510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY AND INSTRUMENT COMBINATION TEMPLATE

A. 510(k) Number:

k163462

B. Purpose for Submission:

Modifications were made to the previously cleared AQT90 FLEX system devices (k112161, k120326) to include a new semi-automated system clean function, a new flash lamp, a redesign of the Test and CAL cartridge housing, and a change in the algorithm to calculate the hematocrit value.

C. Measurand:

Myoglobin

Creatine kinase isoform MB (CKMB)

D. Type of Test:

Quantitative fluorometric immunoassay

E. Applicant:

Radiometer Medical ApS

F. Proprietary and Established Names:

AQT90 Flex Myo Test Kit

AQT90 FLEX CKMB Test Kit

AQT90 FLEX

G. Regulatory Information:

Product Code	Classification	Regulation Section	Panel
DDR	II	866.5680, Myoglobin Immunological Test System	Immunology (82)
JHX	II	862.1215, Creatine phosphokinase/creatine kinase or	Clinical Chemistry (75)

Product Code	Classification	Regulation Section	Panel
		isoenzymes test system	
KHO	I	862.2560, Fluorometer for clinical use	Clinical Chemistry (75)

H. Intended Use:

1. Intended use(s):

   See Indications for use below.

2. Indication(s) for use:

   AQT90 FLEX Myo Test Kit
   The Myo Test is an in vitro diagnostic assay for the quantitative determination of myoglobin in EDTA or lithium heparin whole-blood or plasma specimens on the AQT90 FLEX analyzer in point of care and laboratory settings. It is intended for use as an aid in the rapid diagnosis of heart disease, for example, acute myocardial infarction.

   AQT90 FLEX CKMB Test Kit
   The CKMB Test is an in vitro diagnostic assay for the quantitative determination of creatine kinase isoform MB in EDTA or lithium heparin whole-blood or plasma specimens on the AQT90 FLEX analyzer in point of care and laboratory settings. It is intended for use as an aid in the diagnosis of myocardial infarction.

   AQT90 FLEX
   The AQT90 FLEX analyzer is an immunoassay instrument based on the quantitative determination of time-resolved fluorescence to estimate the concentrations of clinically relevant markers on whole-blood and plasma specimens to which a relevant anticoagulant has been added. It is intended for use in point-of-care and laboratory settings.

3. Special conditions for use statement(s):

   For in vitro diagnostic use; for prescription use only; for point-of-care use.

4. Special instrument requirements:

   Studies were performed using the AQT90 FLEX analyzer.

I. Device Description (Description of Device Modification):

The AQT90 FLEX Myo Test Kit consists of ten Test Cartridges and one Calibration Cartridge. The components are as follows:

Mouse monoclonoal anti-myoglobin capture and tracer antibodies, approximately 500

ng/cup. Bovine serum albumin, bovine γ-globulin, and mouse IgG (blocker substances for heterophilic interference), TRIS buffer, and <0.1% sodium azide.

The AQT90 CKMB Test Kit consists of ten Test Cartridges and one Calibration Cartridge. The components are as follows:

Mouse monoclonoal anti-CKMB capture and tracer antibodies, approximately 600 ng/cup. Bovine serum albumin, bovine γ-globulin, and mouse IgG (blocker substances for heterophilic interference), TRIS buffer, and <0.1% sodium azide.

The AQT90 FLEX is a cartridge-based immunoassay analyzer, based on time-resolved fluorescence using a europium (Eu) chelate as the fluorescent label and was previously cleared under k112161.

The modifications made to the AQT90 FLEX system in the current submission are outlined below:

- System clean has been updated to implement semi-automated system clean using two new accessories: a blank cartridge and cleaning solution tubes and the needle used in the cup wash has been shortened.
- Algorithm used to determine hematocrit value has been updated.
- Flash lamp in detection system has been changed to a new flash lamp.
- The filter, which is located in the liquid pathway after the cup washing step, has been removed.
- Test cartridge and CAL cartridge foil is now pre-laser cut on one side of the foil instead of both sides.
- Recombinant streptavidin which is chemically identical to the old native streptavidin used is now from a new supplier. Streptavidin is used to bind capture antibody onto the cup surface.

J. Substantial Equivalence Information:

1. Predicate device name(s):

Predicate name	510(k) number
AQT90 FLEX Myo Test	k112161
AQT90 FLEX CKMB Test Kit	k120326
AQT90 FLEX analyzer	k112161

2. Comparison with predicate:

AQT90 FLEX Myo Test Kit:

Similarities and Differences		
Item	**Predicate device** AQT90 FLEX Myo Test (k112161)	**Candidate device** AQT90 FLEX Myo Test Kit (k163462)
Intended use	AQT90 FLEX Myo Test is an *in vitro* diagnostic assay for the quantitative determination of myoglobin in EDTA or lithium- heparin whole blood or plasma specimens on the AQT90 FLEX analyzer in point of care and laboratory settings. It is indicated for use as an aid in the rapid diagnosis of heart disease, e.g. acute myocardial infarction.	Same
Principle	Quantitative time-resolved fluorimetric one-step sandwich immunoassay.	Same
Traceability	Scripps M0725	Same
Reportable range	20 to 900 ng/mL	Same
Cartridge foil	Test cartridge foil is pre-laser cut on both sides of the foil	Test cartridge foil is pre-laser cut on one side of the foil

AQT90 FLEX CKMB Test Kit:

AQT90 FLEX CKMB Test Kit		
Item	**Predicate device** AQT90 FLEX CKMB Test Kit, (k120326)	**Candidate device** AQT90 FLEX CKMB Test Kit (k163462)
Intended use	AQT90 FLEX CKMB Test is an *in vitro* diagnostic assay for the quantitative determination of creatine kinase isoform MB in EDTA or lithium-heparin whole blood or plasma specimens on the AQT90 FLEX analyzer in point of care and laboratory settings. It is intended for use as an aid in the diagnosis of myocardial infarction.	Same

Principle	Quantitative time-resolved fluorimetric one-step sandwich immunoassay	Same
Traceability	ERM-AD455/IFCC	Same
Reportable range	1.5 to 300 ng/mL	Same
Cartridge foil	Test cartridge foil is pre-laser cut on both sides of the foil	Test cartridge foil is pre-laser cut on one side of the foil

Analyzer

Similarities and Differences		
Item	**Predicate device** AQT90 FLEX analyzer **(k112161)**	**Candidate device** AQT90 FLEX analyzer **(k163462)**
Intended use	The AQT90 FLEX analyzer is an immunoassay instrument based on the quantitative determination of time-resolved fluorescence to estimate the concentrations of clinically relevant markers on whole-blood and plasma specimens to which a relevant anticoagulant has been added. It is intended for use in point of care and laboratory settings.	Same
System cleaning	System cleaning using customer prepared cleaning sample and test cup	Semi-automated system cleaning using cleaning tube from cleaning solution tubes and blank cup from blank cartridge

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

- CLSI EP5-A3, Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline—Third Edition
- CLSI EP6-A, Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline
- CLSI EP9-A3, Measurement Procedure Comparison and Bias Estimation Using Patient Samples; Approved Guideline—Third Edition
- CLSI EP17-A2, Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline—Second Edition

L. Test Principle:

The AQT90 FLEX is a cartridge-based immunoassay analyzer, based on time-resolved fluorescence using a europium (Eu) chelate as the fluorescent label. The test receptacles for the assay are test cups, which contain the antibodies used for capture of the analyte, and the Eu chelate labeled antibodies used to trace the captured analyte. The sample is added to the test cup together with assay buffer. The cup is then incubated to allow formation of the immuno-complex, and subsequently washed to remove unbound antibodies and sample material. Finally, the cup is exposed to excitation light, and after a delay the emitted light generated by the fluorescent label is measured by single photon counting. The total count is then compared to an assay calibration curve to obtain a quantitative measurement of the analyte's concentration in the sample.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. Precision/Reproducibility:

Precision studies were performed for both the Myo Test Kit and the CKMB Test Kit using whole blood and plasma samples on the AQT90 FLEX system in accordance with the CLSI Guideline EP5-A3.

1. Myo Test Kit:
   In the whole blood precision study, three lithium heparin whole blood samples with different myoglobin concentrations were measured within one day by performing five runs testing five replicates of each sample for a total of 25 measurements per sample. One analyzer and one Myo Test Kit lot were used. One of the samples was a native specimen (L2), one was a diluted native specimen (L1) and one was spiked with antigen (L3).

   Myoglobin whole blood precision results (n=25):

Sample	Mean (ng/mL)	Within run		Between Run		Total	
		SD	%CV	SD	%CV	SD	%CV
L1	57	1.30	2.3	0.00	0.0	1.3	2.3
L2	92	2.57	2.8	0.93	1.0	2.73	3.0
L3	622	14.1	2.3	4.94	0.8	15.0	2.4

   In the plasma precision study, three lithium heparin plasma pools (two native and one antigen spiked plasma specimen pool) were measured across 20 test days, twice a day in duplicate for a total of 80 measurements per sample. One analyzer and one Myo Test Kit lot were used.

Myoglobin plasma precision results (n=80):

Sample	Mean (ng/mL)	Within Run		Between Run		Between Day		Total	
		SD	%CV	SD	%CV	SD	%CV	SD	%CV
L1	53	1.0	2.0	0.47	0.9	0.00	0.0	1.1	2.1
L2	95	1.9	2.0	0.00	0.0	0.84	0.9	2.1	2.2
L3	586	13	2.2	0.00	0.0	0.00	0.0	13	2.2

2. CKMB Test Kit:
In the whole blood precision study, three lithium-heparin whole blood samples with different CKMB concentrations were measured within one day by performing five runs testing five replicates of each sample for a total of 25 measurements per sample. One analyzer and one CKMB Test Kit lot were used. Level one (L1) was a diluted native sample, level 2 and 3 (L2 and L3) were native samples spiked with antigen.

CKMB whole blood precision results (n=25):

Sample	Mean (ng/mL)	Within Run		Between Run		Total	
		SD	%CV	SD	%CV	SD	%CV
L1	2.6	0.13	4.8	0.00	0.0	0.13	4.8
L2	14	0.5	3.5	0.49	3.4	0.70	4.9
L3	204	6.9	3.4	0.00	0.0	6.9	3.4

In the plasma precision study three lithium heparin plasma pools (one native pool, one native pool spiked with patient specimen and one native pool spiked with antigen) were measured across 20 test days, twice a day in duplicate for a total of 80 measurements per sample. One analyzer and one CKMB Test kit lot were used.

CKMB plasma precision results (n=80):

Sample	Mean (ng/mL)	Within Run		Between Run		Between Day		Total	
		SD	%CV	SD	%CV	SD	%CV	SD	%CV
L1	2.3	0.08	3.5	0.026	1.1	0.00	0.0	0.084	3.7
L2	8.4	0.21	2.5	0.083	1.0	0.088	1.0	0.24	2.8
L3	209	3.9	1.9	1.4	0.7	1.8	0.9	4.6	2.2

b. Linearity/assay reportable range:

Linearity studies were conducted for both the Myo Test Kit and the CKMB Test Kit using whole blood and plasma samples on the AQT90 FLEX system according to CLSI guideline EP6-A.

1. Myo Test Kit :
A linearity study was performed with lithium heparin whole blood and lithium heparin plasma samples. A linearity series with a total of 11 sample levels were prepared by serially diluting a high concentration sample with a low concentration

sample. The samples were measured in replicates of ten using one MyoTest Kit lot and one analyzer during one day. The measured mean myoglobin concentrations for each sample type were as follows:

Whole blood: 12.9, 15.6, 34.0, 70.8, 144.4, 275.9, 467.2, 682.4, 897.5, 1148.6, and 1208.3 ng/mL

Plasma: 15.4, 17.2, 31.4, 59.2, 116.5, 224.4, 375.9, 550.5, 738.5, 1045.8, and 1052.3 ng/mL

The second order fit was significant for whole blood, and the third order fit was significant for plasma. The non-linearity degree (%) was calculated to evaluate linearity. The results showed that the deviation from linearity did not exceed 10% for either whole blood or plasma.

The claimed measuring range for Myo is 20 – 900 ng/mL for whole blood and plasma.

2. CKMB Test Kit:

A linearity study was performed with lithium heparin whole blood and lithium heparin plasma samples. A linearity series with a total of 11 sample levels were prepared by serially diluting a high CKMB concentration sample with a low CKMB concentration sample. The linearity series samples were measured in replicates of 10 using one Test Kit lot and one analyzer during one day. The measured mean CKMB concentrations for each sample type were as follows:

Whole blood: 1.3, 1.7, 9.0, 15.0, 21.7, 50.4, 98.8, 177.6, 252.8, 330.4, and 331.7 ng/mL

Plasma: 1.5, 1.8, 8.5, 13.1, 19.0, 42.5, 90.2, 158.5, 220.1, 289.3, and 291.2 ng/mL

The second and third order fits were not significant for whole blood, thus the whole blood assay was considered to be acceptably linear. The third order fit was significant for plasma, and the non-linearity degree (%) was calculated to evaluate linearity. The results showed that the deviation from linearity did not exceed 10% for plasma.

The claimed measuring range for CKMB is 1.5 – 300 ng/mL for whole blood and plasma.

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

Traceability:

AQT90 FLEX Myo Test Kit: The antigen material, M0725 by Scripps, was used to establish the metrological traceability chain of the AQT90 FLEX Myo assay in k112161 and remains unchanged.

AQT90 FLEX CKMB Test Kit: The antigen material, ERM-AD455/IFCC material, was used to establish the metrological traceability chain of the AQT90 FLEX CKMB assay in k120326 and remains unchanged.

d. *Detection limit:*

Limits of detection studies followed the guidelines in CLSI EP17-A2. For the limit of blank (LoB) and limit of detection (LoD) studies the sponsor set the Type I and II error risks to 5 %.

LoB: The LoB study was performed by measuring four blank samples with five replicates on three days using two test kit lots and two AQT90 FLEX analyzers (one lot/analyzer). The total number of measurements per test kit lot across all samples and days was 60 and a nonparametric method was used.

LoD and LoQ: The study was performed with lithium heparin whole blood and lithium heparin plasma samples. Ten samples per matrix were measured using two test kit lots and two AQT90 FLEX analyzers (one lot/analyzer). Each sample was measured in 45 replicates per lot.

The LoD was calculated using the estimated LoB and the SD_{total} of the low concentration samples.

To determine the LoQ, a power function was fit to the concentration versus CV_{total} plot using data from all samples. For the Myo Test Kit, the intersection of this fit and 10% CV_{total} was used to determine the LoQ. For the CKMB Test Kit, the intersection of this fit and the 20% CV_{total} was used to determine the LoQ.

The results for the Myo Test Kit are summarized below:

	Whole Blood (ng/mL)	Plasma (ng/mL)
LoB	0.020	0.020
LoD	0.058	0.044
LoQ	0.35	0.22

The LoB, LoD and LoQ claims for the Myo Test Kit in the package insert are: 0.5 ng/mL, 1.0 ng/mL and 1.0 ng/mL respectively.

The measuring range of the Myo test is 20 – 900 ng/mL.

The results for the CKMB Test Kit are summarized below:

	Whole Blood (ng/mL)	Plasma (ng/mL)
LoB	0.076	0.076
LoD	0.21	0.15
LoQ	1.0	0.21

The LoB, LoD and LoQ claims for the CKMB Test Kit in the package insert are: 0.5 ng/mL, 1.0 ng/mL and 1.0 ng/mL respectively.

The measuring range of the CKMB test is 1.5 to 300 ng/mL.

e. Analytical specificity:

Potential interference of the Myo Test Kit with common endogenous and exogenous substances were evaluated in k112161 and the claims are unchanged.

Potential interference of the CKMB Test Kit with common endogenous and exogenous substances were evaluated in k120326 and the claims are unchanged.

f. Assay cut-off:

Not applicable.

2. Comparison studies:

a. Method comparison with predicate device:

Method comparison studies were conducted in accordance with the CLSI guideline EP09-A3. The studies were conducted in-house. One Myo Test Kit lot and one CKMB Test Kit lot were used for each method comparison study, respectively. Lithium heparin plasma samples were run in duplicate using two candidate AQT90 FLEX analyzers with modified software and modified reagent and two predicate AQT90 FLEX analyzers with unmodified software and the original reagent. The first data set of the duplicate runs was used in the regression analysis.

1. Myo Test Kit: a total of 103 native lithium heparin plasma samples were tested for the method comparison study. The results ranged from 26 to 897 ng/mL. The result of the regression analysis is shown below.

   Passing-Bablok regression: $y = 1.01x – 0.14$, $r^2 = 1.00$

2. CKMB Test Kit: a total of 107 lithium heparin plasma samples (including 5 spiked samples) were tested for the method comparison study. The results ranged

from 1.5 to 296 ng/mL. The result of the regression analysis is shown below.

Passing-Bablok regression: $y = 0.99x – 0.18$, $r^2 = 1.00$

b. Matrix comparison:

A matrix comparison study was performed to validate the interchangeable use of four matrices when analyzing Myo and CKMB on the AQT90 FLEX system: EDTA whole blood and plasma and lithium heparin whole blood and plasma. One Myo Test Kit lot and one CKMB Test Kit lot were used in the study.

1. Myo study: A matrix comparison study was perfomed by testing a total of 127 native sample sets with myoglobin values spanning the measuring range (22 to 892 ng/mL). Passing-Bablok regression analyses were performed and the results of these studies are shown below:

   LiHep plasma (y) = 0.99 LiHep WB (x) - 1.0 (n= 125; r^2= 1.0)
   EDTA plasma (y) = 0.96 EDTA WB (x) - 1.4 (n= 125; r^2= 1.0)
   EDTA WB (y) = 1.01 LiHep WB (x) + 0.8 (n= 127; r^2= 1.0)
   EDTA plasma (y) = 0.99 LiHep plasma (x) + 0.2 (n= 124; r^2= 1.0)
   EDTA WB (y) = 1.03 LiHep plasma (x) + 1.6 (n= 125; r^2= 1.0)

2. CKMB study: A matrix comparison study was performed by testing a total of 112 sample sets (105 native and 7 spiked). The sample CKMB concentration spanned the measuring range (1.5 to 297 ng/mL). Passing-Bablok regression analyses were performed and the results of these studies are shown below:

   LiHep plasma (y) = 0.99 LiHep WB (x) + 0.01 (n= 106; r^2= 1.0)
   EDTA plasma (y) = 0.99 EDTA whole blood (x) - 0.02 (n= 104; r^2= 1.0)
   EDTA WB (y) = 1.02 LiHep WB (x) + 0.01 (n= 103; r^2= 1.0)
   EDTA plasma (y) = 1.01 LiHep plasma (x) - 0.04 (n= 101; r^2= 1.0)
   EDTA WB (y) = 1.03 LiHep plasma (x) - 0.02 (n= 104; r^2= 1.0)

3. <u>Clinical studies</u>:

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 expected values for the Myo test kit were established in k112161 and the claims remain unchanged. The 97.5th percentile was determined to be 75 ng/mL for women and 142 ng/mL for men.

The expected values for the CKMB test kit were established in k120326 and the claims are unchanged. The 97.5th percentile was determined to be 6.9 ng/mL for women and 11 ng/mL for men.

N. Instrument Name:

AQT90 FLEX analyzer

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 __X__ or No _____

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 from the barcode on the blood collection tube. The code is read automatically by the analyzer.

4. Specimen Sampling and Handling:

   Blood is drawn into a blood collection tube. The blood collection tube is placed directly in the analyzer. A volume of sample is automatically drawn from the tube through its rubber seal. The closed tube is discarded and the used immunoassay cup is discarded into a closed waste bin in the analyzer.

5. Calibration:

   The analyzer can be automatically calibrated by means of calibration cartridges at the time of test cartridge lot change.

6. Quality Control:

   AQT FLEX LQC Multi-CHECK, Levels 1, 2 and 3 (cleared in k112161).

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

Not applicable.

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 a substantial equivalence decision.