

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

A. 510(k) Number:

k083878

B. Purpose for Submission:

Clearance of a new device

C. Measurand:

Lupus anticoagulant

D. Type of Test:

Dilute venom clotting assay

E. Applicant:

R² Diagnostics, Inc.

F. Proprietary and Established Names:

LupoTek Detectin VL

LupoTek Correctin VL

PlasmaCon LA

G. Regulatory Information:

1. Regulation section:

21 CFR §864.8950, Russell viper venom reagent

21 CFR §864.5425, Multipurpose system for in vitro coagulation studies

2. Classification:

Class II

3. Product code:

GIR, Reagent, Russell viper venom

GGC, Control, plasma, abnormal

4. Panel:

81 Hematology

H. Intended Use:

1. Intended use(s):

LupoTek Detectin VL and Correctin VL test kits are qualitative tests intended to aid in the detection of lupus anticoagulants (LA) in citrated human plasma by the dilute Russell's viper venom method in professional clinical laboratories.

PlasmaCon LA is intended for use as an LA positive, abnormal quality control plasma to monitor the performance of diagnostic assays, performed in professional clinical laboratories, for the presence of lupus anticoagulants in citrated plasma.

2. Indication(s) for use:

Same as Intended Use

3. Special conditions for use statement(s):

For prescription use only.

4. Special instrument requirements:

Not applicable

I. Device Description:

LupoTek Detectin VL and LupoTek Correctin VL use Vipera lebetina venom rather

than *Vipera russelli* (Russell’s Viper) venom in the dRVVT assay for lupus anticoagulant. LupoTek DetecTin is a lyophilized reagent containing a low concentration of phospholipid, anti-heparin agents, calcium, buffers, stabilizers and a dye. LupoTek DetecTin VL is available in 2 mL vials. LupoTek CorrecTin is a lyophilized reagent containing a high concentration of phospholipid, anti-heparin agents, calcium, buffers, stabilizers and a dye. LupoTek CorrecTin is available in 1 mL vials.

PlasmaCon LA is a lyophilized reagent prepared from citrated plasma from known LA donors and normal donors and contains buffer and stabilizers.

J. Substantial Equivalence Information:

1. Predicate device name(s):
 STA[®]-Staclot[®] DRVV Screen and STA[®]-Staclot[®] DRVV Confirm
 American Diagnostica LATrol Abnormal Control
2. Predicate 510(k) number(s):
 k061805
 k935254
3. Comparison with predicate:

Similarities		
Item	Device	Predicate
	LupoTek DetecTin VL & LupoTek CorrecTin VL	STA [®] -Staclot [®] DRVV Screen & DRVV Confirm
Intended Use	LupoTek DetecTin VL and CorrecTin VL test kits are qualitative tests intended to aid in the detection of lupus anticoagulants (LA) in citrated human plasma by the dilute Russell’s viper venom method in professional clinical laboratories.	Intended for the detection of lupus anticoagulants (LA) in plasma by the dilute Russell’s viper venom method (1) performed with analyzers of the STA line suitable to these reagents.
Patient sample	Citrated human plasma	Same
Analyte	Lupus Anticoagulant	Same
Principle	LupoTek DetecTin VL is a Russell’s viper venom method performed at low concentrations of phospholipid designed as a screening reagent. LupoTek CorrecTin VL is a Russell’s viper venom method performed at high phospholipid concentration designed to neutralize the LA and corrects the clotting time.	STA [®] -Staclot [®] DRVV Screen is a Russell’s viper venom method performed at low concentrations of phospholipid to screen test plasma. STA [®] -Staclot [®] DRVV Confirm is a Russell’s viper venom method performed at higher phospholipid concentration to neutralize the LA present in the test plasma.

Differences		
Item	Device	Predicate
	LupoTek DetecTin VL & LupoTek CorrecTin VL	STA [®] -Staclot [®] DRVV Screen & DRVV Confirm
Venom source	Vipera lebetina	Vipera russelli
Reconstituted stability	24 hr - 2-8°C; 8 hr - room temp	72 hr on board stability

Similarities		
Item	Device	Predicate
	PlasmaCon LA	American Diagnostica LATrol Abnormal Control & LATrol Normal Control
Intended Use	PlasmaCon LA is intended for use as an LA positive, abnormal quality control plasma to monitor the performance of diagnostic assays, performed in professional clinical laboratories, for the presence of lupus anticoagulants in citrated plasma.	Plasmas developed for use as part of daily quality control procedures for Lupus Anticoagulant (LA) testing.
Matrix	Lyophilized citrated human plasma positive for LA.	Same
Principle	The LA in the abnormal control plasma lengthens the clotting times of LA sensitive diagnostic assays.	Same
Analyte	Lupus anticoagulantA	Same

Differences		
Item	Device	Predicate
	PlasmaCon LA	American Diagnostica LATrol Abnormal Control & LATrol Normal Control
Reconstituted stability	8 hr - 2-8°C; 4 hr - room temp	8 hr - 2-8°C

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

CLSI EP5-A2, Evaluation of Precision Performance of Quantitative Measurement Methods, Approved Guideline, 2004

CLSI EP12-A2, User Protocol for Evaluation of Qualitative Test Performance Approved Guideline, 2nd Ed., 2008

CLSI C28-A2, Defining, Establishing and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline, 2004

CLSI H21-A5 Collection, Transport and Processing of Blood Samples for Testing Plasma-Based Coagulation Assays and Molecular Hemostasis Assays; Approved Guideline, 2008

Guidance for Industry and FDA Staff: Statistical Guidance on Reporting Results from Studies Evaluating Diagnostic Tests, 2007

L. Test Principle:

Vipera lebetina venom, like Vipera russelli (Russell’s viper) venom, directly activates Factor X without requiring Factor VII. Factor Xa in the presence of calcium, phospholipid, and Factor V/Va will activate prothrombin to thrombin. Once present, thrombin will cleave fibrinogen to fibrin and the fibrin polymerizes into a solid clot.

Lupus anticoagulants are phospholipid dependent antibodies. Low levels of phospholipid are inadequate to neutralize the antibody/inhibitor, whereas, high phospholipid levels will. The low level of phospholipid in LupoTek DetecTin VL is sensitive to the present of lupus anticoagulants (LA). The high level of phospholipid in LupoTek CorrecTin VL renders the reagent insensitive to LA.

PlasmaCon LA is used to monitor testing variable in laboratory quality control system for assays sensitive to the presence of LA.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. *Precision/Reproducibility:*

Repeatability (within-run precision) studies were performed on three lots of LupoTek DetecTin VL, three lots of LupoTek CorrecTin VL and three lots of PlasmaCon LA. Results (clotting time in seconds) were determined from testing two runs per day over 20 days on the STA Compact analyzer according to CLSI EP5-A2. The mean, SD and 95% CI were calculated for each analyte. The %CV of the average clotting times was < 5% and was within the acceptance criteria of ≤ 5% for repeatability and ≤ 10% for within–device precision.

DetecTin VL

DetecTin VL lot #	Repeatability, %CV		Within-device, %CV	
	#NP2460	#LA0560	#NP2460	#LA0560
DT2330	1.7%	1.2%	3.2%	3.3%
DT2340	1.1%	1.5%	4.2%	4.4%
DT2350	1.0%	1.4%	3.3%	3.3%
Root mean sq.	1.3%	1.4%	3.6%	3.7%

CorrecTin VL

Correctin VL lot #	Repeatability, %CV		Within-device, %CV	
	#NP2460	#LA0560	#NP2460	#LA0560
CT4210	1.4%	1.5%	3.5%	2.8%
CT4220	0.9%	1.1%	4.0%	2.4%
CT4250	1.1%	1.3%	3.4%	2.6%
Root mean sq.	1.1%	1.3%	3.7%	2.6%

PlasmaCon LA

PlasmaCon LA lot#	Repeatability, %CV		Within-device, %CV	
	#DetecTin VL DT2350		#CorrecTin VL CT4250	
LA0540	1.2%	3.3%	1.0%	3.2%
LA0550	1.5%	3.1%	1.3%	2.8%
LA0560	1.4%	3.3%	1.3%	2.3%
Root mean sq.	1.4%	3.3%	1.2%	2.8%

Pooled precision data clotting time (secs)

	Detectin VL (3 lots)		CorrecTin VL (3 lots)	
	PlasmaCon N #NP2460	PlasmaCon LA #LA0560	PlasmaCon N #NP2460	PlasmaCon LA #LA0560
Mean secs	38.1	82.4	32.9	37.6
SD	1.4	5.8	3.7	4.2
95% CI	35.3 – 41.0	70.8 – 94.1	25.6 – 40.3	29.1 – 46.1

b. Linearity/assay reportable range:

Not applicable

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

The reconstituted stability of the LupoTek DetecTin VL, CorrecTin VL and PlasmaCon LA were assessed by longitudinal studies. With criteria of an age-related trend and a maximum shift of 10% of the zero point clotting time, the predicted reconstituted stability of the LupoTek DetecTin VL and CorrecTin VL reagents is 24 hours when stored at 2-8°C and 8 hours when stored at room temperature (23-25°C).

The reconstituted stability of PlasmaCon LA is 8 hours when stored at 2-8°C and 4 hours at room temperature.

d. Detection limit:

Not applicable

e. Analytical specificity:

Interference studies of LupoTek DetecTin VL and CorrecTin VL were determined on a Stago Compact analyzer. Interferent was spiked into pooled normal plasma and serial dilutions were prepared. The maximum concentration tolerated in the assay was defined as the highest concentration of interferent relative to any change in the recovered value of the based PNP clotting time was less than 10%. The maximum concentrations were:

Interferent	Maximum concentration tested	Maximum tolerated concentration
Hemolysis	500 mg/dL	500 mg/dL
Icterus	20 mg/dL	1 mg/dL
Lipemia	2,000 mg/dL triglyceride	2,000 mg/dL triglyceride
Unfractionated Heparin	2.0 U/mL	0.6 U/mL

f. *Assay cut-off:*

The cutoff for the LupoTek DetecTin VL and CorrecTin VL was determined by ROC analysis. Plasma from 122 patients was obtained from referring laboratories. These plasmas were de-identified, but a diagnosis was provided by the laboratory. For those samples diagnosed as LA positive, the samples were tested by ISTH guidelines and included two or more assays of different principles, one of which demonstrates phospholipid dependence (i.e., the ability of excess phospholipid to neutralize the antibody).

Each sample was evaluated with LupoTek DetecTin VL, CorrecTin VL, and Diagnostica Stago DRVV Screen and DRVV Confirm in R²'s laboratory.

Normalized ratios (NR) were calculated according to the following equation:

$$NR = \frac{[\text{Screen reagent time of sample}/\text{Screen reagent time of PNP}]}{[\text{Confirm reagent time of sample}/\text{Confirm reagent time of PNP}]}$$

Each sample was classified as TP, FP, TN or FN in reference to the clinical status (diagnosis) provided by the referring lab for the LupoTek and predicate reagents. Results were classified according to the following:

True positive (TP): positive by both the NR and clinical status

False positive (FP): positive by the NR but negative by clinical status

True negative (TN): negative by both the NR and clinical status

False negative (FN): negative by NR but positive by clinical status

2. Comparison studies:

a. *Method comparison with predicate device:*

Method comparison was conducted on 122 patients analyzed on the STA Compact in an internal study to determine the cutoff for the LupoTek DetecTin VL/CorrecTin VL normalized ratio. Subjects included a mix of known LA patients and other miscellaneous clinical conditions.

Another study using 155 patient samples were analyzed in three laboratories using LupoTek DetecTin VL and CorrecTin VL, and Diagnostica Stago DRVV Screen and DRVV Confirm on STA Compact analyzers. Samples were a mix of known LA patients and other miscellaneous clinical conditions.

Each sample was classified as being positive or negative for LA for each of the reagents (assays) by calculating the normalized ratio. Percent agreement was reported as follows:

Percent Agreement LupoTek reagents vs. Stago reagents				
	Pooled data	Site 1	Site 2	Site 3
PPA (95% CI)	98% (91.9-99.4%)	100% (89.3-100%)	96% (80.5-99.3%)	97% (82.8-99.4)
NPA (95% CI)	96% (88.0-98.5%)	96% (80.5-99.3%)	94% (80.9-98.4%)	100% (72.3-100%)
Overall Agreement	97%	98%	95%	97%

- b. *Matrix comparison:*
Fresh/frozen study: Patient samples were obtained from known normals (n=20) and known LA positive (n=11) donors. Each sample was tested before freezing at -70°C, and after freezing and storage, the samples were thawed in a 37°C water bath. The difference between the fresh and frozen samples was calculated and expressed in raw seconds and in percent of the fresh value. The normalized ratios (NR) were calculated for each pair of fresh sample and frozen sample and examined for any change that would result in changing the diagnosis of LA. The study found random shifts in fresh versus frozen samples; however, there was no change in NR which prompted a change in diagnosis of the 31 samples. The normalized ratios of the LA positive samples were essentially unchanged.
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):
None
4. Clinical cut-off:
Not applicable
5. Expected values/Reference range:
A study of 131 non-hospitalized healthy donors (as determined by screening with a PT and APTT) were analyzed with LupoTek DetecTin VL and CorrecTin VL on a Stago STA Compact analyzer. Samples were double centrifuged and testing was performed in duplicate. The geometric mean and standard deviation of the clotting times were calculated and the ranges were calculated as the mean \pm 2 SD.

The mean PlasmaCon LA clot times (as determined in the precision study) with DetecTin VL and CorrecTin VL were 83.7 and 39.7, respectively. Results demonstrate an abnormally prolonged clotting time with DetecTin VL and a corrected time within the normal range with CorrecTin VL.

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.