1000 U/L for CKI and 3-125 U/L for MBI). Theoretical concentrations were computed for all intermediate pools based on the initial concentrations of the high and low pools. Five replicate tests were run on the Dimension RxL analyzer for each level, using a

randomized testing order. Mean concentration was computed for each level. Recoveries ranged from 99 to 101% for CKI and from 99 to 102% for MBI. The linear regression equation was $y = 0.4 + 1.009x$, $r = 0.99997$ for CKI and $y = -0.99906 + 1.0137x$, $r = 0.99992$ for MBI.

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

Traceability and value assignment involves preparation of anchor pools and master pools. The anchor pool is prepared from pooled normal and high human serum and is assigned by the IFCC Reference Method. Three levels of CK master pools are manufactured by adding the appropriate volume of CK stock, with a known concentration into an aqueous human serum albumin calibrator base. Level 1 of the CK master pool, containing no analyte is assigned zero U/L. Levels 2 and 3 of the CK master pool are assigned by the IFCC reference method and verified against the anchor pools using multiple Dimension instruments and replicates.

Five levels of CKMB master pools are manufactured by adding the appropriate volume of CKMB stock, with a known concentration, into an aqueous human serum albumin matrix. Level 1 contains no analyte and is assigned zero U/L. Levels 2 - 5 of the CK master pool are assigned by the IFCC reference method and verified against the anchor pools using multiple Dimension instruments and replicates. The final bottle values for commercial lots are assigned to levels 2 and 3 of the of Dimension® CKI/MBI Calibrator, using CKMB IFCC master pools. The final bottle values for each level of commercial lots are assigned against the master pools using multiple instruments and reagent lots.

Stability: The shelf life and open stability of the CKI/MBI calibrator have been demonstrated using real time data. The predetermined acceptance criteria and protocols were reviewed and found to be acceptable. The CKI/MBI calibrator has a target shelf life of 12 months when stored at -20°C. The calibrator must be thawed at room temperature before use. Once the cap is removed, the assigned values are stable for 14 days when recapped immediately and stored at 2-8 °C.

d. *Detection limit:*

CLSI/NCCLS EP17-A, Protocols for Determination of Limits of Detection and Limits of Quantitation, was referenced by the sponsor.

The Limit of Blank (LoB) calculation was performed with N=3 replicates per sample on each of 3 days on the Dimension RxL analyzer. Two reagent lots, 2 instrument systems, 4 blank samples and 4 low analyte serum samples were tested. This gave 36 measurements for each of 8 samples, 144 each total blank and low analyte sample measurements. For the Dimension® CKI Flex®

reagent cartridge, the Limit of Blank was estimated to be 5 U/L. For the Dimension® MBI Flex® reagent cartridge, the Limit of Blank was estimated to be 1 U/L.

CLSI EP17-A was followed to determine the Limit of Detection, with proportions of false positives (α) less than 5% and false negatives (β) less than 5%; based on 288 determinations, with 144 blank and 144 low level samples. LOD is the lowest concentration that can be detected reliably.

The calculation of the Limit of Detection was performed by the following formula:

$$\text{LoD} = \text{LoB} + (cp) \times (sd)$$

$$\text{CKI: } 5 \text{ U/L} + (1.646) \times (1.3) = 7 \text{ U/L}$$

$$\text{MBI: } 1 \text{ U/L} + (1.646) \times (1.2) = 3 \text{ U/L}$$

e. *Analytical specificity:*

Testing was performed using the paired difference approach described in the guideline document, CLSI EP7-A2. Potential interferents were spiked into aliquots of a fresh sample pool and analyzed as patient samples. Spiked sample results were compared to control samples prepared without the potential interferent.

| | Substance Concentration (mg/dL) | Analyte Test Level (U/L) | % Bias (+/-) |
|-------------------------|---------------------------------------|-----------------------------|-----------------|
| CKI | 100 | 200 | 8 |
| | | 611 | 4 |
| Bilirubin, Unconjugated | 80 | 200 | -1 |
| | | 611 | 0 |
| Bilirubin, Conjugated | 80 | 200 | 2 |
| | | 611 | 0 |
| Lipemia, Intralipid | 3000 | 200 | -1 |
| | | 611 | -2 |
| | | 53 | 4 |
| Bilirubin, Conjugated | 40 | 20 | -5 |
| Lipemia, Intralipid | 20 | 53 | 10 |
| | | 20 | 10 |
| Hemoglobin, Hemolysate | 20 | 53 | 8 |
| | | 22 | 9 |

An extensive list of substances were tested for CKI and MBI and were found to have <10 % interference. The list is included in the package inserts for the CKI and MBI assays.

f. Assay cut-off:

Not applicable (N/A)

2. Comparison studies:

a. Method comparison with predicate device:

The CLSI EP9-A2, Method Comparison and Bias Estimation Using Patient Samples guidance document was followed to perform the method comparison studies for the Dimension® CKI and MBI methods. The predicate devices selected for the method comparison were:

Roche Diagnostic Systems Inc. CK-NAC Reagent (K834502)

Roche Diagnostic Systems Inc. CK-MB Reagent (K003158)

Lithium heparin plasma samples were used in the studies. For CKI 90 samples with values ranging from 38 to 953 U/L were used for the study. For MBI 98 samples with values ranging from 5 to 122 U/L were used. An additional study was conducted for CKI using 54 serum and plasma samples with values ranging from 10 to 985 U/L, comparing the CKI assay to the IFCC reference method. The testing was performed on the Dimension RxL analyzer. The results of the studies are shown in the table below.

| Assay | Comparative method | slope | intercept | r | N |
|-------|--------------------|-------|-----------|-------|----|
| CKI | IFCC | 1.06 | 0.35 | 0.999 | 54 |
| | Roche CK | 1.04 | 6.07 | 1.000 | 90 |
| MBI | Roche CKMB | 1.01 | -1.3 | 0.986 | 98 |

b. Matrix comparison:

Recommended specimen types for the CKI and MBI assays are serum, sodium and/or lithium heparin plasma, and EDTA. For CKI, 68 matched pairs of serum and each plasma sample type were tested. For MBI, 51 matched pairs for each plasma type for serum and plasma were tested across the assay range. The results are shown in the table below :

| Dimension® (CKI) Flex® reagent cartridge | | | | | |
|--|-------|-----------|-------|----|-------------|
| | slope | intercept | r | n | range (U/L) |
| Sodium heparin | 1.01 | -4.36 | 0.999 | 68 | 48-885 |
| Lithium heparin | 1.01 | -4.48 | 0.999 | 68 | 49-890 |
| EDTA | 0.99 | -1.39 | 0.999 | 68 | 51-825 |
| Dimension® (MBI) Flex® Reagent Cartridge | | | | | |
| Sodium heparin | 0.95 | -0.43 | 0.995 | 51 | 7-100 |
| Lithium heparin | 0.97 | -0.69 | 0.996 | 51 | 9-102 |
| EDTA | 1.00 | 0.62 | 0.998 | 51 | 9-107 |

3. Clinical studies:

a. *Clinical Sensitivity:*

N/A

b. *Clinical specificity:*

N/A

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

N/A

4. Clinical cut-off:

N/A

5. Expected values/Reference range:

CLSI C28-A2, How to Define and Determine Reference Intervals in the Clinical Laboratory was followed. Reference interval studies from the predicate devices were confirmed in a small bridging study for the Dimension® CKI and MBI methods, under the following bibliography:

Klein G, Berger A, Bertholf R et al. Abstract: Multicenter Evaluation of Liquid Reagents for CK, CK-MB and LDH with Determination of Reference Intervals on Hitachi Systems. Clin Chem 2001; 47:Suppl. A30

Thomas L, Müller M, Schumann G, Weidemann G et al. Consensus of DGKL and VDGH for interim reference intervals on enzymes in serum. J Lab Med 2005;29:301–308.

CKI

Males: 39 – 308 U/L

Females: 26 – 192 U/L

Combined: 26 – 308 U/L

MBI

7 – 25 U/L

The cited reference intervals for CKI were confirmed in a small bridging study by running 20 samples from females age 24-64 and 20 samples from males age 25-61. The cited reference intervals for MBI were confirmed in a small bridging study by running 60 samples from females age 18-64 and from 64 males age 18-61. Validation testing was performed on the Dimension RxL analyzer.

N. Proposed Labeling:

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

O. Conclusion:

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