510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY

A. 510(k) Number:

k103555

B. Purpose for Submission:

New submission

C. Measurand:

Platelet aggregation

D. Type of Test:

Platelet aggregometer assays: ADPtest (10 μM ADP) and ASPItest (0.5 mM Arachidonic Acid)

E. Applicant:

Verum Diagnostica GmbH

F. Proprietary and Established Names:

Multiplate 5.0 aggregometer

ADPtest

ASPItest

G. Regulatory Information:

1. Regulation section:

   864.5700 – Automated Platelet Aggregation System

2. Classification:

   Class II

3. Product code:

JOZ System, Automated Platelet Aggregation

4. Panel:

   Hematology (81)

H. Intended Use:

1. Intended use(s):

   Instrument- The Multiplate 5.0 aggregometer is intended for in vitro use to measure platelet aggregation in response to Arachidonic acid or ADP in citrated whole blood samples for the qualitative assessment of platelet function.

   Reagent- The ADPtest reagent is a lyophilized preparation of adenosine-5-diphosphate for in vitro diagnostic use to measure platelet aggregation for the qualitative assessment of platelet function. For professional laboratory use only.

   Reagent- The ASPItest reagent is a lyophilized preparation of arachidonic acid (AA) for in vitro diagnostic use to measure platelet aggregation for the qualitative assessment of platelet function. For professional laboratory use only.

   Controls- For use as an assayed quality control verification of the resistance measure of impedance aggregometry.

   For Professional Use Only.

2. Indication(s) for use:

   Same as intended use.

3. Special conditions for use statement(s):

   For Prescription Use Only120

4. Special instrument requirements:

   The Multiplate 5.0 ASPItest (0.5 mM Arachidonic acid) and ADPtest (10 µM ADP) are to be run on the Verum Multiplate 5.0 whole blood aggregometer.

I. Device Description:

The Multiplate 5.0 aggregometer is a platelet aggregometer for the analysis of platelet function in whole blood. It provides a five channel aggregometer and an integrated computer system with associated software and is connected to a computer screen, keyboard, mouse, and an electronic pipette.

Included with the aggregometer are reagents for ADP or Arachidonic acid assays (ADPtest or ASPItest reagents respectively). These reagents activate platelets through specific platelet membrane receptor/signal transduction pathways and are therefore, used for determination of platelet function or alterations in function.

J. Substantial Equivalence Information:

1. Predicate device name(s):

   Chrono-Log Whole Blood Lumi-Aggregometer

2. Predicate 510(k) number(s):

   k050265

3. Comparison with predicate:

Similarities		
Item	Device	Predicate k050265
Intended Use	The Multiplate 5.0 aggregometer is intended for in vitro use to measure platelet aggregation in reponse to Arachidonic acid or ADP in citrated whole blood samples for the qualitative assessment of platelet function	For in-vitro diagnostic use for measuring platelet aggregation and ATP secretion in whole blood or platelet rich plasma.
Matrix	Citrated (3.2%) whole blood	Citrated (3.2 and 3.8%) whole blood and Platelet Rich Plasma
Test Method	Platelet aggregation	Same, predicate also measures ATP secretion
Principle of Operation	Electrical impedance	Same
Assay type	ADP or Arachidonic Acid	Same

Differences		
Item	Device	Predicate
Reported Units	Units (U)	Ohms (Ω) for whole blood Percent (%) for PRP Nanomole (nM) for ATP release
Method of Reporting	Software utilized for data management	Alternative reporting by connection to a strip chart recorder

Differences		
Item	Device	Predicate
Number of Channels	5 channels	2 or 4 channels
Sensor units per channel	One per channel	Two per channel
Controls	Liquid control	None

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

Format for Traditional and Abbreviated 510(k)s-Guidance for Industry and FDA Staff

510(k) Submissions for Coagulation Instruments- Guidance for Industry and FDA Staff

In Vitro Diagnostic Devices: Guidance for the Preparation of 510(k) Submissions

General Principles of Software Validation; Final Guidance for Industry and FDA Staff

Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices- Guidance for Industry and FDA Staff

H58-A Platelet Function Testing by Aggregometry; Approved Guideline

L. Test Principle:

The principle of measurement of the Multiplate device is electrical impedance. An electrical current passes through individual sets of electrodes. When the electrodes come into contact with a whole blood sample platelets bind to and cover the electrodes in a small monolayer. As the platelets become activated after exposure to a specific platelet agonist, the platelets strongly adhere to the electrodes and begin to aggregate. An increase in the number of platelets adhering to the electrodes increases the resistance (impedance) between the pair of electrodes. The Multiplate software plots these changes as a curve. The instrument transforms the measured signal into units (U), which are dependent on the change of resistance. The aggregation is plotted against the time and the area under the measuring curve is expressed as units (U).

M. Performance Characteristics (if/when applicable):

1. <u>Analytical performance:</u>

   a. Precision/Reproducibility:

   Donor samples containing low (<34U for ADP and <32U for AA), medium

(between 34 and 52U for ADP and between 32 and 48U for AA) and high (>52U for ADP and >48U for AA) platelet function levels were tested with three lots of reagents, using three different devices and two different operators. For each configuration, samples were measured in duplicate. The experiment was repeated for 10 days for high and medium platelet function level samples. Low platelet function samples were repeated for 5 days.

The percent positive and negative agreement for the ADPtest and ASPItest at low and high level platelet function samples was 100%. At medium platelet levels, the following observations were made:

ADPtest- The measurements for precision were performed with freshly drawn blood from donors, tested with three different lots of reagent, using three different devices, and two different operators. For each configuration two replicates were measured. The experiment was repeated for a minimum of five days with a new blood draw on each day. Samples from one donor each with high, medium, and low platelet function levels were tested. Agreement for the high and low platelet function level samples was 100% for device and lot variabilities. Lot-to-lot variability with medium platelet function levels around the cut-off determined a mean of 15.7 (15-17) for samples determined to have decreased platelet function level and 43.7 (43-45) for samples which exhibit normal platelet function. Comparably, the mean observations for the device variability study were 16.3 (11-24) for samples with decreased platelet function, and 43.7 (36-49) for normal samples. The repeatability study showed similar results as the reproducibility study.

ASPItest- The measurements for precision were performed with freshly drawn blood from donors, tested with three different lots of reagents, using three different devices, and two different operators. For each configuration two replicates were measured. The experiment was repeated for a minimum of five days with a new blood draw on each day. Samples from one donor each with at high, medium, and low platelet function levels were tested. Agreement for the high and low platelet function level samples was 100% for device and lot variabilities. Lot-to-lot variability with medium platelet function levels around the cut-off determined a mean of 28 (23-34) for samples determined to have decreased platelet function level and 32 (26-37) for samples which exhibit normal platelet function. Likewise, the mean observations for device variability study were 28 (22-37) for samples with decreased platelet function, and 32 (23-38) for normal samples. The repeatability study showed similar results as the reproducibility study.

b. Linearity/assay reportable range:

Increasing concentrations of platelet function antagonists (Aspirin for the Arachidonic acid assay and Thienopyridine for the ADP assay) were added to blood samples from healthy donors prior to measurement. The linear range

was determined by linear regression.

Platelet agonist	Platelet antagonist	Linear Range
Arachidonic acid	Aspirin	20-61 U
ADP	P2Y12 receptor antagonist (Thienopyridine)	25-56 U

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

Controls - The control material that is available for the Verum Multiplate 5.0 aggregometer consists of two liquids of different ionic strengths. The liquid quality control is an artificial quality control to ensure the quality of the electronic parts and sensors of the Multiplate system by evaluating the resistance measurement of the system. Because the controls are used for a functional test, they do not contain a specific analyte. Rather, mixing of the 2 controls at varying proportions provides two distinct levels of resistance that are representative of two distinct ranges or measurements on the Verum Multiplate system.

Expected Values - Value assignment for the liquid control material is performed by comparison testing at 11 sites for a total of 200 measurements per control, assessed as amplitude of the electrical signal produced by the control, expressed in Amplitude Units (AU). In accordance with CLSI guideline C28-A3c, a reference range is established using the inner 90% confidence interval.

Control Level 1	
Lower Limit (AU)	50.6721
90% CI (AU)	48.7624-52.5418
Upper Limit (AU)	75.1331
90% CI (AU)	73.1240-77.0471
Control Level 2	
Lower Limit (AU)	101.2910
90% CI (AU)	99.0841-103.3680
Upper Limit (AU)	142.8217
90% CI (AU)	140.3830-145.2971

Results were rounded to the next full integer. Based on the CI limits, acceptable values for control measurements were set at 50-75 AU for level 1 and 100-140 AU for level 2. Each new lot of liquid control material is tested and must meet established performance values and pass accelerated stability testing.

Stability claims - Stability of the lyophilized reagents, frozen reagents, reconstituted reagents, controls and test cells was determined. The shelf life

stability of the control material was established by performing accelerated and real-time stability studies. Expiration dates are assigned based on real time stability. All test passed the acceptance criteria of a mean difference of claimed stability time point and t=0 of $\leq$ 12%.

Reagent stability

	Storage Condition	No. of samples at t=0	No. of samples at t=claimed timepoint	Claimed stability
Lyophilized ADPtest and ASPItest reagent	2-8°C	5	10	2 years
Frozen ADPtest andASPItest reagent	-20°C	10	10	4 weeks
Thawed ADPtest and ASPItest reagent	Room Temperature (RT)	5	5	24 hours

Salt solution stability

	Storage Condition	No. of samples at t=0	No. of samples at t=claimed timepoint	Claimed stability
NaCl/$CaCl_2$	2-8°C	4	8	1 year

Control stability

	Storage Condition	No. of samples at t=0	No. of samples at t=claimed timepoint	Claimed stability
Shelf life- liquid controls	2-8°C	25	5	2 years
Open vial- liquid controls	RT	25	5	24 hours

Test cell stability

	Storage Condition	No. of samples at t=0	No. of samples at t=claimed timepoint	Claimed stability
Shelf life- test cells	RT	10	10	14 months

d. Detection limit:

Not applicable

e. Analytical specificity:

Not applicable

f. Assay cut-off:

260 healthy volunteers with no known bleeding disorders who reported to have abstained from intake of anti-platelet agents were tested with the Verum Multiplate 5.0 aggregometer Arachidonic acid and ADP assays in three centers. One measurement was omitted as outlier. The reference intervals were calculated as the inner 90% confidence interval. Results are summarized in the table below:

Test	No. of Measurements	Mean (U)	Standard Deviation (U)	5th Percentile (U)	95th Percentile (U)	Reference Interval (U)
Arachidonic acid (0.5mM)	260	63.4	14.8	40	91	40-91
ADP (10µM)	259	67.1	14.3	43	92	43-92

The ranges for normal and abnormal platelet function are therefore defined as follows:

Assay	Normal platelet function	Abnormal platelet function
ADPtest	43-92 U	< 43 U
ASPItest	40-91 U	< 40 U

2. Comparison studies:

a. Method comparison with predicate device:

Whole blood samples from adult patients suspected of platelet dysfunction were collected at one EU and two U.S. clinical sites. Samples were measured in singlicate using the Chrono-Log and Multiplate assay ADP and Arachidonic Acid assays. Using the previously determined cut-offs, samples were determined to have normal or abnormal platelet function. The positive and negative percent agreements of the Multiplate to its predicate Chrono-Log were calculated.

Arachidonic Acid		Chrono-Log		
		Normal	Abnormal	Total
Multiplate	Normal	91	28	119
	Abnormal	0	52	52
	Total	91	80	171

ADP		Chrono-Log		
		Normal	Abnormal	Total
Multiplate	Normal	38	60	98
	Abnormal	3	70	73
	Total	41	130	171

	Arachidonic Acid		ADP	
	Positive Percent Agreement	Negative Percent Agreement	Positive Percent Agreement	Negative Percent Agreement
Agreement	100%	65%	93%	54%
95% Confidence Interval	[96%, 100%]	[54%, 75%]	[81%, 97%]	[45%, 62%]

b. Matrix comparison:

Not applicable.

3. Clinical studies:

a. Clinical Sensitivity and Specificity:

The evaluation of the platelet function status (normal/abnormal) via the Multiplate 5.0 aggregometer was compared to the clinical assessment of a three member adjudication panel using the patient clinical history. To this end, 260 patients suspected of platelet dysfunction were tested at three clinical sites using the Verum Multiplate 5.0 or the predicate device using the ADP and Arachidonic Acid reagents. The presence of normal or abnormal platelet function was determined using the cut-off of <43U for ADPtest and <40U for ASPItest. Due to restricted access to patient data through the local IRB at one site, the patient history files (including laboratory results, clinical history, clinical procedures, demographic data, etc.) of 171 study patients were further assessed by 2 adjudicators for presence of abnormal platelet function based on the information in each subject's clinical history. In case of disagreement, a third panel member made the final determination. Patient sample histories were numbered sequentially and no identifiers allowed for patient identification or identification of the clinical testing site.

	Arachidonic Acid		ADP	
	Sensitivity	Specificity	Sensitivity	Specificity
Multiplate	93%	67%	59%	80%
95% Confidence Interval	[85%, 97%]	[44%, 84%]	[46%, 70%]	[63%, 90%]
Predicate Device	88%	67%	41%	87%
95% Confidence Interval	[78%, 93%]	[44%, 84%]	[30%, 54%]	[70%, 95%]

c. Other clinical supportive data (when a. is not applicable):

Not applicable.

4. Clinical cut-off**:**

Assay	Normal platelet function	Abnormal platelet function
ADPtest	43-92 U	< 43 U
ASPItest	40-91 U	< 40 U

Expected values/Reference range:

Test	No. of Measurements	Mean (U)	Standard Deviation (U)	5^{th} Percentile (U)	95^{th} Percentile (U)	Reference Interval (U)
ASPItest (0.5mM Arachidonic acid)	260	63.4	14.8	40	91	40-91
ADPtest (10µM ADP)	259	67.1	14.3	43	92	43-92

N. Instrument Name:

Verum Multiplate 5.0

O. System Descriptions:

1. Modes of Operation:

The instrument is semi-automated. The software manages data collection.

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:

   A patient ID can be manually assigned using the patient ID option of the program menu.

4. Specimen Sampling and Handling:

   300 µL each of $NaCl/CaCl_2$ diluent solution for the ADPtest or NaCl diluent for the ASPItest and the citrated whole blood sample are manually pipetted into the test cell.

5. Calibration:

   Not applicable.

6. Quality Control:

   The Multiplate analyzer is based on the detection of the change of electrical resistance during platelet aggregation. Two controls (solution 1 and 2) of different ionic strengths (50-75 AU and 100-140 AU respectively) are included as quality control material. An internal electronic quality control check is available to ensure electrical system performance.

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 substantial equivalence decision.