DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

U.S. Food and Drug Administration
Center for Devices and Radiological Health
Document Mail Center - WO66-G609
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002

January 3, 2013

Liposcience
c/o Suzette Warner
2500 Summer Blvd.
Raleigh, NC 27616 US

Document No: k113830
Re: k113830
Received: December 27, 2011

Categorization Notification

Regulations codified at 42 CFR 493.17 et. seq., implementing the Clinical Laboratory Improvement Amendments of 1988, require the Secretary to provide for the categorization of specific clinical laboratory test systems by the level of complexity. Based upon these regulations, the following commercially marketed test system or assay for the analyte is categorized below:

Test System/Analyte (s) : (SEE ATTACHMENT)

This complexity categorization is effective as of the date of this notification and will be reported on FDA's home page http://www.fda.gov/cdrh/clia. This categorization information may be provided to the user of the commercially marketed test system or assay as specified for the analyte indicated. It will also be announced in a Federal Register Notice, which will provide opportunity for comment on the decision. FDA reserves the right to reevaluate and recategorize this test based upon the comments received in response to the Federal Register Notice.

If you change the test system name or your company's name or if a distributor's name replaces your name, you must request another categorization by sending in the revised labeling along with a letter to FDA referencing the document number above.

If you have any questions regarding this complexity categorization, please contact

Sincerely yours,

Alberto Gutierrez, Ph.D.
Director
Office of *In Vitro* Diagnostic Device
Evaluation and Safety
Center for Devices and Radiological Health

ATTACHMENT

Document Number : k113830

Test System: Vantera Clinical Analyzer (NMR LipoProfile Test)
Analyte : LDL-Particle Number
Complexity : HIGH

Test System: Vantera Clinical Analyzer (NMR LipoProfile Test)
Analyte : HDL Cholesterol
Complexity : HIGH

Test System: Vantera Clinical Analyzer (NMR LipoProfile Test)
Analyte : Triglyceride
Complexity : HIGH

Mcdonald, Lisa *

From: Mcdonald, Lisa *
Sent: Thursday, January 10, 2013 10:29 AM
To: 'suzette.warner@liposcience.com'
Cc: DCCLetters
Subject: K113830 CLIA LETTER
Attachments: k113830.pdf

CLIA Routing Slip

Document No : k113830

Re : k113830

Division: DCTD
Branch: CRDB

Applicant: Liposcience
Contact Name: Suzette Warner
Contact Address: 2500 Summer Blvd., Raleigh, NC 27616 US
Contact Phone(s): (919) 256-1326
Contact Fax(es): (919) 256-1149
Contact Email: SUZETTE.WARNER@LIPOSCIENCE.COM
Trade Name: Vantera chinial analyzer

DMC Date Received: December 27, 2011
Division Date Received: December 29, 2011

Categorization Information

CLIA Reviewer: Elizabeth O'Keeffe [EKO]
Date Review Completed: December 5, 2012

Date Branch Concurred: 12/27/2012 RAC
Date Coordinator Concurred:
Effective Date: JAN 03 2013

Test Systems/Analytes/Grading

(See Attachment)

ATTACHMENT

Document Number : k113830

Test System : Vantera Clinical Analyzer (NMR LipoProfile Test)
Analyte : LDL-Particle Number
Complexity : HIGH [14]
Knowledge [3]; Training and Experience [2]; Reagents Preparation [1];
Operational Steps [1]; Quality Control [2];
Troubleshooting and Maintenance [3]; Interpretation and Judgment [2]
Rationale : CHEM-168

Test System : Vantera Clinical Analyzer (NMR LipoProfile Test)
Analyte : HDL Cholesterol
Complexity : HIGH [14]
Knowledge [3]; Training and Experience [2]; Reagents Preparation [1];
Operational Steps [1]; Quality Control [2];
Troubleshooting and Maintenance [3]; Interpretation and Judgment [2]
Rationale : CHEM-168

Test System : Vantera Clinical Analyzer (NMR LipoProfile Test)
Analyte : Triglyceride
Complexity : HIGH [14]
Knowledge [3]; Training and Experience [2]; Reagents Preparation [1];
Operational Steps [1]; Quality Control [2];
Troubleshooting and Maintenance [3]; Interpretation and Judgment [2]
Rationale : CHEM-168

NMR LIPOPROFILE® test

NMR *LipoProfile*® test on Vantera® Clinical Analyzer by LipoScience

For *In Vitro* Diagnostic Use Only

INTENDED USE

The *NMR LipoProfile*® test by LipoScience, used with Vantera® Clinical Analyzer, an automated NMR spectrometer, measures lipoprotein particles to quantify LDL particle number (LDL-P), HDL cholesterol (HDL-C), and triglycerides (TG) in serum and plasma using nuclear magnetic resonance (NMR) spectroscopy. LDL-P and these NMR-derived concentrations of triglycerides and HDL-C are used in conjunction with other lipid measurements and clinical evaluation to aid in the management of lipoprotein disorders associated with cardiovascular disease.

SUMMARY AND EXPLANATION

Lipoprotein (HDL, LDL, and VLDL) particles play key roles in atherogenesis and their concentrations in plasma or serum are important cardiovascular disease (CVD) risk factors. For clinical use, lipoprotein levels are traditionally estimated by measuring one or more of their lipid constituents. The cholesterol within LDL and HDL particles (LDL-C and HDL-C) is used to approximate serum or plasma LDL and HDL levels, while total plasma triglycerides approximate VLDL levels. The *NMR LipoProfile*® test by LipoScience employs a novel automated process to measure NMR signals from LDL, HDL, and VLDL particles simultaneously [1]. The detected lipoprotein signals are proportional in amplitude to the numbers of lipoprotein particles emitting the signals, enabling a calculation of their concentrations. LDL is reported in terms of particle numbers (LDL-P) providing another measure of a patient's LDL level.

Lipoproteins that interact with the arterial wall set in motion the cascade of events leading to atherosclerosis [2]. LDL is the major atherogenic lipoprotein and is identified in ATP III guidelines as the primary target of treatment for reducing coronary heart disease risk [3]. According to a report from the American Diabetes Association (ADA) and American College of Cardiology (ACC), measurement of LDL-C may not accurately reflect the true burden of atherogenic LDL particles, especially in those patients with the typical lipoprotein abnormalities of cardiometabolic risk [4]. The ADA/ACC report also states that measurements of apolipoprotein B or LDL-P may more closely quantitate the atherogenic lipoprotein load. [4] Thus, they may aid in the management of patients with elevated risk of CVD. LDL-P measured by the *NMR LipoProfile*® test by LipoScience has been shown to be a determinant of CVD risk in two prospective case-control studies [5, 6].

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510(k) Summary

LIPOSCIENCE

AUG 30 2012

A. 510(k) Number: K113830

B. Submitter Contact Information:

Submitter:
LipoScience, Inc.
2500 Sumner Boulevard
Raleigh, NC 27616
Ph: (919) 256-1326
Fax: (919) 256-1149

Contact Person:
Suzette Warner
Manager, Regulatory Affairs
LipoScience, Inc.
Ph: (919) 256-1326
Fax: (919) 256-1149
Suzette.Warner@liposcience.com

C. Device Name:

Trade Name: Vantera® Clinical Analyzer
Common Name: *NMR LipoProfile®* test on Vantera® Clinical Analyzer
Classification Names:

Instrumentation for clinical multiplex test system, 21 CFR 862.2570, Product Code NSU
Lipoprotein test system, 21 CFR 862.1475, Product Code MRR and LBS
Cholesterol test system 21 CFR 862.1175, Product Code LBS
Triglyceride test system, 21 CFR 862.1705, Product Code CDT

Panel: Clinical Chemistry (75)

D. Legally Marketed Device to which Equivalence is Claimed (Predicate Device):

NMR Profiler and *NMR Lipoprofile* test	k111516
Luminex LX 100/200 Instrument	k073506

E. Device Description:

For the Instrument

The Vantera Clinical Analyzer is a clinical laboratory analyzer that employs nuclear magnetic resonance spectroscopic detection to quantify multiple analytes in biological fluid specimens, specifically blood plasma and serum.

The Vantera Clinical Analyzer system design is divided into 3 major subassemblies: a sample handling assembly, an NMR subassembly, and an enclosure. The Vantera Clinical Analyzer control system is distributed across three separate computers:

- The Host (1U) controls user interface, data handling, results calculation, system startup and shutdown.
- The Process Control (4U) schedules and manages all activities required to process a sample, controls all hardware in the sample handling subsystem, and manages remote access to the system.
- The NMR Control Computer controls all magnet operations.

  Two of these computers are contained within the Sample Handling Subassembly (1U and 4U) and one in the NMR Subassembly (NMR Console).

For the Assay

The *NMR LipoProfile* test involves measurement of the 400 MHz proton NMR spectrum of a plasma/serum sample, deconvolution of the composite signal at approximately 0.8 ppm to produce signal amplitudes of the lipoprotein subclasses that contribute to the composite plasma/serum signal, and conversion of these subclass signal amplitudes to lipoprotein subclass concentrations. The ~0.8 ppm plasma NMR signal arises from the methyl group protons of the lipids carried in the LDL, HDL and VLDL subclasses of varying diameters. The NMR signals from the various lipoprotein subclasses have unique and distinctive frequencies and lineshapes, each of which is accounted for in the deconvolution analysis model. Each subclass signal amplitude is proportional to the number of subclass particles emitting the signal, which enables subclass particle concentrations to be calculated from the subclass signal amplitudes derived from the spectral deconvolution analysis. LDL subclass particle concentrations, in units of nanomoles of particles per liter (nmol/L), are summed to give the reported total LDL particle concentration (LDL-P). By employing conversion factors assuming that the various lipoprotein subclass particles have cholesterol and triglyceride contents characteristic of normolipidemic individuals, HDL cholesterol and triglyceride concentrations are also derived.

F. Indications for Use

For the Instrument

The Vantera Clinical Analyzer is an automated laboratory test analyzer which measures the 400 MHz proton nuclear magnetic resonance (NMR) spectrum of clinical samples to produce signal amplitudes, converting these signal amplitudes to analyte concentration. The device includes a 400 MHz NMR spectrometer and software to analyze digitized

spectral data. This instrumentation is intended to be used with NMR based assays to detect multiple analytes from clinical samples by technologists trained in laboratory techniques, procedures and on the use of the analyzer.

For the Assay
The *NMR LipoProfile*test, when used with the Vantera Clinical Analyzer, an automated NMR spectrometer, measures lipoprotein particles to quantify LDL particle number (LDL-P), HDL cholesterol (HDL-C), and triglycerides in human serum and plasma using nuclear magnetic resonance (NMR) spectroscopy. LDL-P and these NMR-derived concentrations of HDL-C and triglycerides are used in conjunction with other lipid measurements and clinical evaluation to aid in the management of lipoprotein disorders associated with cardiovascular disease.

G. Technological Characteristics and Substantial Equivalence:

The Vantera Clinical Analyzer is as safe and effective as the predicate device, k073506. The Vantera has similar intended use and indication for use as well as the same multi-analyte capability and the same system calibration requirement as the predicate device. The minor technological differences between the Vantera and the predicate device raise no new issues of safety or effectiveness.

Instrument Comparison Table

	Luminex LX 100/200 Instrument **(Predicate)**	***Vantera Clinical Analyzer*** **(Proposed Device)**
510(k) Number	k073506	Pending
Intended Use / Indications for Use	The Luminex LX 100/200 Instrument is a clinical multiplex test system intended to measure and sort multiple signals generated in an *In Vitro* diagnostic assay from a clinical sample. This instrumentation is used with a specific assay to measure multiple similar analytes that establish a single indicator to aid in diagnosis. The device includes a signal reader unit, raw data storage mechanisms, data acquisition software and software to process detected signals.	similar
Technology	Bead based multiplexing	Nuclear magnetic resonance
Multi-Analyte	Yes	same
Detection Method	Fluorescent	400 MHz proton NMR Spectrum
System Fluidics	Utilizes system fluidics to deliver sample to the site of sample analysis	same
Specimen Sampling and Handling	Samples are manually prepared then presented to system.	Serum/Plasma Samples are diluted onboard system
System Calibration	System calibration required	same

	***Luminex LX 100/200 Instrument* (Predicate)**	***Vantera Clinical Analyzer* (Proposed Device)**
Quality Control Checks	System level quality control checks available e.g. Classification (CON1) and reporter (CON2)	similar E.g. Signal to noise ratio – internal system check that occur during system calibration
Specimen Identification	Barcode reader entry of sample ID	same
Data Acquisition Software	Posses data acquisition software and software to process detected signals	same

Similarity to the Predicate Device (Assay)

Performance data further demonstrate that the Vantera Clinical Analyzer when used with the *NMR LipoProfile* test is as safe and effective as its predicate device, k111516. As with the predicate test, the NMR LipoProfile test on Vantera is intended for the separation and quantification of LDL-P, HDL-C and triglycerides in serum and plasma, measurements of which are used in conjunction with other lipid measurements and clinical evaluation to aid in the management of lipoprotein disorders associated with cardiovascular disease.

Assay General Attributes

	***LipoScience NMR LipoProfile®* test and NMR Profiler (Predicate)**	**Vantera® Clinical Analyzer for use with *NMR LipoProfile®* test (Proposed Device)**
510(k) Number	k111516	Pending
Intended Use / Indications for Use	The NMR LipoProfile® test, used with the NMR Profiler, an automated nuclear magnetic resonance (NMR) spectrometer, measures lipoprotein particles to quantify LDL particle number (LDL-P), HDL cholesterol (HDL-C), and triglycerides in serum and plasma using NMR spectroscopy. LDL-P and these NMR-derived concentrations of triglycerides and HDL-C are used in conjunction with other lipid measurements and clinical evaluation to aid in the management of lipoprotein disorders associated with cardiovascular disease. This test is performed and provided as a service by LipoScience Laboratory.	similar
Patient Population	General	same
Instrument Platform	NMR Profiler	Vantera Clinical Analyzer
Specimen	Human serum and plasma	same
Analyzer	400 MHz NMR Spectrometer	same

	***LipoScience NMR LipoProfile®* test and NMR Profiler (Predicate)**	**Vantera® Clinical Analyzer for use with *NMR LipoProfile®* test (Proposed Device)**
Reagents and Materials	• NMR Diluent 1 - aqueous solution containing Na_2EDTA (5.0mM), $CaCl_2$ (1.0mM), KCL(120mM), Na_2HPO_4-$7H_20$(50mM), (50mM), pH 7.4, 6.0 M NaOH, 1.0 M HCl. • NMR WASH - Triton X-100- 0.1%v/v, Liqui Nox 0.1% v/v in Type 2 water, pH 10.0, sodium bicarbonate (anhydrous), sodium carbonate (anhydrous), 6.0 M NaOH • NMR Calibrator - aqueous solution of Trimethyl Acetate (TMA) disodium salt (15.0 mM) containing Na_2EDTA (5.0 mM), CaC_2 (3.0 mM), KCl (120 nM), D_2O 10% v/v • NMR LipoProfile Quality Control materials 1 and 2 contains two levels of pooled human serum-based control material, labeled Control 1 and Control 2, with pre-determined target ranges, containing sodium azide as a preservative.	Similar

	***LipoScience NMR LipoProfile®* test and NMR Profiler (Predicate)**	**Vantera® Clinical Analyzer for use with *NMR LipoProfile®* test (Proposed Device)**
Spectral Deconvolution Computational Process	Linear least-squares with singular value decomposition of the spectra from each specimen.	Same
Reference Range	Distribution of LDL-P Observed in Reference population – MESA	Distribution of LDL-P observed in a general apparently healthy population of men and women

We performed analytical validations to demonstrate that the *NMR LipoProfile®* test on the Vantera Clinical Analyzer is equivalent to the *NMR LipoProfile®* test on the NMR Profiler. The comparative analytical performance is found in tables below.

Analytical Performance for LDL-P

LDL-P (nmol/L)	**Vantera clinical analyzer for use with the *NMR LipoProfile* test**			**Predicate Device k111516**		
LoB	0			0		
LoD	40.7			41		
LoQ	132			157		
Measuring Range	300-3500 nmol/L			300-3500 nmol/L		
Linearity Regression	y=1.02x+7.82			y=0.99x-22.37		
Linearity R^2	0.9949			0.9979		
Within-Run Precision	**Level 1**	**Level 2**	**Level 3**	**Level 1**	**Level 2**	**Level 3**
Mean	842.6	1309.5	1837.7	908	1493	1967
SD	48.5	39.1	50.3	45.4	64.8	72.8
CV%	5.8%	3.0%	2.7%	5.0%	4.3%	3.7%
Within-Lab Precision	**Level 1**	**Level 2**	**Level 3**	**Level 1**	**Level 2**	**Level 3**
Mean	988.6	1266.7	1943.5	920.4	1508.3	1991.8
SD	48.84	32.57	63.42	70.5	67.7	84.6
CV%	5.3%	4.0%	3.9%	7.6%	4.5%	4.3%
Method Comparison	Linear regression: y=1.03x-36.60, R=0.978			Linearity Regression: y=0.98x+45.2, R=0.973		
Medical Decision Limits	No change.			1000, 1300 and 1600 nmol/L		
Interference Study	7 Endogenous and 23 Exogenous were tested. Salicyclic acid at ≥ 1.3mmol/L was determined to interfere with LDL-P and Clopidogrel hydrogensulfate at ≥ 95.7 µmol/L was determined to interfere with LDL-P			5 Endogenous and 22 Exogenous were tested, no interference was found.		
Specimen Stability	Lipotube: Refrigerated Stability: 6 days			Lipotube: Refrigerated Stability: 5 days		

Triglycerides Analytical Performance Summary

TG (mg/dL)	Vantera clinical analyzer for use with the *NMR LipoProfile* test			Predicate Device k111516		
LoB	1.1			1.4		
LoD	2.4			2.6		
LoQ	4			2.6		
Measuring Range	5			1100		
Linearity Regression	y=1.008x-0.3979			y=0.95x-12.21		
Linearity R^2	0.9999			0.999		
Within-Run Precision	**Level 1**	**Level 2**	**Level 3**	**Level 1**	**Level 2**	**Level 3**
Mean	70.1	169.2	356.1	81.0	140.6	649.5
SD	1.6	3.5	4.2	2.1	2.5	8.7
CV%	2.3%	2.1%	1.2%	2.6%	1.8%	1.3%
Within-Lab Precision	**Level 1**	**Level 2**	**Level 3**	**Level 1**	**Level 2**	**Level 3**
Mean	68.8	166.3	352.2	78.4	145.4	624.6
SD	1.59	3.92	9.36	2.8	3.7	15.4
CV%	2.3%	2.4%	2.7%	3.6%	2.6%	2.5%
Method Comparison	Linear regression: y=1.00x+0.92, R=0.998			Linear regression: y=1.00x+1.25, R=1.00		
Medical Decision Limits	No change.			Normal (<150) Borderline-High (150-199) High (200-499) Very High (≥500)		
Interference Study	7 Endogenous and 23 Exogenous were tested, no interference was found.			5 Endogenous and 22 Exogenous were tested, no interference was found except Ibuprofen may interfere with TG measurement at and above 210µg/mL.		
Specimen Stability	Lipotube: Refrigerated Stability: 6 days			Lipotube: Refrigerated Stability: 10 days		

HDL-C Analytical Performance Summary

HDL-C (mg/dL)	**Vantera clinical analyzer for use with the *NMR LipoProfile* test**			**Predicate Device k111516**		
LoB	2.7			4.3		
LoD	3.5			5.2		
LoQ	4			5.2		
Measuring Range	7-140			7-140		
Linearity Regression	y=1.049x-0.3459			y=1.004x-0.5956		
Linearity R^2	0.9961			0.9998		
Within-Run Precision	**Level 1**	**Level 2**	**Level 3**	**Level 1**	**Level 2**	**Level 3**
Mean	29.1	51.1	86.9	23.7	54.9	95.1
SD	1.17	1.43	2.29	0.5	1.0	0.9
CV%	4.0%	2.8%	2.6%	2.0%	1.9%	0.9%
Within-Lab Precision	**Level 1**	**Level 2**	**Level 3**	**Level 1**	**Level 2**	**Level 3**
Mean	28.9	50.7	85.2	23.7	56.7	96.1
SD	0.80	1.02	1.51	0.8	1.1	1.7
CV%	2.8%	2.0%	1.8%	3.3%	2.0%	1.8%
Method Comparison	Linear regression: y=1.04x-1.20, R=0.989			Linear regression: y=1.00x+0.03, R=0.999		
Medical Decision Limits	No change.			Low(<40), High(≥60)		
Interference Study	7 Endogenous and 23 Exogenous were tested, no interference was found.			5 Endogenous and 22 Exogenous were tested, no interference was found.		
Specimen Stability	Lipotube: Refrigerated Stability: 6 days			Lipotube: Refrigerated Stability: 10 days		

H. Performance Data – Non-Clinical:

Analytical Sensitivity

The analytical sensitivity of the *NMR LipoProfile* test measurements of LDL-P, HDL-C, and triglycerides was determined as the lowest concentration measurable with acceptable precision and accuracy. Limits of quantification (LoQ), Limit of Blank (LoB) and Limit of Detection (LoD) for LDL-P, HDL-C and Triglycerides following EP17-A are listed

LDL-P
Five serum pools containing very low concentration were tested in replicates of 4 for 3 days. The Limit of Quantification (LoQ) was mathematically calculated for LDL-P by plotting the %CV on the Y-axis against low concentration pools and determined to be: LoQ = 132 nmol/L.
Non-lipoprotein specimens were analyzed 60 consecutive times for 3 days. The Limit of Blank (LoB) was calculated non-parametrically for LDL-P and determined to be: LoB = 0.0 nmol/L.
Five serum pools containing very low concentration were tested in replicates of 4 for 3 days. The Limit of Detection (LoD) was calculated parametrically for LDL-P and determined to be: LoD = 40.7 nmol/L.

HDL-C
Five serum pools containing very low concentration were tested in replicates of 4 for 3 days. The Limit of Quantification (LoQ) was mathematically calculated for HDL-C by plotting the %CV on the Y-axis against low concentration pools and determined to be: LoQ = 4 mg/dL.
Non-lipoprotein specimens were analyzed 60 consecutive times for 3 days. The Limit of Blank (LoB) was calculated non-parametrically for HDL-C and determined to be: LoB = 2.7 mg/dL.
Five serum pools containing very low concentration were tested in replicates of 4 for 3 days. The Limit of Detection (LoD) was calculated parametrically for HDL-C and determined to be: LoD = 3.5 mg/dL.

Triglycerides
Five serum pools containing very low concentration were tested in replicates of 4 for 3 days. The Limit of Quantification (LoQ) was mathematically calculated for Triglycerides by plotting the %CV on the Y-axis against low concentration pools and determined to be: LoQ = 4 mg/dL.
Non-lipoprotein specimens were analyzed 60 consecutive times for 3 days. The Limit of Blank (LoB) was calculated non-parametrically for Triglycerides and determined to be: LoB = 1.1 mg/dL.
Five serum pools containing very low concentration were tested in replicates of 4 for 3 days. The Limit of Detection (LoD) was calculated parametrically for Triglycerides and determined to be: LoD = 2.4 mg/dL.

Assay Precision

Within-run precision and within-laboratory precision were determined by testing 20 replicates of three patient serum pools in the same run and in 20 different runs over 20 days. The pools were analyzed according to EP-5A. The results of this testing are summarized below:

Within-run Precision (n=20)

	Pool #1			Pool #2			Pool #3		
	Mean	**SD**	**%CV**	**Mean**	**SD**	**%CV**	**Mean**	**SD**	**%CV**
LDL-P, nmol/L	842.6	48.5	5.8	1309.5	39.1	3.0	1837.7	50.3	2.7
HDL-C, mg/dL	29.1	1.17	4.0	51.1	1.43	2.8	86.9	2.29	2.6
Triglycerides, mg/dL	70.1	1.6	2.3	169.2	3.5	2.1	356.1	4.2	1.2

Within-Laboratory Precision (n=80)

	Pool #1			Pool #2			Pool #3		
	Mean	**SD**	**%CV**	**Mean**	**SD**	**%CV**	**Mean**	**SD**	**%CV**
LDL-P, nmol/L	988.6	52.20	5.3	1266.7	50.08	4.0	1943.5	75.11	3.9
HDL-C, mg/dL	28.9	0.80	2.8	50.7	1.02	2.0	85.2	1.51	1.8
Triglycerides, mg/dL	68.8	1.59	2.3	166.3	3.92	2.4	352.2	9.36	2.7

Reproducibility

A reproducibility study was conducted in accordance to EP5-A2 at 3 sites incorporating five levels of serum panels at or around the medical decision limits. The panels were tested for 5 days, 6 runs per day, 2 replicates per run. The overall precision estimates are described below.

	LDL-P (nmol/L)				
Pool #	**1**	**11**	**7**	**3**	**9**
NMR 8001	**Panel 1**	**Panel 2**	**Panel 3**	**Panel 4**	**Panel 5**
Mean (nmol/L)	513.4	1129.4	1361.6	1957.7	3286.5
n	60	60	60	59	60
SD (nmol/L)	32.86	65.60	87.36	103.55	197.94
CV (%)	6.4	5.8	6.4	5.3	6.0
min (nmol/L)	431	988	1163	1641	2938
max (nmol/L)	573	1318	1510	2179	3636
median (nmol/L)	517	1127	1380.5	1962	3288.5
NMR 8002	**Panel 1**	**Panel 2**	**Panel 3**	**Panel 4**	**Panel 5**
Mean (nmol/L)	566.7	1260.6	1364.5	2050.7	3204.7
n	59	60	59	59	60
SD (nmol/L)	39.22	38.00	76.99	65.41	85.41
CV (%)	6.9	3.0	5.6	3.2	2.7
min (nmol/L)	457	1168	1155	1843	3036
max (nmol/L)	660	1346	1555	2176	3419
median (nmol/L)	574	1258.5	1366	2050	3197
NMR 8003	**Panel 1**	**Panel 2**	**Panel 3**	**Panel 4**	**Panel 5**
Mean (nmol/L)	479.8	1156.3	1304.4	1980.6	3153.3
n	58	60	60	60	60
SD (nmol/L)	45.00	70.60	113.21	91.78	165.47
CV (%)	9.4	6.1	8.7	4.6	5.2
min (nmol/L)	388	871	891	1671	2561
max (nmol/L)	558	1255	1491	2136	3386
median (nmol/L)	485.5	1167	1337	1999	3192
All	**Panel 1**	**Panel 2**	**Panel 3**	**Panel 4**	**Panel 5**
Mean (nmol/L)	520.2	1182.1	1343.4	1996.2	3214.8
n	177	180	179	178	180
SD (nmol/L)	52.94	82.19	97.37	96.39	165.44
95% CI (nmol/L)	47.94- 59.11	74.48-91.68	88.22- 108.66	87.31- 107.59	149.93- 184.55
CV (%)	10.2	7.0	7.2	4.8	5.1
min (nmol/L)	388	871	891	1641	2561
max (nmol/L)	660	1346	1555	2179	3636
median (nmol/L)	491	1165	1330	2006	3179

	HDL-C (mg/dL)				
Pool #	**1**	**8**	**4**	**10**	**11**
NMR 8001	**Panel 1**	**Panel 2**	**Panel 3**	**Panel 4**	**Panel 5**
Mean (mg/dL)	21.5	33.4	53.7	80.1	92.1
n	60	60	60	60	60
SD (mg/dL)	0.75	1.39	1.81	3.70	2.61
CV (%)	3.5	4.2	3.4	4.6	2.8
min (mg/dL)	20	30	49	74	87
max (mg/dL)	23	36	57	88	97
median (mg/dL)	21.5	34	54	78.5	92
NMR 8002	**Panel 1**	**Panel 2**	**Panel 3**	**Panel 4**	**Panel 5**
Mean (mg/dL)	19.4	29.2	52.3	72.9	87.5
n	59	60	60	60	60
SD (mg/dL)	0.68	1.13	1.34	1.49	1.28
CV (%)	3.5	3.9	2.6	2.0	1.5
min (mg/dL)	17	27	48	70	85
max (mg/dL)	21	31	56	76	90
median (mg/dL)	19	29	52	73	88
NMR 8003	**Panel 1**	**Panel 2**	**Panel 3**	**Panel 4**	**Panel 5**
Mean (mg/dL)	19.4	28.3	49.9	74.4	84.9
n	58	60	60	60	60
SD (mg/dL)	0.90	1.41	2.36	4.26	3.39
CV (%)	4.6	5.0	4.7	5.7	4.0
min (mg/dL)	17	24	41	66	72
max (mg/dL)	21	31	53	83	89
median (mg/dL)	19	28	50	73	86
All	**Panel 1**	**Panel 2**	**Panel 3**	**Panel 4**	**Panel 5**
Mean (mg/dL)	20.1	30.3	52.0	75.8	88.2
n	177	180	180	180	180
SD (mg/dL)	1.26	2.60	2.45	4.56	3.91
95% CI (mg/dL)	1.14- 1.41	2.35- 2.90	2.22- 2.73	4.14- 5.09	3.55- 4.36
CV (%)	6.3	8.6	4.7	6.0	4.4
min (mg/dL)	17	24	41	66	72
max (mg/dL)	23	36	57	88	97
median (mg/dL)	19	28	50	73	86

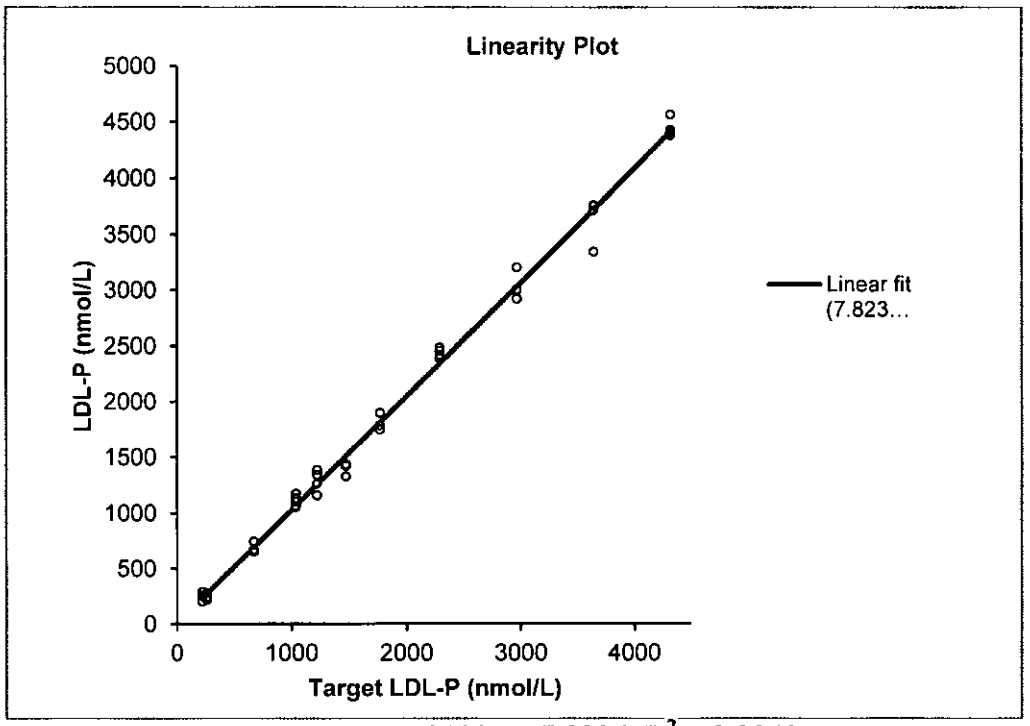
	TG (mg/dL)				
Pool #	**2**	**4**	**3**	**6**	**9**
NMR 8001	**Panel 1**	**Panel 2**	**Panel 3**	**Panel 4**	**Panel 5**
Mean (mg/dL)	66.1	70.3	133.5	153.5	343.3
n	60	60	59	60	60
SD (mg/dL)	1.84	2.15	4.35	5.92	7.09
CV (%)	2.8	3.1	3.3	3.9	2.1
min (mg/dL)	61	64	120	129	321
max (mg/dL)	69	73	141	163	356
median (mg/dL)	66	71	134	155	345
NMR 8002	**Panel 1**	**Panel 2**	**Panel 3**	**Panel 4**	**Panel 5**
Mean (mg/dL)	70.3	74.6	141.4	169.7	361.1
n	59	60	59	60	60
SD (mg/dL)	1.30	1.59	3.03	3.10	5.01
CV (%)	1.8	2.1	2.1	1.8	1.4
min (mg/dL)	68	72	131	160	341
max (mg/dL)	74	82	149	176	372
median (mg/dL)	70	74	142	170	361
NMR 8003	**Panel 1**	**Panel 2**	**Panel 3**	**Panel 4**	**Panel 5**
Mean (mg/dL)	66.5	70.4	134.3	160.9	339.8
n	60	60	60	60	60
SD (mg/dL)	2.70	3.44	4.77	7.10	18.50
CV (%)	4.1	4.9	3.5	4.4	5.4
min (mg/dL)	57	58	119	123	267
max (mg/dL)	71	74	145	169	357
median (mg/dL)	67	72	135	162	346
All	**Panel 1**	**Panel 2**	**Panel 3**	**Panel 4**	**Panel 5**
Mean (mg/dL)	67.6	71.8	136.4	161.4	348.0
n	179	180	178	180	180
SD (mg/dL)	2.76	3.21	5.41	8.66	14.99
95% CI (mg/dL)	2.50-3.08	2.91- 3.59	4.90- 6.03	7.75- 9.66	13.59- 16.72
CV (%)	4.1	4.5	4.0	5.4	4.3
min (mg/dL)	57	58	119	123	267
max (mg/dL)	74	82	149	176	372
median (mg/dL)	67	71	135	162	344

Linearity

Three serum pools were prepared from patient specimens with low, medium and high values of LDL-P, HDL-C and Triglycerides as determined by *NMR LipoProfile* test. Each were mixed and diluted in different proportions to produce eleven (for LDL-P) or Twelve (12) (TG and HDL-C) different samples with widely varying target concentrations. Mean values from analysis of four replicates of each pool were compared to the expected target values to determine the percent bias for each sample. The serum pools were analyzed according to EP6-A. Tables and regression plots of the linearity data for LDL-P, HDL-P and Triglycerides are given below:

LDL-P Measuring Range: 300-3500 nmol/L

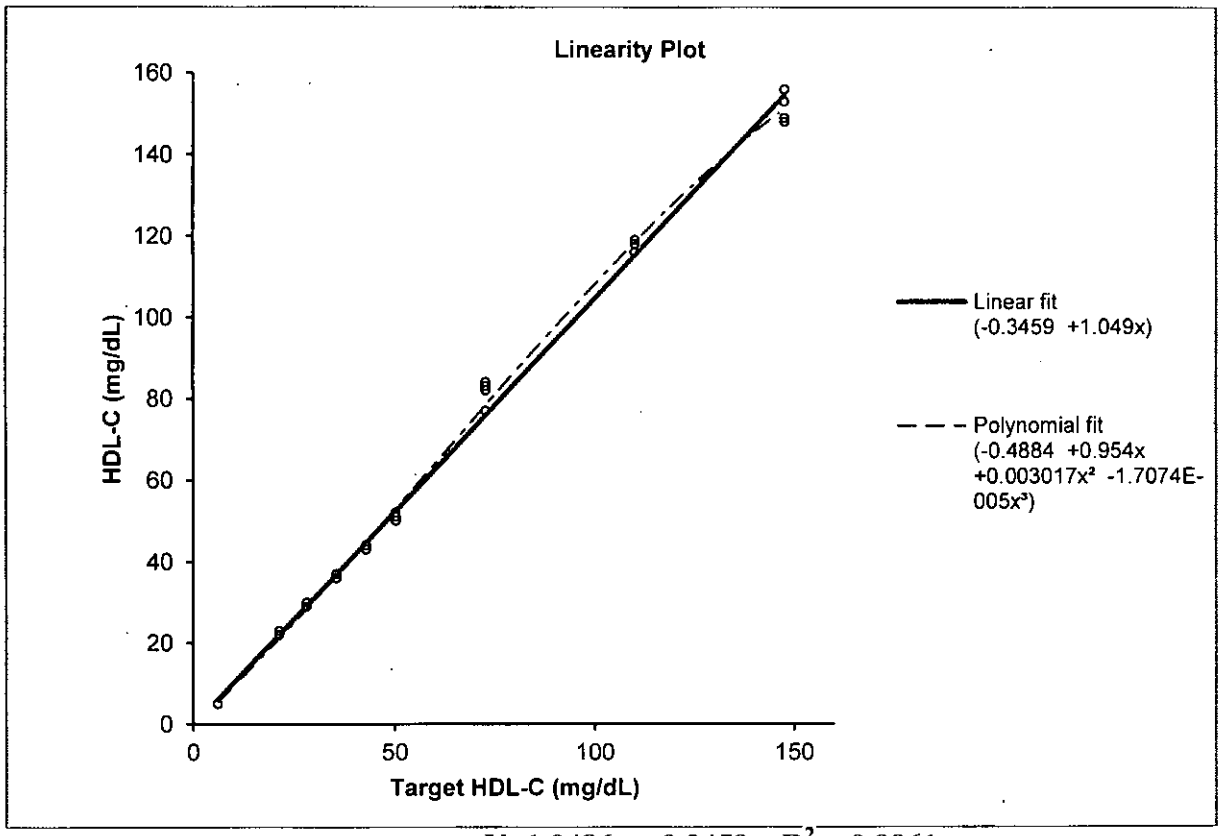
Level	1	2	3	4	5	6	7	8	9	10	11
Target value	225.4	263.375	673.75	1039.25	1222	1473.28	1770.25	2291.41	2968.22	3645.03	4321.84
Observed Mean	248.8	243.8	682.0	1115.0	1285.8	1402.3	1829.8	2437.5	3032.3	3644.3	4442.8
% Bias	10.3	-7.5	1.2	7.3	5.2	-4.8	3.4	6.4	2.2	0.0	2.8



$Y=1.0193x + 7.8226, R^2 = 0.9949$

HDL-C Measuring Range: 7-140 mg/dL

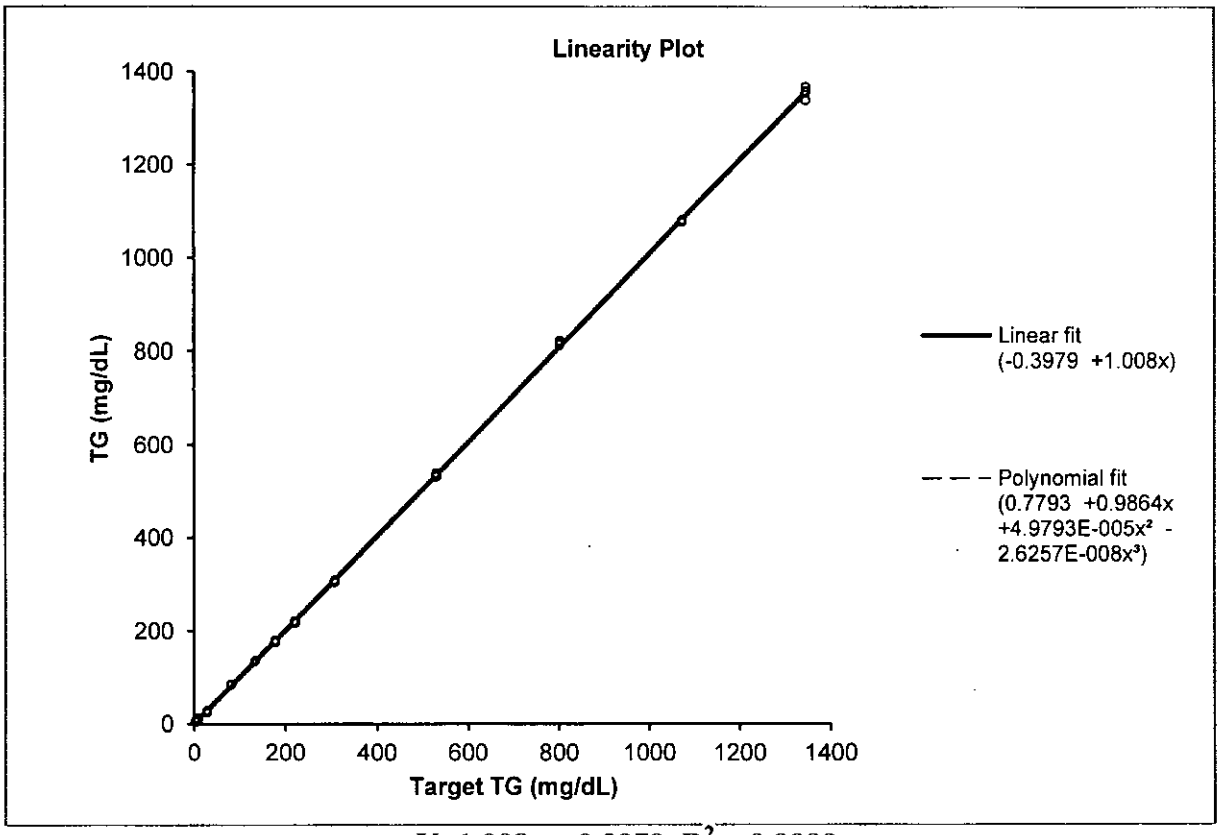
Level	1	2	3	4	5	6	7	8	9
Target value	6.13	21.44	28.19	35.56	42.94	50.31	72.75	110.25	147.75
Observed Mean	5.00	22.50	29.25	36.25	43.25	50.75	81.50	117.25	151.50
% Bias	-	5.0	3.8	1.9	0.7	0.9	12.0	6.3	2.5



$Y=1.0486x - 0.3459$, $R^2 = 0.9961$

Triglycerides Measuring Range: 5-1100 mg/dL

Level	1	2	3	4	5	6	7	8	9	10	11	12	13
Target value	3.8	5.1	9.2	29.0	82.5	134.6	178.1	221.5	308.4	531.0	802.6	1074.2	1345.7
Observed average	5.5	6.8	11.0	26.3	84.5	135.0	177.8	219.3	306.0	536.0	816.8	1079.0	1356.3
% Bias	43.1	31.7	19.2	-9.5	2.4	0.3	-0.2	-1.0	-0.8	0.9	1.8	0.5	0.8



$Y=1.008x - 0.3979$, $R^2 = 0.9999$

Reportable Range

The following are the reportable ranges for LDL-P, HDL-C and Triglycerides:

LDL-P	300 – 3500 nmol/L
HDL-C	7 – 140 mg/dL
Triglycerides	5 – 1100 mg/dL

Traceability, Stability, Assigned values (controls, calibrators)

The NMR Reference Standard

The NMR Reference Standard, TMA (Trimethylacetic acid, Sodium salt), is used as the NMR calibrator for the Vantera Clinical Analyzer. TMA is used routinely as a calibrator once daily during instrument startup to establish daily normalization factors. It also serves as a quality assessment tool to ensure quality NMR spectra are produced by the NMR analyzer.

The stability of the TMA calibrator material and storage conditions was evaluated for a period of 18 months across multiple NMR Analyzers. It was stored at room temperature and refrigerated at 4°C, in glass bottles and plastic bottles. TMA samples were evaluated for TMA signal methyl integrals every other month. The quality of the TMA spectra was not affected by the storage conditions during the study. The NMR Reference Standard is stable for 18 months in either glass or plastic bottle regardless of room temperature or refrigerated storage.

Liquichek™ Lipids Control

Liquichek™ Lipids Control material for LDL-P is frozen human serum in two pools, Level 1 and Level 2, prepared and packaged by Bio-Rad Laboratories. To assign values, new lots of Liquicheck™ Lipids Control material are run on 3 qualified Vantera Clinical Analyzers in house for 3 days. Means, Standard Deviations and % CVs are computed and new values are assigned.
The Liquicheck™ Lipids Control material is stable up to 6 months. Change in recovery over this period was estimated to be less than 0-6% for LDL-P.

Interfering Substances

Endogenous substances normally found in blood and exogenous substances (common and prescription drugs) were evaluated for potential interference with the *NMR LipoProfile®* test by LipoScience. Seven endogenous agents and twenty three drugs were screened for potential interfering effects to *NMR LipoProfile* test using concentrations in accordance to CLSI EP7-A2 guidelines.

Endogenous

Potential Interferent	***Test Concentration***
Hemoglobin	0.5 g/dL
Bilirubin, unconj.	342 µmol/L 20 mg/dL
Creatinine	442 µmol/L 5 mg/dL
Urea	42.9 mmol/L 260 mg/dL
Uric acid	1.4 mmol/L 23.5 mg/dL
Protein (albumin)	6 g/dL60g/L
Bilirubin, conj	342 µmol/L 28.9 mg/dL

Exogenous (OTC drugs, etc.)

Potential Interferent	***Test Concentration***	***Potential Interferent***	***Test Concentration***
Acetaminophen	1324 µmol/L	Metformin Hydrochloride	3.62 mmol/L
Acetylsalicylic acid	3.62 mmol/L	Metoprolol tartrate	18.7 µmol/L
Atorvastatin	600 µg Eq/L	Naproxen Sodium	2170 µmol/L
Clopidogrel hydrogensulfate**	95.7 µmol/L	Nicotinic Acid Sodium salt	8.28 mmol/L
Enalaprilat Dihydrate	0.86 µmol/L	Nifedipine	1156 nmol/L
Fenofibrate	125 µmol/L	Pioglitazone hydrochloride	152.7µmol/L
Furosemide	181 µmol/L	Piroxicam	181 µmol/L
Glipizide	4.48 µmol/L	Pravastatin	107.5 µmol/L
Hydralazine hydrochloride	915.4 µmol/L	Salicylic Acid*	1.3 mmol/L
Heparin	3000U/L	Simvastatin	114.7 µmol/L
Ibuprofen Sodium salt	2425 µmol/L		
Isosorbide dinitrate	636 nmol/L		
Menhaden oil (Fish Oil)	2.4 mg/mL		

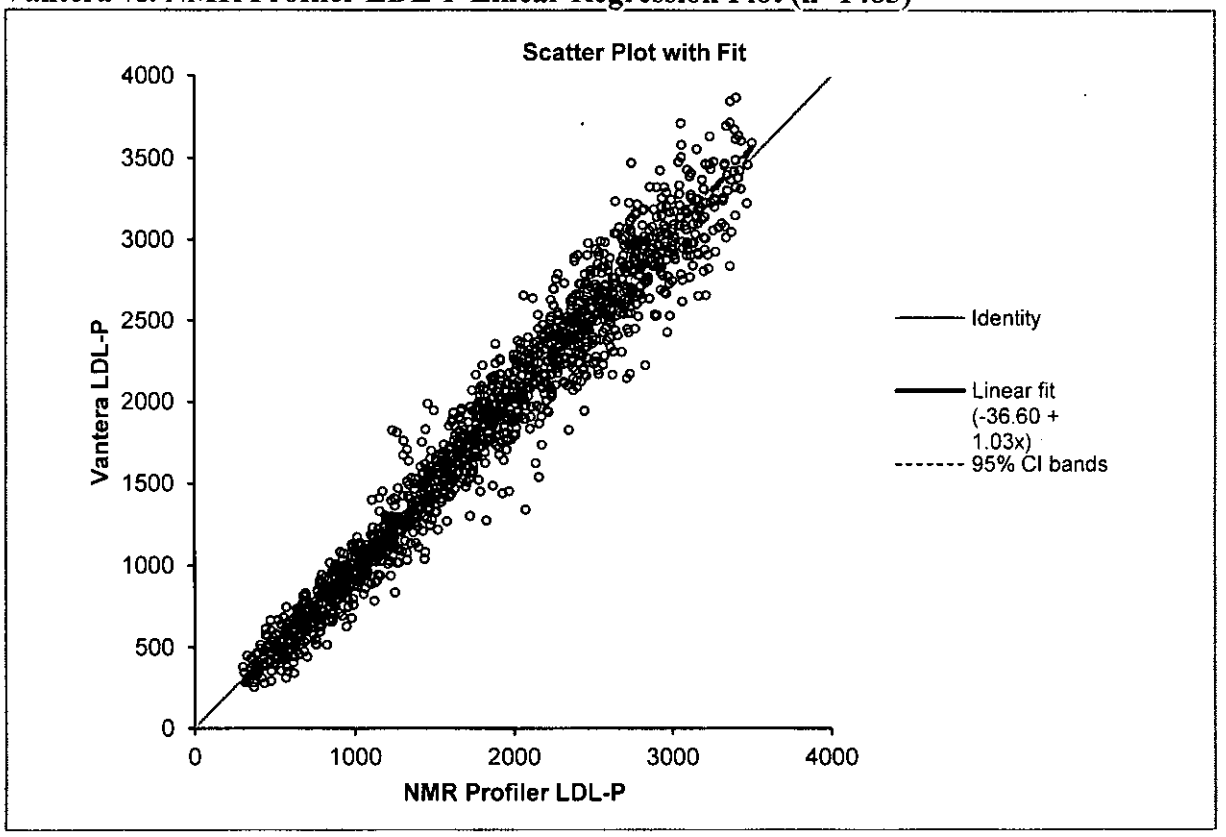
*Salicyclic acid at ≥ 1.3mmol/L was determined to interfere with LDL-P
**Clopidogrel hydrogensulfate at ≥ 95.7 µmol/L was determined to interfere with LDL-P

H. Method Comparison – Non-Clinical:

Method Comparison – LDL-P

Method comparison was evaluated by using serum samples across the reportable range of the *NMR LipoProfile* test for LDL-P on the Vantera Clinical Analyzer. LDL-P concentrations ranged from 303.0 to 3505.0nmol/L.

Vantera vs. NMR Profiler LDL-P Linear Regression Plot (n=1483)

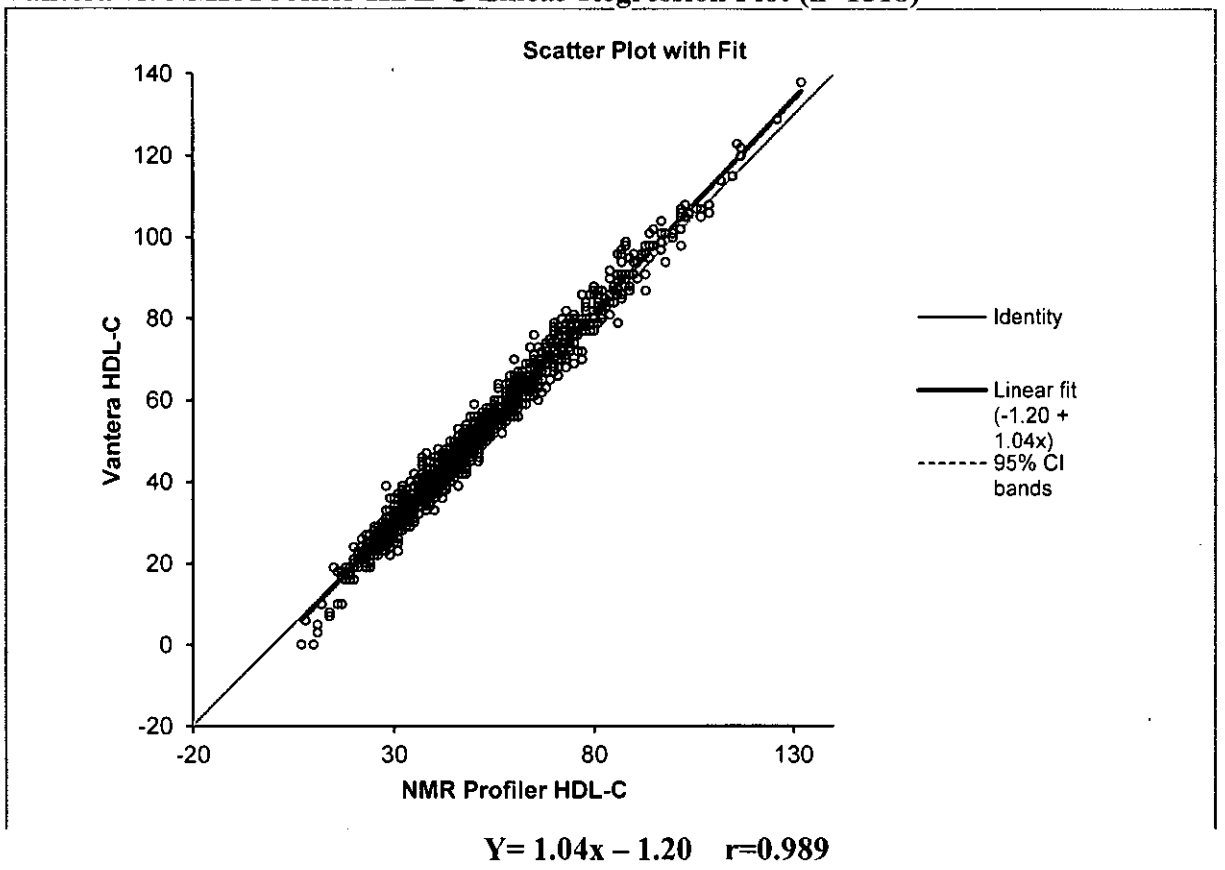


Y=1.03x – 36.60 r=0.978

Method Comparison – HDL-C

Method comparison was evaluated by using serum samples across the reportable range of the *NMR LipoProfile* test for HDL-C on the Vantera Clinical Analyzer. HDL-C concentrations ranged from 7.0 to 132 mg/dL.

Vantera vs. NMR Profiler HDL-C Linear Regression Plot (n=1518)

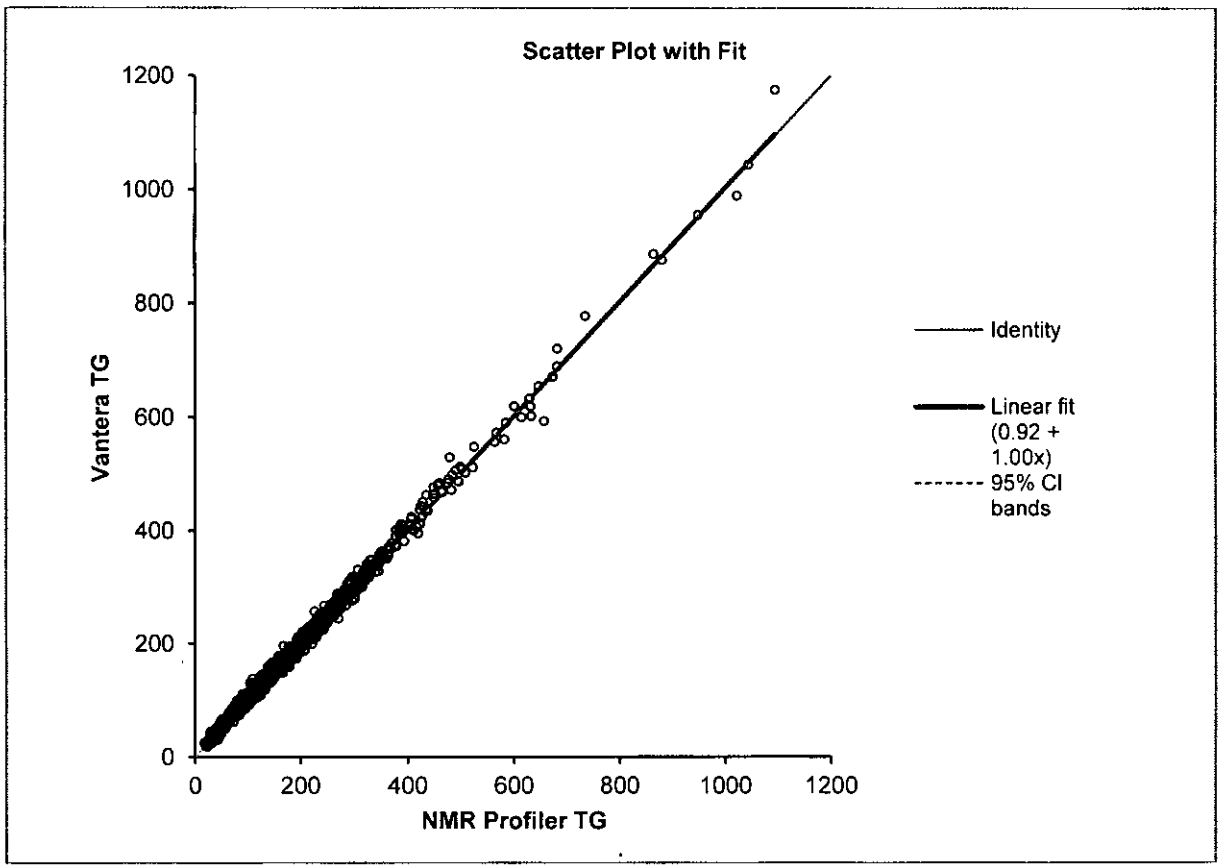


Y= 1.04x – 1.20 r=0.989

Method comparison Triglycerides

Method comparison was evaluated by using serum samples across the reportable range of the *NMR LipoProfile* test for Triglycerides on the Vantera Clinical Analyzer. Triglyceride concentrations ranged from 18.0 to 1095.0 mg/dL.

Vantera vs. NMR Profiler TG Linear Regression Plot (n=1520)



Y=1.00x + 0.92 r=0.998

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

Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices.

Class II Special Controls Guidance Document: Instrumentation for Clinical Multiplex Test Systems

EP5-A2: Evaluation of Precision Performance of Quantitative Measurement Methods; Approves Guideline – Second Edition

EP6-A: Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline

EP7-A2: Interference Testing in Clinical Chemistry; Approved Guideline – Second Edition

EP9-A2: Method Comparison and Bias Estimation Using Patient Samples; Approved Guideline – Second Edition

EP17-A: Protocols for Determination of Limits of Detection and Limits of Quantification; Approved Guideline

EP14-A2: Evaluation of Matrix Effects: Approved Guideline – Second Edition

C28-A3: Defining, Establishing, and Verifying Reference Intervals in the Clinical

C53-A: Characterization and Qualification of Commutable Reference Materials for Laboratory Medicine; Approved Guideline

IEC 61010-1:2001-2nd Edition: Safety requirements for electrical equipment for measurement, control and laboratory use Part: General requirements

This device has not been tested by the Cholesterol Reference Method Laboratory Network.

M. 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

1. Clinical cut-off:

Not Applicable

2. Expected values/Reference range:

In order to determine the distribution of LDL-P levels expected in a representative sampling of the general population, serum samples (n=452) were analyzed from apparently healthy men (n=158) and women (n=294) (ranging from 18 to 84 years). The following table provides the concentrations of LDL-P by percentile in this reference population:

Distribution of LDL-P Observed in a Reference Population

	All (n=452)	Men (n=158)	Women (n=294)	All (n=452)	Men (n=158)	Women (n=294)
Percentile	LDL-P (nmol/L)	LDL-P (nmol/L)	LDL-P (nmol/L)	LDL-C (mg/dL)	LDL-C (mg/dL)	LDL-C (mg/dL)
5	539	528	542	63	62	65
10	643	713	638	75	76	75
20	784	883	749	84	90	83
30	909	1004	863	94	100	91
40	1009	1087	970	102	107	98
50	1127	1241	1070	109	113	109
60	1248	1366	1202	118	128	115
70	1396	1505	1322	129	137	124
80	1572	1676	1482	140	147	136
90	1894	1941	1818	157	161	151
95	2047	2169	1986	169	171	169

Based on the recommendations from a National Lipids Association expert panel, suggested reference values are provided in Table 2. The recommendation by the NLA has not been validated by a clinical study. Each laboratory should verify the validity of these reference values for the population it serves.

Recommended LDL-P Reference Values

LDL-P, nmol/L			
Classification			
	Intermediate		
Low / Normal	*Moderate*	*Borderline High*	*High*
< 1000	1000-1299	1300-1599	≥ 1600

HDL Cholesterol and Triglycerides
The following reference values for patient classification have been recommended by the NCEP and Adult Treatment Panel III Guidelines for HDL cholesterol and triglycerides for the assessment and management of CVD risk. Each laboratory should verify the validity of these reference values for the population it serves.

HDL Cholesterol, mg/dL	
Classification	
Low	*High*
< 40	≥ 60

Triglycerides, mg/dL			
Classification			
Normal	*Borderline High*	*High*	*Very High*
< 150	150-199	200-499	≥ 500

O. System Description:

1. Modes of Operation:

   The Vantera Clinical Analyzer is a 400 MHz proton nuclear magnetic resonance spectrometer.

2. Software:

   The FDA has reviewed the applicant's Hazard Analysis and software development process for this line of product type:

   Yes _____ No_____

3. Specimen Identification:

   Bar code of source tube

4. Specimen Sampling and Handling:

   The processing of specimens on the Vantera Clinical Analyzer starts with their placement on the system. The user places serum or plasma specimen tubes in racks, and then places the racks on the system. After reading the bar code on a specimen tube, the system schedules the test or tests to be performed. The specimen is then aliquoted by the Metering Arm and is transferred to a dilution cup. Samples are prepared by diluting 2-fold (1:1) with specimen Diluent 1 performed by the Metering Arm assembly.

5. Calibration:

   The instrument is calibrated with an aqueous solution of Trimethyl Acetate (TMA) as a disodium salt (15.0 mM) containing Na_2EDTA (5.0 mM), $CaCl_2$ (3.0 mM), KCl (120mM), D_2O 10% v/v.

6. Quality Control:

   It is recommended that two levels of quality control materials are tested in the same manner as patient samples, before or during patient sample processing for each analyte being tested. To verify system performance, analyze control materials:

- After calibration
- According to federal, state or local regulations or at least once every day when patient testing is being performed.

Refer to the Liquichek™ Lipids Controls LDL-P value assignment card for LDL-P Target Ranges. It is recommended that each laboratory establish its own mean and acceptance range for each new lot of controls. Patient results should not be reported if the Quality Control values are not within the expected range.

Real-time quality control data indicate that stability for BioRad Liquichek Lipids controls is at least 6 months. A stability study is currently ongoing to extend the dating for the Bio-Rad Liquichek Lipids Controls.

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.

DEPARTMENT OF HEALTH & HUMAN SERVICES
Food and Drug Administration

10903 New Hampshire Avenue
Silver Spring, MD 20993

LipoScience, Inc.
c/o Suzette Warner
2500 Sumner Boulevard
Raleigh, NC 27616

AUG 30 2012

Re: k113830
Trade Name: Vantera® Clinical Analyzer; NMR LipoProfile® test on Vantera Clinical Analyzer
Regulation Number: 21 CFR §862.2570
Regulation Name: Instrumentation for clinical multiplex test systems
Regulatory Class: Class II
Product Codes: NSU, MRR, LBS, CDT
Dated: July 27, 2012
Received: July 30, 2012

Dear Ms. Warner:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to such additional controls. Existing major regulations affecting your device can be found in Title 21, Code of Federal Regulations (CFR), Parts 800 to 895. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Parts 801 and 809); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); and good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820).

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801), please contact the Office of In Vitro Diagnostic Device Evaluation and Safety at (301) 796-5450. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding postmarket surveillance, please contact CDRH's Office of Surveillance and Biometric's (OSB's) Division of Postmarket Surveillance at (301) 796-5760. For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm for the CDRH's Office of Surveillance and Biometrics/Division of Postmarket Surveillance...

You may obtain other general information on your responsibilities under the Act from the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (301) 796-5680 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm

Sincerely yours,

Courtney H. Lias, Ph.D.
Director
Division of Chemistry and Toxicology Devices
Office of *In Vitro* Diagnostic Device
Evaluation and Safety
Center for Devices and Radiological Health

Enclosure

Indication for Use

510(k) Number (if known): K113830

Device Name: Vantera® Clinical Analyzer

Indications for Use:

The Vantera® Clinical Analyzer is an automated laboratory test analyzer which measures the 400 MHz proton nuclear magnetic resonance (NMR) spectrum of clinical samples to produce signal amplitudes, converting these signal amplitudes to analyte concentration. The device includes a 400 MHz NMR spectrometer and software to analyze digitized spectral data. This instrumentation is intended to be used with NMR based assays to detect multiple analytes from clinical samples.

Prescription Use __X__ (21 CFR Part 801 Subpart D) And/Or Over the Counter Use ___. (21 CFR Part 801 Subpart C)

(PLEASE DO NOT WRITE BELOW THIS LINE; CONTINUE ON ANOTHER PAGE IF NEEDED)

Concurrence of CDRH, Office of In Vitro Diagnostic Device Evaluation and Safety (OIVD)

Division Sign-Off
Office of In Vitro Diagnostic Device
Evaluation and Safety

510(k) K113830

Indication for Use

510(k) Number (if known): K113830

Device Name: NMR LipoProfile® test on Vantera® Clinical Analyzer

Indications for Use:

The *NMR LipoProfile®* test, when used with the Vantera® Clinical Analyzer, an automated NMR spectrometer, measures lipoprotein particles to quantify LDL particle number (LDL-P), HDL cholesterol (HDL-C), and triglycerides in human serum and plasma using nuclear magnetic resonance (NMR) spectroscopy. LDL-P and these NMR-derived concentrations of HDL-C and triglycerides are used in conjunction with other lipid measurements and clinical evaluation to aid in the management of lipoprotein disorders associated with cardiovascular disease.

Prescription Use __X__ (21 CFR Part 801 Subpart D) And/Or Over the Counter Use ____. (21 CFR Part 801 Subpart C)

(PLEASE DO NOT WRITE BELOW THIS LINE; CONTINUE ON ANOTHER PAGE IF NEEDED)

Concurrence of CDRH, Office of In Vitro Diagnostic Device Evaluation and Safety (OIVD)

Division Sign-Off
Office of In Vitro Diagnostic Device
Evaluation and Safety

510(k) K113830

K113830

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

U.S. Food and Drug Administration
Center for Devices and Radiological Health
Document Control Center WO66-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

February 28, 2012

LIPOSCIENCE
2500 SUMMER BLVD.
RALEIGH, NORTH CAROLINA 27616
ATTN: SUZETTE WARNER

510k Number: K113830
Product: VANTERA CHINIAL ANALYZER
On Hold As of 2/24/2012

We are holding your above-referenced Premarket Notification (510(k)) for 30 days pending receipt of the additional information that was requested by the Office of Device Evaluation. Please remember that all correspondence concerning your submission MUST cite your 510(k) number and be sent in duplicate to the Document Mail Center at the above letterhead address. Correspondence sent to any address other than the one above will not be considered as part of your official premarket notification submission. Also, please note the new Blue Book Memorandum regarding Fax and E-mail Policy entitled, "Fax and E-Mail Communication with Industry about Premarket Files Under Review. Please refer to this guidance for information on current fax and e-mail practices at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089402.htm.

The deficiencies identified represent the issues that we believe need to be resolved before our review of your 510(k) submission can be successfully completed. In developing the deficiencies, we carefully considered the statutory criteria as defined in Section 513(i) of the Federal Food, Drug, and Cosmetic Act for determining substantial equivalence of your device. We also considered the burden that may be incurred in your attempt to respond to the deficiencies. We believe that we have considered the least burdensome approach to resolving these issues. If, however, you believe that information is being requested that is not relevant to the regulatory decision or that there is a less burdensome way to resolve the issues, you should follow the procedures outlined in the "A Suggested Approach to Resolving Least Burdensome Issues" document. It is available on our Center web page at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/MedicalDeviceProvisionsofFDAModernizationAct/ucm136685.htm.

If after 30 days the additional information (AI), or a request for an extension of time, is not received, we will discontinue review of your submission and proceed to delete your file from our review system (21 CFR 807.87(l)). Please note our guidance document entitled, "Guidance for Industry and FDA Staff, FDA and Industry Actions on Premarket Notification (510(k)) Submissions: Effect on FDA Review Clock and Performance Assessment". If the submitter does submit a written request for an extension, FDA will permit the 510(k) to remain on hold for up to a maximum of 180 days from the date of the AI request. The purpose of this document is to assist agency staff and the device industry in understanding how various FDA and industry actions that may be taken on 510(k)s should affect the review clock for purposes of meeting the Medical Device User Fee and Modernization Act. You may review this document at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089735.htm. Pursuant to 21 CFR 20.29, a copy of your 510(k) submission will remain in the Office of Device Evaluation. If you then wish to resubmit this 510(k) notification, a new number will be assigned and your submission will be considered a new premarket notification submission.

Please remember that the Safe Medical Devices Act of 1990 states that you may not place this device into commercial distribution until you receive a decision letter from FDA allowing you to do so.

If you have procedural questions, please contact the Division of Small Manufacturers International and Consumer Assistance (DSMICA) at (301)796-7100 or at their toll-free number (800)638-2041, or contact the 510k staff at (301)796-5640.

Sincerely yours,

Marjorie Shulman
Consumer Safety Officer
Premarket Notification Section
Office of Device Evaluation
Center for Devices and Radiological Health

Grayson, Giovanna *

From: Grayson, Giovanna *
Sent: Tuesday, February 28, 2012 8:33 AM
To: 'suzette.warner@liposcience.com'
Subject: Hold Letter
Attachments: image002.png

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
U.S. Food and Drug Administration
Center for Devices and Radiological Health
Document Control Center, WO66-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

February 28, 20
WARNER
SUZETTE
LIPOSCIENCE
2500 SUMMER BLVD.
RALEIGH, NORTH CAROLINA 27616
ATTN: SUZETTE WARNER

510k Number: K113830

Product: VANTERA CHINIAL ANALYZER

On Hold As of 2/24/2012

We are holding your above-referenced Premarket Notification (510(k)) for 30 days pending receipt of the additional information that was requested by the Office of Device Evaluation. Please remember that all correspondence concerning your submission MUST cite your 510(k) number and be sent in duplicate to the Document Mail Center at the above letterhead address. Correspondence sent to any address other than the one above will not be considered as part of your official premarket notification submission. Also, please note the new Blue Book Memorandum regarding Fax and E-mail Policy entitled, "Fax and E-Mail Communication with Industry about Premarket Files Under Review. Please refer to this guidance for information on current fax and e-mail practices at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089402.htm.

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Sincerely yours,

Marjorie Shulman
Consumer Safety Officer
Premarket Notification Section
Office of Device Evaluation
Center for Devices and Radiological Health

Grayson, Giovanna *

From: Microsoft Outlook
To: 'suzette.warner@liposcience.com'
Sent: Tuesday, February 28, 2012 8:33 AM
Subject: Relayed: Hold Letter

Delivery to these recipients or distribution lists is complete, but delivery notification was not sent by the destination:

'suzette.warner@liposcience.com'

Subject: Hold Letter

Sent by Microsoft Exchange Server 2007

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

U.S. Food and Drug Administration
Center for Devices and Radiological Health
Document Control Center WO66-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

December 29, 2011

LIPOSCIENCE
2500 SUMMER BLVD.
RALEIGH, NORTH CAROLINA 27616
ATTN: SUZETTE WARNER

510k Number: K113830
Received: 12/27/2011
Product: VANTERA CHINIAL ANALYZER

The Center for Devices and Radiological Health (CDRH), Office of Device Evaluation (ODE), has received the Premarket Notification you submitted in accordance with Section 510(k) of the Federal Food, Drug, and Cosmetic Act(Act) for the above referenced product. We have assigned your submission a unique 510(k) number that is cited above. Please refer prominently to this 510(k) number in any future correspondence that relates to this submission. We will notify you when the processing of your premarket notification has been completed or if any additional information is required. YOU MAY NOT PLACE THIS DEVICE INTO COMMERCIAL DISTRIBUTION UNTIL YOU RECEIVE A LETTER FROM FDA ALLOWING YOU TO DO SO.

On May 21, 2004, FDA issued a Guidance for Industry and FDA Staff entitled, "FDA and Industry Actions on Premarket Notification (510(k)) Submissions: Effect on FDA Review Clock and Performance Assessment". The purpose of this document is to assist agency staff and the device industry in understanding how various FDA and industry actions that may be taken on 510(k)s should affect the review clock for purposes of meeting the Medical Device User Fee and Modernization Act. Please review this document at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089735.htm.

In future premarket submissions, we encourage you to provide an electronic copy of your submission. By doing so, you will save FDA resources and may help reviewers navigate through longer documents more easily. Under CDRH's eCopy Program, you may replace one paper copy of any premarket submission (e.g., 510(k), IDE, PMA, HDE) with an electronic copy. For more information about the program, including the formatting requirements, please see http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/ucm134508.htm.

We remind you that Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amended the PHS Act by adding new section 402(j) (42 U.S.C. § 282(j)), which expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices. Section 402(j) requires that a certification form (http://www.fda.gov/opacom/morechoices/fdaforms/FDA-3674.pdf) accompany 510(k)/HDE/PMA submissions. The agency has issued a draft guidance titled: "Certifications To Accompany Drug, Biological Product, and Device Applications/Submissions: Compliance with Section 402(j) of The Public Health Service Act, Added By Title VIII of The Food and Drug Administration

Amendments Act of 2007" (http://www.fda.gov/oc/initiatives/fdaaa/guidance_certifications.html). According to the draft guidance, 510(k) submissions that do not contain clinical data do not need the certification form.

The Clinical Laboratory Improvement Amendments of 1988 (CLIA) requires the categorization of commercially marketed test systems by level of complexity. If your device is a test system that requires categorization you will be notified of your complexity as an enclosure with any clearance letter.

Please remember that all correspondence concerning your submission MUST be sent to the Document Mail Center (DMC) at the above letterhead address. Correspondence sent to any address other than the one above will not be considered as part of your official premarket notification submission. Also, please note the new Blue Book Memorandum regarding Fax and E-mail Policy entitled, "Fax and E-Mail Communication with Industry about Premarket Files Under Review". Please refer to this guidance for information on current fax and e-mail practices at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089402.htm.

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Sincerely,

510(k) Staff

Grayson, Giovanna *

From: Microsoft Outlook
To: 'suzette.warner@liposcience.com'
Sent: Thursday, December 29, 2011 8:32 AM
Subject: Relayed: ack letter

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Subject: ack letter

Sent by Microsoft Exchange Server 2007

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Attachments: image002.png

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
U.S. Food and Drug Administration
Center for Devices and Radiological Health
Document Control Center, WO66-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

December 29, 2011

WARNER
SUZETTE
LIPOSCIENCE
2500 SUMMER BLVD.
RALEIGH, NORTH CAROLINA 27616
ATTN: SUZETTE WARNER

510k Number: K113830
Received: 12/27/2011
Product: VANTERA CHINIAL ANALYZER

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Sincerely,

510(k) Staff

K113830
CH / DCTD

LIPOSCIENCE

FDA CDRH DMC
DEC 27 2011
Received
K45

December 23, 2011

Food and Drug Administration
Center for Devices and Radiological Health
Office of Device Evaluation
Document Mail Center WO66-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Re: 510(k) Notification for Vantera® Clinical Analyzer for use with the *NMR LipoProfile* test

Dear Sir or Madam:

In accordance with Section 510(k) of the Federal Food, Drug, and Cosmetic Act, LipoScience, Inc. hereby notifies the Food and Drug Administration (FDA) of its intent to market a new device, the Vantera Clinical Analyzer for use with the *NMR LipoProfile* test.

The Vantera Clinical Analyzer is a Nuclear Magnetic Resonance (NMR) based clinical chemistry analyzer operating under the same NMR-based technology as the LipoScience NMR Profiler System. Like other clinical chemistry analyzers, the Vantera Clinical Analyzer automates specimen handling, sample preparation, data acquisition, results calculation and all interfaces to the clinical laboratory infrastructure. Like the NMR Profiler, the Vantera provides quantitative measure of multiple analytes in blood plasma and serum using nuclear magnetic resonance spectroscopy. The Vantera Clinical Analyzer has been developed under FDA design controls and is manufactured per FDA regulations specified in 21 CFR 820. The Vantera is intended to run multiple in vitro diagnostic tests utilizing NMR technology. The initial menu will consist of the same analytes run in the FDA cleared *NMR LipoProfile* test (k111516), a cardiovascular diagnostic test that uses NMR spectroscopy to uniquely provide rapid, simultaneous, and direct measurement of LDL-P, HDL-C and Triglycerides.

Please note that the Vantera® Clinical Analyzer was identified as "Numera" during the initial development phase. As a result, some development documents referenced in this submission may still utilize the previous name. References to the Vantera system and the Numera system are identical in their meaning.

LipoScience, Inc. is submitting this Traditional 510(k) Notification for the Vantera Clinical Analyzer for use with the *NMR LipoProfile®* test. Per the instructions accessed at "Electronic Copies for Pre-Market Submissions", an electronic copy is being provided with the submission and it is an exact duplicate of the original paper submission.

TYPE OF SUBMISSION

Traditional

PAYMENT IDENTIFICATION NUMBER

The MDUFMA PIN is (b)(4) [redacted]

REFERENCE 510(k) NUMBER

K073506, March 7, 2008
K111516, September 27, 2011

DEVICE TYPE

The Vantera Clinical Analyzer is a clinical laboratory analyzer that employs nuclear magnetic resonance spectroscopic detection to quantify multiple analytes in biological fluid specimens, specifically blood plasma and serum.

MODEL NUMBER AND NAME

003-00095ADH – Vantera System

SUBMITTER

LipoScience, Inc
2500 Sumner Boulevard
Raleigh, NC 27616

OFFICIAL CORRESPONDENT

Suzette Warner
Regulatory Affairs Manager
Tel – (919) 256-1326
Fax - (919) 256-1149
Email – suzette.warner@lipocscience.com

CONFIDENTIALITY

We request as outlined under 21 CFR 807.95 that FDA treat this premarket notification and our intent to market as confidential commercial information under the conditions and requirements of CFR 807.95.

CLASSIFICATION

CFR 862.2570, Instrumentation for clinical multiplex test systems
CFR 862.1475, Lipoprotein Test System
CFR862.1705, Triglyceride Test System
CFR 862.1660, Quality Control Material
CFR 862.1150, Calibrator

CLASS

Class II (Special Controls)
Class I

PANEL

Clinical Chemistry (75)

PRODUCT CODE

NSU, Instrumentation for Clinical Multiplex Test Systems
MRR, Lipoprotein test system
LBS, Lipoprotein test system
CDT, Triglyceride test system
JJY, Quality Control Material
JIT, Calibrator

PREVIOUS FDA DOCUMENTS

510(k) #k063841- NMR LipoProfile test and NMR Profiler, Control; cleared by FDA on July 23, 2008.
510(k) #k111516 NMR LipoProfile test and NMR Profiler; cleared by FDA on September 27, 2011.

BASIS FOR THE SUBMISSION

This is a new instrumentation for clinical multiplex system to be used with *NMR LipoProfile* test.

QUESTION	YES	NO
Is the device intended for prescription use (21 CFR 801 Subpart D)?	Yes	
Is the device intended for over-the-counter use (21 CFR 801 Subpart C)?		No
Does the device contain components derived from a tissue or other biologic source?		No
Is the device provided sterile?		No
Is the device intended for single use?		No
Is the device a reprocessed single use device?		No
If yes, does this device type require reprocessed validation data?		No
Does the device contain a drug?		No
Does the device contain a biologic?		No
Does the device use software?	Yes	
Does the submission include clinical information?	No	
Is the device implanted?		No

We trust that the information provided in this 510(k) premarket notification is sufficient for FDA to find the proposed device substantial equivalent to its predicate devices for the listed indications. Please do not hesitate to contact me should you have any questions or require any additional information.

Sincerely,

Suzette Warner

Suzette M. Warner

Enclosure

Section 1: Medical Device User Fee Cover Sheet

Form Approved: OMB No. 0910-511. See Instructions for OMB Statement.

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION **MEDICAL DEVICE USER FEE COVER SHEET**	PAYMENT IDENTIFICATION NUMBER: (b)(4) Write the Payment Identification number on your check.

A completed cover sheet must accompany each original application or supplement subject to fees. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment and mailing instructions can be found at: http://www.fda.gov/oc/mdufma/coversheet.html

1. COMPANY NAME AND ADDRESS (include name, street address, city state, country, and post office code)	2. CONTACT NAME
LIPOSCIENCE INC 2500 Sumner Blvd. Raleigh NC 27616 US	Suzette Warner 2.1 E-MAIL ADDRESS suzette.warner@liposcience.com 2.2 TELEPHONE NUMBER (include Area code) 919-256-1326
1.1 EMPLOYER IDENTIFICATION NUMBER (EIN) (b)(4)	2.3 FACSIMILE (FAX) NUMBER (Include Area code) 919-256-1149

3. TYPE OF PREMARKET APPLICATION (Select one of the following in each column; if you are unsure, please refer to the application descriptions at the following web site: http://www.fda.gov/oc/mdufma

Select an application type:	3.1 Select a center
[X] Premarket notification(510(k)); except for third party	[X] CDRH
[ ] 513(g) Request for Information	[ ] CBER
[ ] Biologics License Application (BLA)	3.2 Select one of the types below
[ ] Premarket Approval Application (PMA)	[X] Original Application
[ ] Modular PMA	Supplement Types:
[ ] Product Development Protocol (PDP)	[ ] Efficacy (BLA)
[ ] Premarket Report (PMR)	[ ] Panel Track (PMA, PMR, PDP)
[ ] Annual Fee for Periodic Reporting (APR)	[ ] Real-Time (PMA, PMR, PDP)
[ ] 30-Day Notice	[ ] 180-day (PMA, PMR, PDP)

4. ARE YOU A SMALL BUSINESS? (See the instructions for more information on determining this status)

[X] YES, I meet the small business criteria and have submitted the required qualifying documents to FDA

NO, I am not a small business

4.1 If Yes, please enter your Small Business Decision Number: SBD118181

5. FDA WILL NOT ACCEPT YOUR SUBMISSION IF YOUR COMPANY HAS NOT PAID AN ESTABLISHMENT REGISTRATION FEE THAT IS DUE TO FDA. HAS YOUR COMPANY PAID ALL ESTABLISHMENT REGISTRATION FEES THAT ARE DUE TO FDA?

[X] YES (All of our establishments have registered and paid the fee, or this is our first device, and we will register and pay the fee within 30 days of FDA's approval/clearance of this device.)

[ ] NO (If "NO," FDA will not accept your submission until you have paid all fees due to FDA. This submission will not be processed; see http://www.fda.gov/cdrh/mdufma for additional information)

6. IS THIS PREMARKET APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCEPTIONS? IF SO, CHECK THE APPLICABLE EXCEPTION.

[ ] This application is the first PMA submitted by a qualified small business, including any affiliates

[ ] This biologics application is submitted under section 351 of the Public Health Service Act for a product licensed for further manufacturing use only

[ ] The sole purpose of the application is to support conditions of use for a pediatric population

[ ] The application is submitted by a state or federal government entity for a device that is not to be distributed commercially

7. IS THIS A SUPPLEMENT TO A PREMARKET APPLICATION FOR WHICH FEES WERE WAIVED DUE TO SOLE USE IN A PEDIATRIC POPULATION THAT NOW PROPOSES CONDITION OF USE FOR ANY ADULT POPULATION? (If so, the application is subject to the fee that applies for an original premarket approval application (PMA).

[ ] YES [X] NO

PAPERWORK REDUCTION ACT STATEMENT

Public reporting burden for this collection of information is estimated to average 18 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to the address below.

Department of Health and Human Services, Food and Drug Administration, Office of Chief Information Officer, 1350 Piccard Drive, 4th Floor Rockville, MD 20850

[Please do NOT return this form to the above address, except as it pertains to comments on the burden estimate.]

8. USER FEE PAYMENT AMOUNT SUBMITTED FOR THIS PREMARKET APPLICATION

(b)(4) 18-Aug-2011

Form FDA 3601 (01/2007)

Section 2: CDRH Premarket Review Submission Coversheet and Screening Checklist

Table of Contents

2.1 CDRH Premarket Review Submission Coversheet

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

CDRH PREMARKET REVIEW SUBMISSION COVER SHEET

Form Approval
OMB No. 0910-0120
Expiration Date: December 31, 2013
See OMB Statement on page 5.

Date of Submission	User Fee Payment ID Number	FDA Submission Document Number *(if known)*
December 23, 2011	(b)(4)	Not Known

SECTION A TYPE OF SUBMISSION

PMA	PMA & HDE Supplement	PDP	510(k)	Meeting
☐ Original Submission	☐ Regular (180 day)	☐ Original PDP	☒ Original Submission:	☐ Pre-510(K) Meeting
☐ Premarket Report	☐ Special	☐ Notice of Completion	☒ Traditional	☐ Pre-IDE Meeting
☐ Modular Submission	☐ Panel Track (PMA Only)	☐ Amendment to PDP	☐ Special	☐ Pre-PMA Meeting
☐ Amendment	☐ 30-day Supplement		☐ Abbreviated (Complete section I, Page 5)	☐ Pre-PDP Meeting
☐ Report	☐ 30-day Notice		☐ Additional Information	☐ Day 100 Meeting
☐ Report Amendment	☐ 135-day Supplement		☐ Third Party	☐ Agreement Meeting
☐ Licensing Agreement	☐ Real-time Review			☐ Determination Meeting
	☐ Amendment to PMA & HDE Supplement			☐ Other *(specify)*:
	☐ Other			

IDE	Humanitarian Device Exemption (HDE)	Class II Exemption Petition	Evaluation of Automatic Class III Designation (De Novo)	Other Submission
☐ Original Submission	☐ Original Submission	☐ Original Submission	☐ Original Submission	☐ 513(g)
☐ Amendment	☐ Amendment	☐ Additional Information	☐ Additional Information	☐ Other *(describe submission)*:
☐ Supplement	☐ Supplement			
	☐ Report			
	☐ Report Amendment			

Have you used or cited Standards in your submission? ☒ Yes ☐ No *(If Yes, please complete Section I, Page 5)*

SECTION B SUBMITTER, APPLICANT OR SPONSOR

Company / Institution Name	Establishment Registration Number *(if known)*		
LipoScience, Inc/	3007701857		
Division Name *(if applicable)*	**Phone Number *(including area code)***		
N/A	919-256-1326		
Street Address	**FAX Number *(including area code)***		
2500 Sumner Boulevard	919-256-1149		
City	**State / Province**	**ZIP/Postal Code**	**Country**
Raleigh	NC	27616	USA
Contact Name			
Suzette Warner			
Contact Title	**Contact E-mail Address**		
Regulatory Affairs Manager	suzette.warner@liposcience.com		

SECTION C APPLICATION CORRESPONDENT (e.g., consultant, if different from above)

Company / Institution Name			
Division Name *(if applicable)*	**Phone Number *(including area code)***		
Street Address	**FAX Number *(including area code)***		
City	**State / Province**	**ZIP Code**	**Country**
Contact Name			
Contact Title	**Contact E-mail Address**		

FORM FDA 3514 (12/10) Page 1 of 5 Pages

SECTION D1 REASON FOR APPLICATION - PMA, PDP, OR HDE

- ☐ New Device
- ☐ Withdrawal
- ☐ Additional or Expanded Indications
- ☐ Request for Extension
- ☐ Post-approval Study Protocol
- ☐ Request for Applicant Hold
- ☐ Request for Removal of Applicant Hold
- ☐ Request to Remove or Add Manufacturing Site
- ☐ Process change:
  - ☐ Manufacturing ☐ Packaging
  - ☐ Sterilization
  - ☐ Other *(specify below)*
- ☐ Response to FDA correspondence:
- ☐ Change in design, component, or specification:
  - ☐ Software/Hardware
  - ☐ Color Additive
  - ☐ Material
  - ☐ Specifications
  - ☐ Other *(specify below)*
- ☐ Labeling change:
  - ☐ Indications
  - ☐ Instructions
  - ☐ Performance Characteristics
  - ☐ Shelf Life
  - ☐ Trade Name
  - ☐ Other *(specify below)*
- ☐ Location change:
  - ☐ Manufacturer
  - ☐ Sterilizer
  - ☐ Packager
- ☐ Report Submission:
  - ☐ Annual or Periodic
  - ☐ Post-approval Study
  - ☐ Adverse Reaction
  - ☐ Device Defect
  - ☐ Amendment
- ☐ Change in Ownership
- ☐ Change in Correspondent
- ☐ Change of Applicant Address
- ☐ Other Reason *(specify)*:

SECTION D2 REASON FOR APPLICATION - IDE

- ☐ New Device
- ☐ New Indication
- ☐ Addition of Institution
- ☐ Expansion / Extension of Study
- ☐ IRB Certification
- ☐ Termination of Study
- ☐ Withdrawal of Application
- ☐ Unanticipated Adverse Effect
- ☐ Notification of Emergency Use
- ☐ Compassionate Use Request
- ☐ Treatment IDE
- ☐ Continued Access
- ☐ Change in:
  - ☐ Correspondent/Applicant
  - ☐ Design/Device
  - ☐ Informed Consent
  - ☐ Manufacturer
  - ☐ Manufacturing Process
  - ☐ Protocol - Feasibility
  - ☐ Protocol - Other
  - ☐ Sponsor
- ☐ Report submission:
  - ☐ Current Investigator
  - ☐ Annual Progress Report
  - ☐ Site Waiver Report
  - ☐ Final
- ☐ Response to FDA Letter Concerning:
  - ☐ Conditional Approval
  - ☐ Deemed Approved
  - ☐ Deficient Final Report
  - ☐ Deficient Progress Report
  - ☐ Deficient Investigator Report
  - ☐ Disapproval
  - ☐ Request Extension of Time to Respond to FDA
  - ☐ Request Meeting
  - ☐ Request Hearing
- ☐ Other Reason *(specify)*:

SECTION D3 REASON FOR SUBMISSION - 510(k)

- ☒ New Device
- ☐ Additional or Expanded Indications
- ☐ Change in Technology
- ☐ Other Reason *(specify)*:

SECTION E ADDITIONAL INFORMATION ON 510(K) SUBMISSIONS

Product codes of devices to which substantial equivalence is claimed

1	NSU	2	MRR	3	LBS	4	CDT
5	JJY	6	JIT	7		8	

Summary of, or statement concerning, safety and effectiveness information

- [x] 510 (k) summary attached
- [ ] 510 (k) statement

Information on devices to which substantial equivalence is claimed *(if known)*

	510(k) Number		*Trade or Proprietary or Model Name*		*Manufacturer*
1	k073506	1	Luminex LX 100/200 Instrument	1	Luminex Corporation
2	k111516	2	NMR LipoProfile Test and NMR LipoProfiler	2	LipoScience, Inc.
3		3		3	
4		4		4	
5		5		5	
6		6		6	

SECTION F PRODUCT INFORMATION - APPLICATION TO ALL APPLICATIONS

Common or usual name or classification name

Instrumentation for clinical multiplex test systems

	Trade or Proprietary or Model Name for This Device		Model Number
1	Vantera Clinical Analyzer	1	003-00095 ADH
2		2	
3		3	
4		4	
5		5	

FDA document numbers of all prior related submissions *(regardless of outcome)*

1		2		3		4		5		6	
7		8		9		10		11		12	

Data Included in Submission

- [x] Laboratory Testing
- [ ] Animal Trials
- [x] Human Trials

SECTION G PRODUCT CLASSIFICATION - APPLICATION TO ALL APPLICATIONS

Product Code	C.F.R. Section *(if applicable)*	Device Class
NSU	21 CFR 862.2570	☐ Class I ☒ Class II

Classification Panel

Chemistry (75)

☐ Class III ☐ Unclassified

Indications *(from labeling)*

The Vantera® Clinical Analyzer is an automated laboratory test analyzer which measures the 400 MHZ proton nuclear magnetic resonance (NMR) spectrum of clinical samples to produce signal amplitudes, converting these signal amplitudes to analyte concentration. The device includes a 400 MHz NMR spectrometer and an analysis server containing software to analyze digitized spectral data. This instrumentation is intended to be used with NMR based assays to detect multiple analytes from clinical samples.

Note: Submission of the information entered in Section H does not affect the need to submit device establishment registration.

FDA Document Number *(if known)*

SECTION H MANUFACTURING / PACKAGING / STERILIZATION SITES RELATING TO A SUBMISSION

☒ Original ☐ Add ☐ Delete

Facility Establishment Identifier (FEI) Number

☒ Manufacturer ☐ Contract Sterilizer ☐ Contract Manufacturer ☐ Repackager / Relabeler

Company / Institution Name	Establishment Registration Number
LipoScience, Inc.	3007701857
Division Name *(if applicable)*	**Phone Number *(including area code)***
N/A	(919) 212-1999
Street Address	**FAX Number *(including area code)***
2500Sumner Boulevard	(919) 256-1149

City	State / Province	ZIP Code	Country
Raleigh	NC	27616	USA

Contact Name	Contact Title	Contact E-mail Address
Tom Clement	VP, Regulatory and Quality Affairs	tom.clement@liposcience.com

☒ Original ☐ Add ☐ Delete

Facility Establishment Identifier (FEI) Number

☐ Manufacturer ☐ Contract Sterilizer ☒ Contract Manufacturer ☐ Repackager / Relabeler

(b)(4) [redacted]

☐ Original ☐ Add ☐ Delete

Facility Establishment Identifier (FEI) Number

☐ Manufacturer ☐ Contract Sterilizer ☐ Contract Manufacturer ☐ Repackager / Relabeler

Company / Institution Name	Establishment Registration Number
Division Name *(if applicable)*	**Phone Number *(including area code)***
Street Address	**FAX Number *(including area code)***

City	State / Province	ZIP Code	Country

Contact Name	Contact Title	Contact E-mail Address

FORM FDA 3514 (12/10) Add Continuation Page Page 4 of 5 Pages

SECTION I	UTILIZATION OF STANDARDS				
Note: Complete this section if your application or submission cites standards or includes a *"Declaration of Conformity to a Recognized Standard"* statement.					
	Standards No.	Standards Organization	Standards Title	Version	Date
1	EP5-A2	CLSI	Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline	Second Edition	02/01/2010
	Standards No.	Standards Organization	Standards Title	Version	Date
2	EP6-A	CLSI	Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline		02/01/2010
	Standards No.	Standards Organization	Standards Title	Version	Date
3	EP7-A2	CLSI	Interference Testing in Clinical Chemistry; Approved Guideline	Second Edition	02/01/2010
	Standards No.	Standards Organization	Standards Title	Version	Date
4	EP9-A2	CLSI	Method Comparison and Bias Estimation Using Patient Samples; Approved Guideline	Second Edition	02/01/2010
	Standards No.	Standards Organization	Standards Title	Version	Date
5	EP17-A	CLSI	Protocols for Determination of Limits of Detection and Limits of Quantitation; Approved Guideline		02/01/2010
	Standards No.	Standards Organization	Standards Title	Version	Date
6	EP14-A2	CLSI	Evaluation of Matrix Effects; Approved Guideline	Second Edition	02/01/2010
	Standards No.	Standards Organization	Standards Title	Version	Date
7	C28-A3	CLSI	Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline	Third Edition	02/01/2010
Please include any additional standards to be cited on a separate page.					

Public reporting burden for this collection of information is estimated to average 0.5 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
1350 Piccard Drive, Room 400
Rockville, MD 20850

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

SECTION I — UTILIZATION OF STANDARDS

Note: Complete this section if your application or submission cites standards or includes a *"Declaration of Conformity to a Recognized Standard"* statement.

	Standards No.	Standards Organization	Standards Title	Version	Date
1	IEC 61010-1	IEC Standards	Safety requirements for electrical equipment for measurement, control and laboratory use. Part: General Requirements	Second Edition	01/01/2001
2					
3					
4					
5					
6					
7					

Please include any additional standards to be cited on a separate page.

Public reporting burden for this collection of information is estimated to average 0.5 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
1350 Piccard Drive, Room 400
Rockville, MD 20850

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

2.2 Screening Checklist for all Premarket Notification [510(k)] Submissions

510(k) Number: _____

The cover letter clearly identifies the type of 510(k) submission as **(Check the appropriate box)**:

☐	Special 510(k) -	Do Sections 1 and 2
	Abbreviated 510(k) -	Do Sections 1, 3 and 4
X	Traditional 510(k) or no identification provided -	Do Sections 1 and 4

Section 1: Required Elements for All Types of 510(k) submissions:

	Present or Adequate	Missing or Inadequate
Cover letter, containing the elements listed on page 3-2 of the Premarket Notification [510)] Manual.	**Sec 3**	
Table of Contents.	**Sec 0**	
Truthful and Accurate Statement.	**Sec 4**	
Device's Trade Name, Device's Classification Name and Establishment Registration Number.	**Sec 2**	
Device Classification Regulation Number and Regulatory Status (Class I, Class II, Class III or Unclassified).	**Sec 2, 3**	
Proposed Labeling including the material listed on page 3-4 of the Premarket Notification [510)] Manual.	**Sec 13**	
Statement of Indications for Use that is on a separate page in the premarket submission.	**Sec 4**	
Substantial Equivalence Comparison, including comparisons of the new device with the predicate in areas that are listed on page 3-4 of the Premarket Notification [510)] Manual.	**Sec 12**	
510(k) Summary or 510(k) Statement.	**Sec 5**	
Description of the device (or modification of the device) including diagrams, engineering drawings, photographs or service manuals.	**Sec 11**	
Identification of legally marketed predicate device. *****	**Sec 12**	
Compliance with performance standards. ***** [See Section 514 of the Act and 21 CFR 807.87 (d).]	**Sec 18**	
Class III Certification and Summary. ******	**Sec 7**	
Financial Certification or Disclosure Statement for 510(k) notifications with a clinical study. ***** [See 21 CFR 807.87 (i)]	**Sec 8**	
510(k) Kit Certification *******	**Sec 11**	

***** - May not be applicable for Special 510(k)s.
****** - Required for Class III devices, only.
******* - See pages 3-12 and 3-13 in the Premarket Notification [510)] Manual and the Convenience Kits Interim Regulatory Guidance.

Section 2: Required Elements for a SPECIAL 510(k) submission:

	Present	Inadequate or Missing
Name and 510(k) number of the submitter's own, unmodified predicate device.	**N/A**	
A description of the modified device and a comparison to the sponsor's predicate device.	**N/A**	
A statement that the intended use(s) and indications of the modified device, as described in its labeling are the same as the intended uses and indications for the submitter's unmodified predicate device.	**N/A**	
Reviewer's confirmation that the modification has not altered the fundamental scientific technology of the submitter's predicate device.		
A Design Control Activities Summary that includes the following elements (a-c):		
a) Identification of Risk Analysis method(s) used to assess the impact of the modification on the device and its components, and the results of the analysis.	**N/A**	
b) Based on the Risk Analysis, an identification of the required verification and validation activities, including the methods or tests used and the acceptance criteria to be applied.	**N/A**	
c) A Declaration of Conformity with design controls that includes the following statements:	**N/A**	
A statement that, as required by the risk analysis, all verification and validation activities were performed by the designated individual(s) and the results of the activities demonstrated that the predetermined acceptance criteria were met. This statement is signed by the individual responsible for those particular activities.	**N/A**	
A statement that the manufacturing facility is in conformance with the design control procedure requirements as specified in 21 CFR 820.30 and the records are available for review. This statement is signed by the individual responsible for those particular activities.	**N/A**	

Section 3: Required Elements for an ABBREVIATED 510(k)* submission:

	Present	Inadequate or Missing
For a submission, which relies on a guidance document and/or special control(s), a summary report that describes how the guidance and/or special control(s) was used to address the risks associated with the particular device type. (If a manufacturer elects to use an alternate approach to address a particular risk, sufficient detail should be provided to justify that approach.)	**N/A**	
For a submission, which relies on a recognized standard, a declaration of conformity **[**For a listing of the required elements of a declaration of conformity, **SEE Required Elements for a Declaration of Conformity to a Recognized Standard,** which is posted with the 510(k) boilers on the **H drive.]**	**N/A**	

	Present	Inadequate or Missing
For a submission, which relies on a recognized standard without a declaration of conformity, a statement that the manufacturer intends to conform to a recognized standard and that supporting data will be available before marketing the device.	**N/A**	
For a submission, which relies on a non-recognized standard that has been historically accepted by FDA, a statement that the manufacturer intends to conform to a recognized standard and that supporting data will be available before marketing the device.	**N/A**	
For a submission, which relies on a non-recognized standard that has not been historically accepted by FDA, a statement that the manufacturer intends to conform to a recognized standard and that supporting data will be available before marketing the device and any additional information requested by the reviewer in order to determine substantial equivalence.	**N/A**	
Any additional information, which is not covered by the guidance document, special control, recognized standard and/or non-recognized standard, in order to determine substantial equivalence.	**N/A**	

***** - When completing the review of an abbreviated 510(k), please fill out an Abbreviated Standards Data Form (located on the H drive) and list all the guidance documents, special controls, recognized standards and/or non-recognized standards, which were noted by the sponsor.

Section 4: Additional Requirements for ABBREVIATED and TRADITIONAL 510(k) submissions (If Applicable):

	Present	Inadequate or Missing
a) Biocompatibility data for all patient-contacting materials, OR certification of identical material/formulation:	**N/A**	
b) Sterilization and expiration dating information:	**Sec 14**	
i) sterilization process		
ii) validation method of sterilization process		
iii) SAL		
iv) packaging		
v) specify pyrogen free		
vi) ETO residues		
vii) radiation dose		
viii) Traditional Method or Non-Traditional Method		
c) Software Documentation:	**Sec 16**	

Items with checks in the "Present or Adequate" column do not require additional information from the sponsor. Items with checks in the "Missing or Inadequate" column must be submitted before substantive review of the document.

Passed Screening _____Yes _____No
Reviewer: _____
Concurrence by Review Branch: _____
Date: _____

Section 3: Certification of Compliance with Clinical Trials

See OMB Statement on Reverse. Form Approved: OMB No. 0910-0616, Expiration Date: 10-31-2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank (42 U.S.C. § 282(j))

(For submission with an application/submission, including amendments, supplements, and resubmissions, under §§ 505, 515, 520(m), or 510(k) of the Federal Food, Drug, and Cosmetic Act or § 351 of the Public Health Service Act.)

SPONSOR / APPLICANT / SUBMITTER INFORMATION

1. NAME OF SPONSOR/APPLICANT/SUBMITTER
LipoScience, Inc

2. DATE OF THE APPLICATION/SUBMISSION WHICH THIS CERTIFICATION ACCOMPANIES
December 23, 2011

3. ADDRESS *(Number, Street, State, and ZIP Code)*
2500 Sumner Boulevard
Raleigh, NC 27616

4. TELEPHONE AND FAX NUMBERS *(Include Area Code)*
(Tel.) 919-212-1999
(Fax) 919-256-1149

PRODUCT INFORMATION

5. **FOR DRUGS/BIOLOGICS:** Include Any/All Available Established, Proprietary and/or Chemical/Biochemical/Blood/Cellular/Gene Therapy Product Name(s)
FOR DEVICES: Include Any/All Common or Usual Name(s), Classification, Trade or Proprietary or Model Name(s) and/or Model Number(s)
(Attach extra pages as necessary)

Vantera Clinical Analyzer

NMR LipoProfile test

APPLICATION / SUBMISSION INFORMATION

6. TYPE OF APPLICATION/SUBMISSION WHICH THIS CERTIFICATION ACCOMPANIES
☐ IND ☐ NDA ☐ ANDA ☐ BLA ☐ PMA ☐ HDE ☒ 510(k) ☐ PDP ☐ Other

7. INCLUDE IND/NDA/ANDA/BLA/PMA/HDE/510(k)/PDP/OTHER NUMBER *(If number previously assigned)*
N/A

8. SERIAL NUMBER ASSIGNED TO APPLICATION/SUBMISSION WHICH THIS CERTIFICATION ACCOMPANIES

CERTIFICATION STATEMENT / INFORMATION

9. CHECK ONLY ONE OF THE FOLLOWING BOXES *(See instructions for additional information and explanation)*

☒ A. I certify that the requirements of 42 U.S.C. § 282(j), Section 402(j) of the Public Health Service Act, enacted by 121 Stat. 823, Public Law 110-85, do not apply because the application/submission which this certification accompanies does not reference any clinical trial.

☐ B. I certify that the requirements of 42 U.S.C. § 282(j), Section 402(j) of the Public Health Service Act, enacted by 121 Stat. 823, Public Law 110-85, do not apply to any clinical trial referenced in the application/submission which this certification accompanies.

☐ C. I certify that the requirements of 42 U.S.C. § 282(j), Section 402(j) of the Public Health Service Act, enacted by 121 Stat. 823, Public Law 110-85, apply to one or more of the clinical trials referenced in the application/submission which this certification accompanies and that those requirements have been met.

10. IF YOU CHECKED BOX C, IN NUMBER 9, PROVIDE THE NATIONAL CLINICAL TRIAL (NCT) NUMBER(S) FOR ANY "APPLICABLE CLINICAL TRIAL(S)," UNDER 42 U.S.C. § 282(j)(1)(A)(i), SECTION 402(j)(1)(A)(i) OF THE PUBLIC HEALTH SERVICE ACT, REFERENCED IN THE APPLICATION/SUBMISSION WHICH THIS CERTIFICATION ACCOMPANIES *(Attach extra pages as necessary)*
NCT Number(s): N/A

The undersigned declares, to the best of her/his knowledge, that this is an accurate, true, and complete submission of information. I understand that the failure to submit the certification required by 42 U.S.C. § 282(j)(5)(B), section 402(j)(5)(B) of the Public Health Service Act, and the knowing submission of a false certification under such section are prohibited acts under 21 U.S.C. § 331, section 301 of the Federal Food, Drug, and Cosmetic Act.
Warning: A willfully and knowingly false statement is a criminal offense, U.S. Code, title 18, section 1001.

11. SIGNATURE OF SPONSOR/APPLICANT/SUBMITTER OR AN AUTHORIZED REPRESENTATIVE (Sign)
Suzette Warner

12. NAME AND TITLE OF THE PERSON WHO SIGNED IN NO. 11
(Name) Suzette Warner
(Title) Regulatory Affairs Manager

13. ADDRESS *(Number, Street, State, and ZIP Code) (of person identified in Nos. 11 and 12)*
2500 Sumner Boulevard
Raleigh, NC 27616

14. TELEPHONE AND FAX NUMBERS *(Include Area Code)*
(Tel.) 919 256-1326
(Fax) 919-256-1149

15. DATE OF CERTIFICATION
12/9/11

Form FDA 3674 (11/08) (FRONT)

December 23, 2011

Food and Drug Administration
Center for Devices and Radiological Health
Office of Device Evaluation
Document Mail Center WO66-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Re: 510(k) Notification for Vantera® Clinical Analyzer for use with the *NMR LipoProfile* test

Dear Sir or Madam:

In accordance with Section 510(k) of the Federal Food, Drug, and Cosmetic Act, LipoScience, Inc. hereby notifies the Food and Drug Administration (FDA) of its intent to market a new device, the Vantera Clinical Analyzer for use with the *NMR LipoProfile* test.

The Vantera Clinical Analyzer is a Nuclear Magnetic Resonance (NMR) based clinical chemistry analyzer operating under the same NMR-based technology as the LipoScience NMR Profiler System. Like other clinical chemistry analyzers, the Vantera Clinical Analyzer automates specimen handling, sample preparation, data acquisition, results calculation and all interfaces to the clinical laboratory infrastructure. Like the NMR Profiler, the Vantera provides quantitative measure of multiple analytes in blood plasma and serum using nuclear magnetic resonance spectroscopy. The Vantera Clinical Analyzer has been developed under FDA design controls and is manufactured per FDA regulations specified in 21 CFR 820. The Vantera is intended to run multiple in vitro diagnostic tests utilizing NMR technology. The initial menu will consist of the same analytes run in the FDA cleared *NMR LipoProfile* test (k111516), a cardiovascular diagnostic test that uses NMR spectroscopy to uniquely provide rapid, simultaneous, and direct measurement of LDL-P, HDL-C and Triglycerides.

Please note that the Vantera® Clinical Analyzer was identified as "Numera" during the initial development phase. As a result, some development documents referenced in this submission may still utilize the previous name. References to the Vantera system and the Numera system are identical in their meaning.

LipoScience, Inc. is submitting this Traditional 510(k) Notification for the Vantera Clinical Analyzer for use with the *NMR LipoProfile*® test. Per the instructions accessed at "Electronic Copies for Pre-Market Submissions", an electronic copy is being provided with the submission and it is an exact duplicate of the original paper submission.

TYPE OF SUBMISSION

Traditional

PAYMENT IDENTIFICATION NUMBER

The MDUFMA PIN is (b)(4) [redacted]

REFERENCE 510(k) NUMBER

K073506, March 7, 2008
K111516, September 27, 2011

DEVICE TYPE

The Vantera Clinical Analyzer is a clinical laboratory analyzer that employs nuclear magnetic resonance spectroscopic detection to quantify multiple analytes in biological fluid specimens, specifically blood plasma and serum.

MODEL NUMBER AND NAME

003-00095ADH – Vantera System

SUBMITTER

LipoScience, Inc
2500 Sumner Boulevard
Raleigh, NC 27616

OFFICIAL CORRESPONDENT

Suzette Warner
Regulatory Affairs Manager
Tel – (919) 256-1326
Fax - (919) 256-1149
Email – suzette.warner@lipocscience.com

CONFIDENTIALITY

We request as outlined under 21 CFR 807.95 that FDA treat this premarket notification and our intent to market as confidential commercial information under the conditions and requirements of CFR 807.95.

CLASSIFICATION

CFR 862.2570, Instrumentation for clinical multiplex test systems
CFR 862.1475, Lipoprotein Test System
CFR862.1705, Triglyceride Test System
CFR 862.1660, Quality Control Material
CFR 862.1150, Calibrator

CLASS

Class II (Special Controls)
Class I

PANEL

Clinical Chemistry (75)

PRODUCT CODE

NSU, Instrumentation for Clinical Multiplex Test Systems
MRR, Lipoprotein test system
LBS, Lipoprotein test system
CDT, Triglyceride test system
JJY, Quality Control Material
JIT, Calibrator

PREVIOUS FDA DOCUMENTS

510(k) #k063841- NMR LipoProfile test and NMR Profiler, Control; cleared by FDA on July 23, 2008.
510(k) #k111516 NMR LipoProfile test and NMR Profiler; cleared by FDA on September 27, 2011.

BASIS FOR THE SUBMISSION

This is a new instrumentation for clinical multiplex system to be used with *NMR LipoProfile* test.

QUESTION	YES	NO
Is the device intended for prescription use (21 CFR 801 Subpart D)?	Yes	
Is the device intended for over-the-counter use (21 CFR 801 Subpart C)?		No
Does the device contain components derived from a tissue or other biologic source?		No
Is the device provided sterile?		No
Is the device intended for single use?		No
Is the device a reprocessed single use device?		No
If yes, does this device type require reprocessed validation data?		No
Does the device contain a drug?		No
Does the device contain a biologic?		No
Does the device use software?	Yes	
Does the submission include clinical information?	No	
Is the device implanted?		No

We trust that the information provided in this 510(k) premarket notification is sufficient for FDA to find the proposed device substantial equivalent to its predicate devices for the listed indications. Please do not hesitate to contact me should you have any questions or require any additional information.

Sincerely,

Suzette M. Warner

Suzette M. Warner

Enclosure

Table of Contents

OVERVIEW OF VOLUMES

Section 5: Indications for Use Statement

As required, we have prepared the Indications for Use statement on a separate page without headers.

Indications for Use Form

510(k) Number (if known)**:** ___Not Known at this time_____(To be assigned)

Device Name: Vantera® Clinical Analyzer

Indications for Use:

The Vantera® Clinical Analyzer is an automated laboratory test analyzer which measures the 400 MHz proton nuclear magnetic resonance (NMR) spectrum of clinical samples to produce signal amplitudes, converting these signal amplitudes to analyte concentration. The device includes a 400 MHz NMR spectrometer and software to analyze digitized spectral data. This instrumentation is intended to be used with NMR based assays to detect multiple analytes from clinical samples.

Prescription Use _____ (Part 21 CFR 801 Subpart D) AND/OR Over-The-Counter Use _____ (21 CFR 801 Subpart C)

(PLEASE DO NOT WRITE BELOW THIS LINE-CONTINUE ON ANOTHER PAGE OF NEEDED)

_____

Concurrence of CDRH, Office of In Vitro Diagnostic Devices (OIVD)

_____ Division Sign-Off Office of In Vitro Diagnostic Device Evaluation and Safety

510(k)_____

Indications for Use Form

510(k) Number (if known)**:** Not Known at this Time_____(To be assigned)

Device Name: NMR LipoProfile® test on Vantera® Clinical Analyzer

Indications for Use:

The *NMR LipoProfile*® test, when used with the Vantera® Clinical Analyzer, an automated NMR spectrometer, measures lipoprotein particles to quantify LDL particle number (LDL-P), HDL cholesterol (HDL-C), and triglycerides in human serum and plasma using nuclear magnetic resonance (NMR) spectroscopy. LDL-P and these NMR-derived concentrations of HDL-C and triglycerides are used in conjunction with other lipid measurements and clinical evaluation to aid in the management of lipoprotein disorders associated with cardiovascular disease.

Prescription Use _____ (Part 21 CFR 801 Subpart D) AND/OR Over-The-Counter Use _____ (21 CFR 801 Subpart C)

(PLEASE DO NOT WRITE BELOW THIS LINE-CONTINUE ON ANOTHER PAGE OF NEEDED)

_____

Concurrence of CDRH, Office of In Vitro Diagnostic Devices (OIVD)

_____ Division Sign-Off Office of In Vitro Diagnostic Device Evaluation and Safety

510(k)_____

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13.1 Table of Comparison and Differences vs. Predicates

We will present a comparison of the proposed device, Vantera® Clinical Analyzer, and the predicates Table 13-1 through Table 13-2 and then discuss the similarities and differences.

The predicate instrument comparison is broken into several categories:

- Intended Use
- Technology
- Multi-Analyte
- Detection Method
- System Fluidics
- Specimen Sampling and Handling
- System Calibration
- Quality Control Checks
- Specimen ID
- Data Acquisition

The predicate assay comparison is broken into several categories:

- Intended Use
- Patient Population
- Analyzer
- Instrument Platform
- Specimen
- Reagent and Materials
- Spectral Deconvolution Computational Method
- Reference Range

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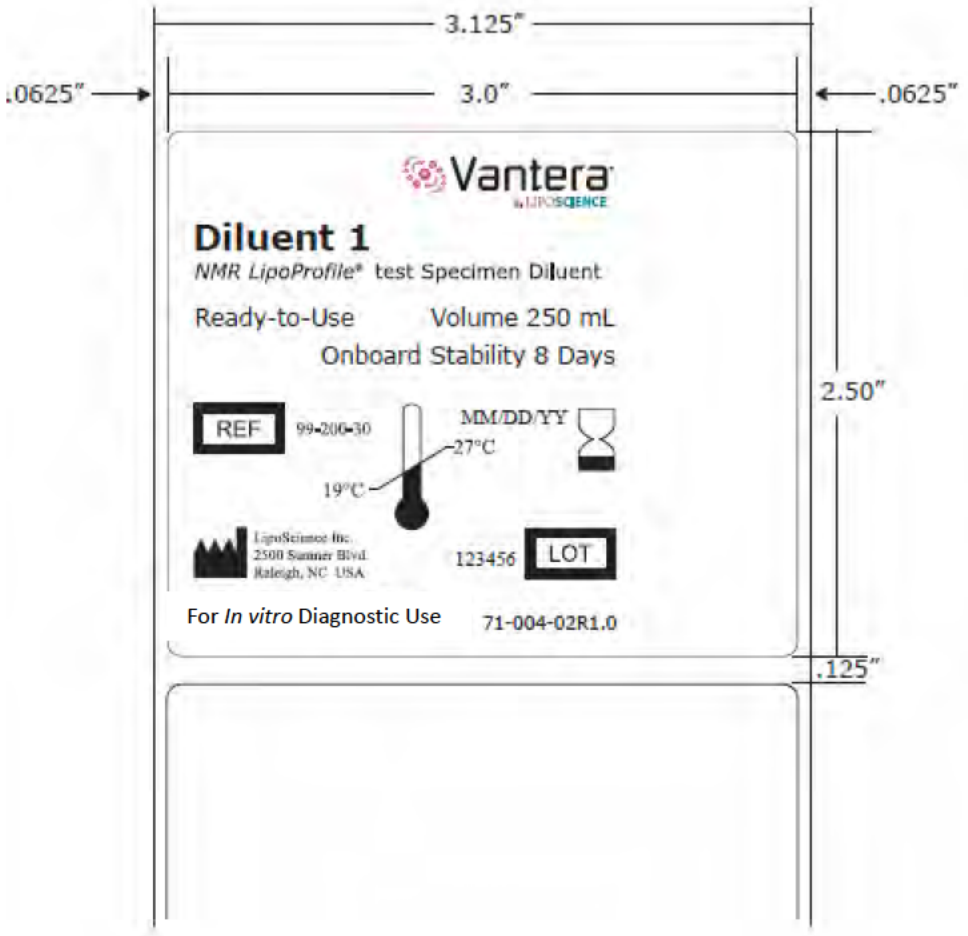
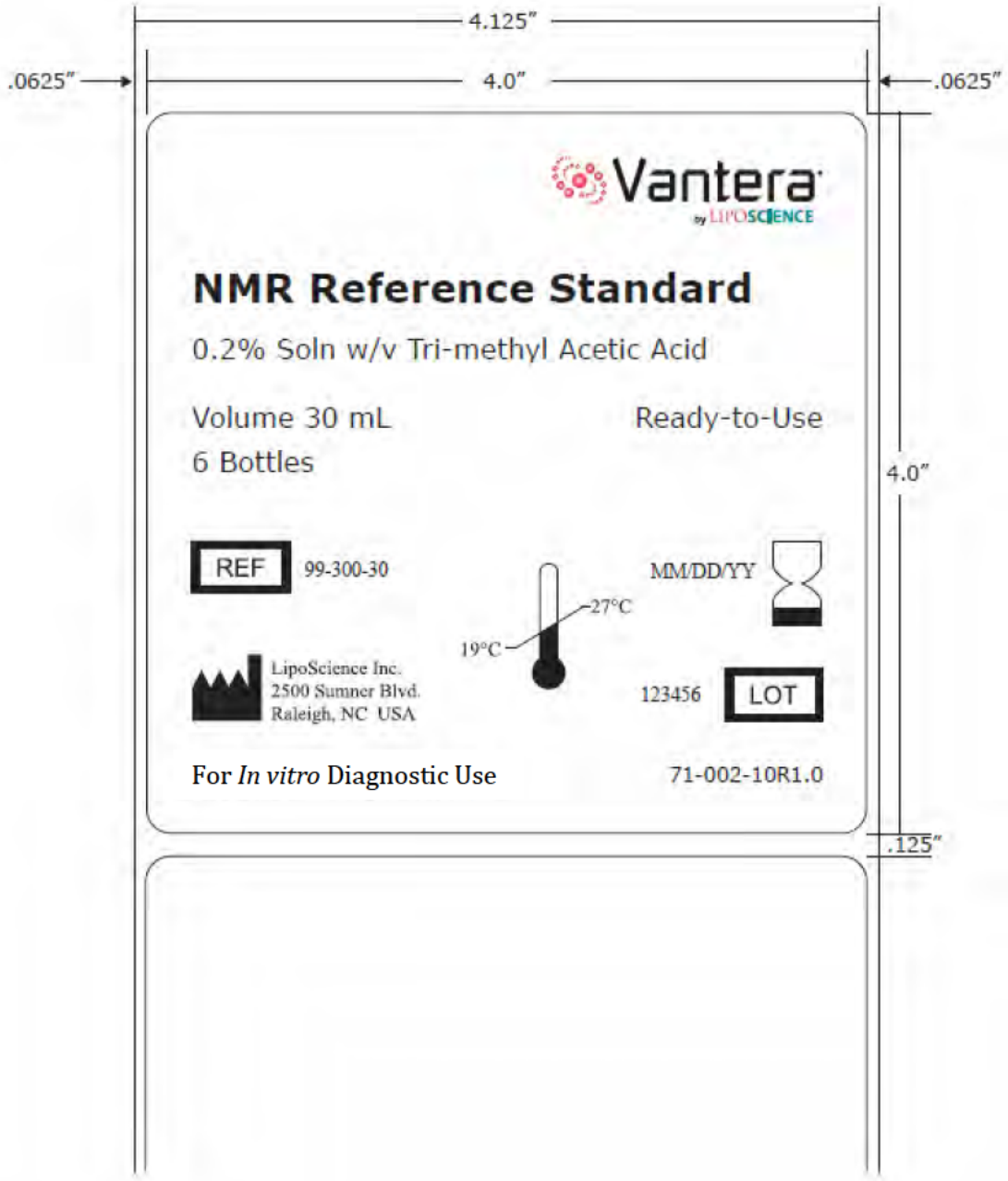
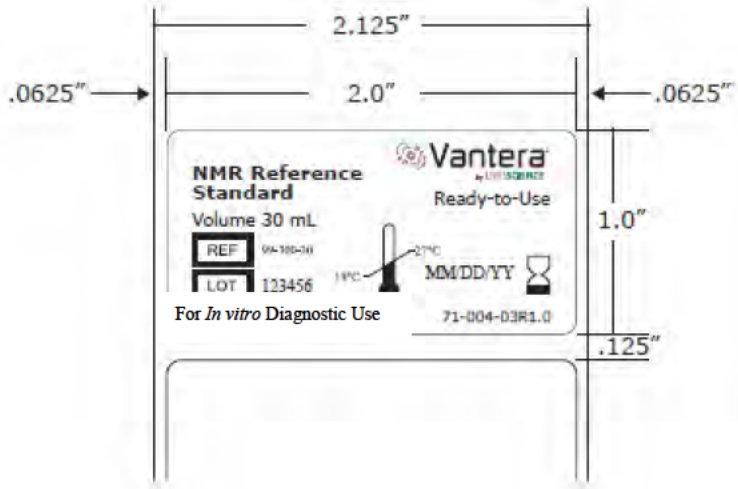
14.1.2 Diluent 1 Bottle Label



14.1.3 Intermediate (Box) NMR Reference Standard Label

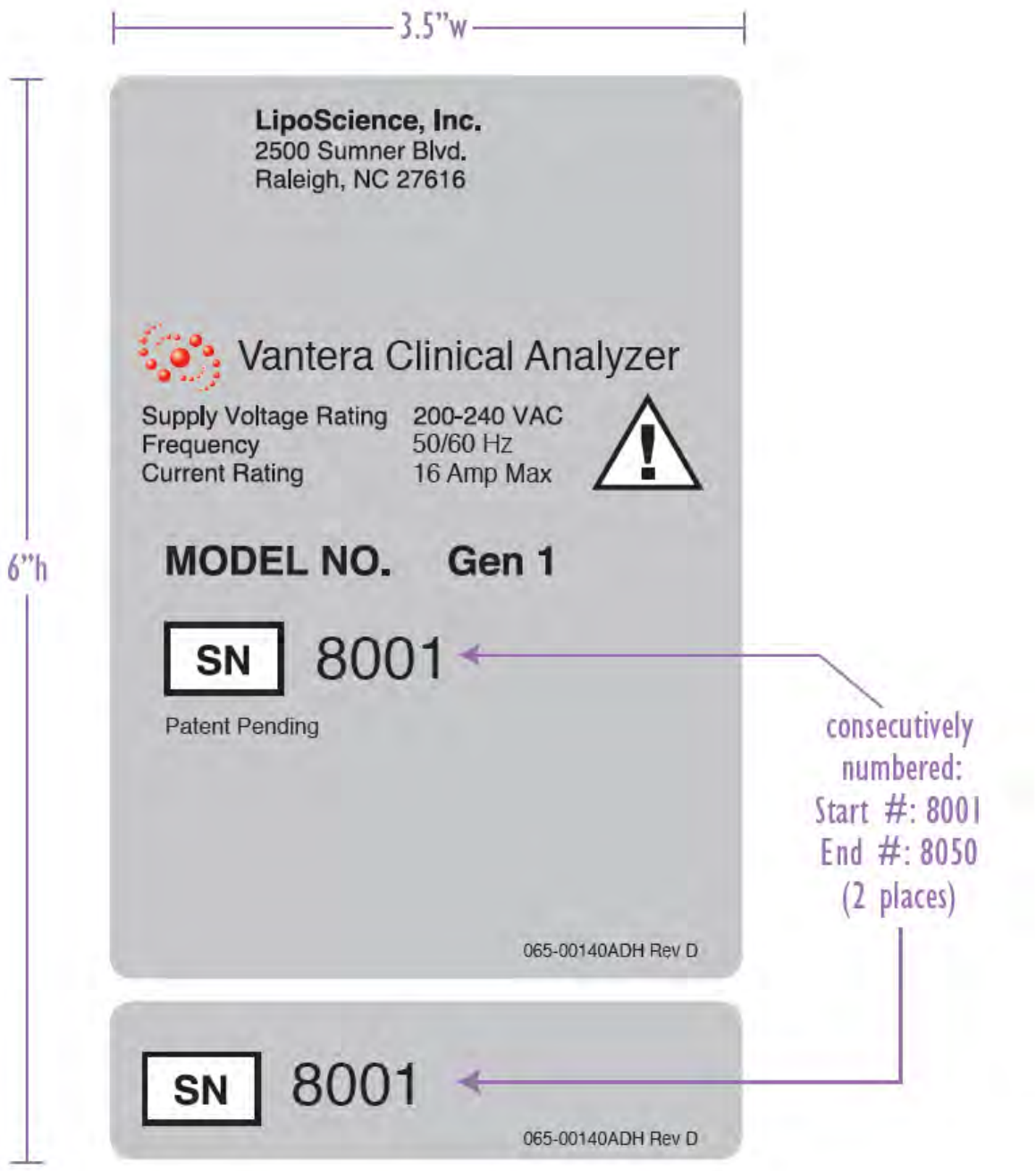


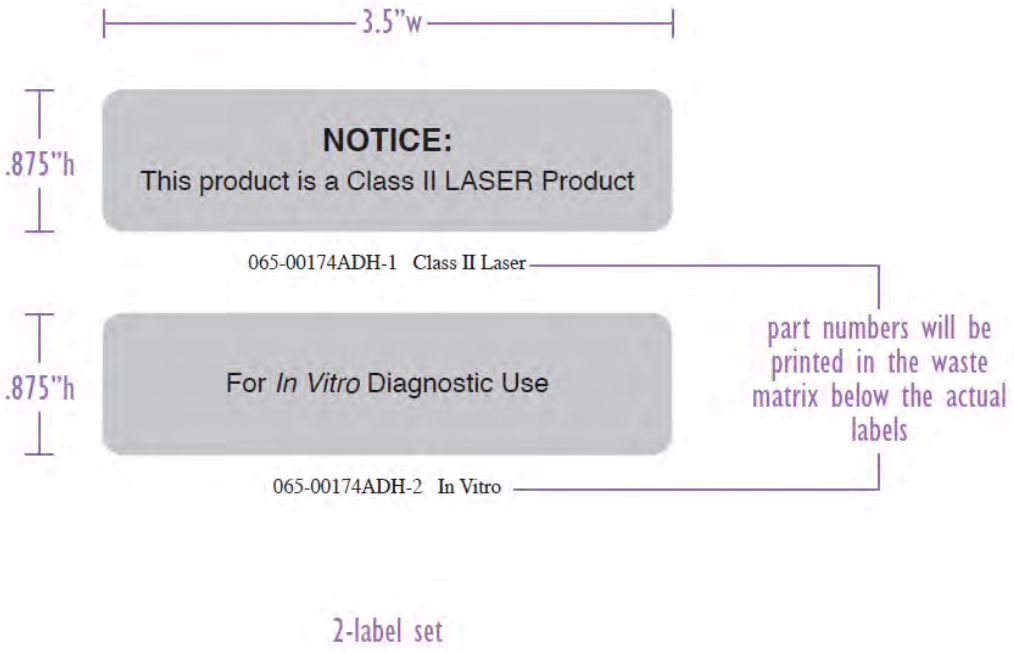
14.1.4 NMR Reference Standard Bottle Label



14.1.5 WASH Bottle Label

14.1.6 Vantera Clinical Analyzer Rating Labels





2-label set

1.25"W X 1.25" H

14.1.7 Proposed NMR *LipoProfile* Product Insert - DRAFT

NMR *LipoProfile*® test on Vantera® Clinical Analyzer by LipoScience

For *In Vitro* Diagnostic Use

INTENDED USE

The *NMR LipoProfile*® test by LipoScience, used with Vantera® Clinical Analyzer, an automated NMR spectrometer, measures lipoprotein particles to quantify LDL particle number (LDL-P), HDL cholesterol (HDL-C), and triglycerides (TG) in serum and plasma using nuclear magnetic resonance (NMR) spectroscopy. LDL-P and these NMR-derived concentrations of triglycerides and HDL-C are used in conjunction with other lipid measurements and clinical evaluation to aid in the management of lipoprotein disorders associated with cardiovascular disease.

SUMMARY AND EXPLANATION

Lipoprotein (HDL, LDL, and VLDL) particles play key roles in atherogenesis and their concentrations in plasma or serum are important cardiovascular disease (CVD) risk factors. For clinical use, lipoprotein levels are traditionally estimated by measuring one or more of their lipid constituents. The cholesterol within LDL and HDL particles (LDL-C and HDL-C) is used to approximate serum or plasma LDL and HDL levels, while total plasma triglycerides approximate VLDL levels. The *NMR LipoProfile*® test by LipoScience employs a novel automated process to measure NMR signals from LDL, HDL, and VLDL particles simultaneously [1]. The detected lipoprotein signals are proportional in amplitude to the numbers of lipoprotein particles emitting the signals, enabling a calculation of their concentrations. LDL is reported in terms of particle numbers (LDL-P) providing another measure of a patient's LDL level.

Lipoproteins that interact with the arterial wall set in motion the cascade of events leading to atherosclerosis [2]. LDL is the major atherogenic lipoprotein and is identified in ATP III guidelines as the primary target of treatment for reducing coronary heart disease risk [3]. According to a report from the American Diabetes Association (ADA) and American College of Cardiology (ACC), measurement of LDL-C may not accurately reflect the true burden of atherogenic LDL particles, especially in those patients with the typical lipoprotein abnormalities of cardiometabolic risk [4]. The ADA/ACC report also states that measurements of apolipoprotein B or LDL-P may more closely quantitate the atherogenic lipoprotein load. [4] Thus, they may aid in the management of patients with elevated risk of CVD. LDL-P measured by the *NMR LipoProfile*® test by LipoScience has been shown to be a determinant of CVD risk in two prospective case-control studies [5, 6].

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14.2 Promotional Information

14.2.1 Vantera Clinical Analyzer Product Specification - DRAFT

Vantera® Clinical Analyzer

Product Specifications

General Characteristics

Capability	Fully automated multi-assay, clinical laboratory analyzer that employs nuclear magnetic resonance spectroscopic detection to quantify multiple analytes in biological fluid specimens.
Configuration	Free Standing
Sample Capacity	Up to 200 Samples (in 20 Vantera® (10 x 1) Tube Racks)
Sample Type	Undiluted serum, plasma
Supported Sample Tubes (Uncapped)	12mm x 75mm
	13mm x 75mm
	13mm x 100mm
	16mm x 100mm
Aspiration Volume	150 µL per test
Assay Fluid Capacity	Up to six - 250ml bar coded bottles
Bulk Fluid Capacity	Two - 5L bottles - 1 wash (supplied by LipoScience) and 1 rinse – de-ionized water (refilled by user)
Waste Capacity	One - 5L bottle
Required Cryogens	Liquid nitrogen (refilled by user) and Liquid helium (refilled by LipoScience Service)
Certifications	U.L.

Environmental Requirements

Room Temperature	63°F to 75°F (17°C to 24°C)
Humidity	20% to 60% RH
Altitude	Not specified
Laboratory Size (Length x Width x Height)	16 ft. x 16 ft. x 9 ft. minimum
Ventilation	45 m^3/min, minimum

Physical Characteristics

Size (Length x Width x Height)	126.00" x 49.00" x 71.00" (320.04 x 124.46 x 180.34 cm)
Weight	2496 lbs. (1132.17 kgs)
Service Access Perimeter	3 ft. (91.44 cm) unobstructed perimeter around the system with a minimum 4 ft. (121.92 cm) path to the system

Electrical Specifications

Voltage	200 - 240 VAC
Current	16 Amps
Frequency	60Hz
Power Connection	Wall-outlet, Hubbel Twist-Lok

Note: The Vantera® Clinical Analyzer should be plugged directly into a UPS, which is in turn plugged directly into facility power. Facility power must meet all building codes to ensure proper grounding of the device.

Other Connections

LIS Support	ASTM 1381 1394 Supported
Connections	Ethernet Connections
	USB Printer Port
	RS-232 serial port for UPS; RS-232 serial port for LIS
Laboratory Compressed Air	90 - 100 psi, 20 L/min, minimum
	Requires ¼-inch male NPT connector at the wall
Filtered Air Supply	Comply with ISO8573-1, Class 4

LipoScience, Inc.
2500 Sumner Blvd, Raleigh NC 27616
877-547-6837 I www.liposcience.com

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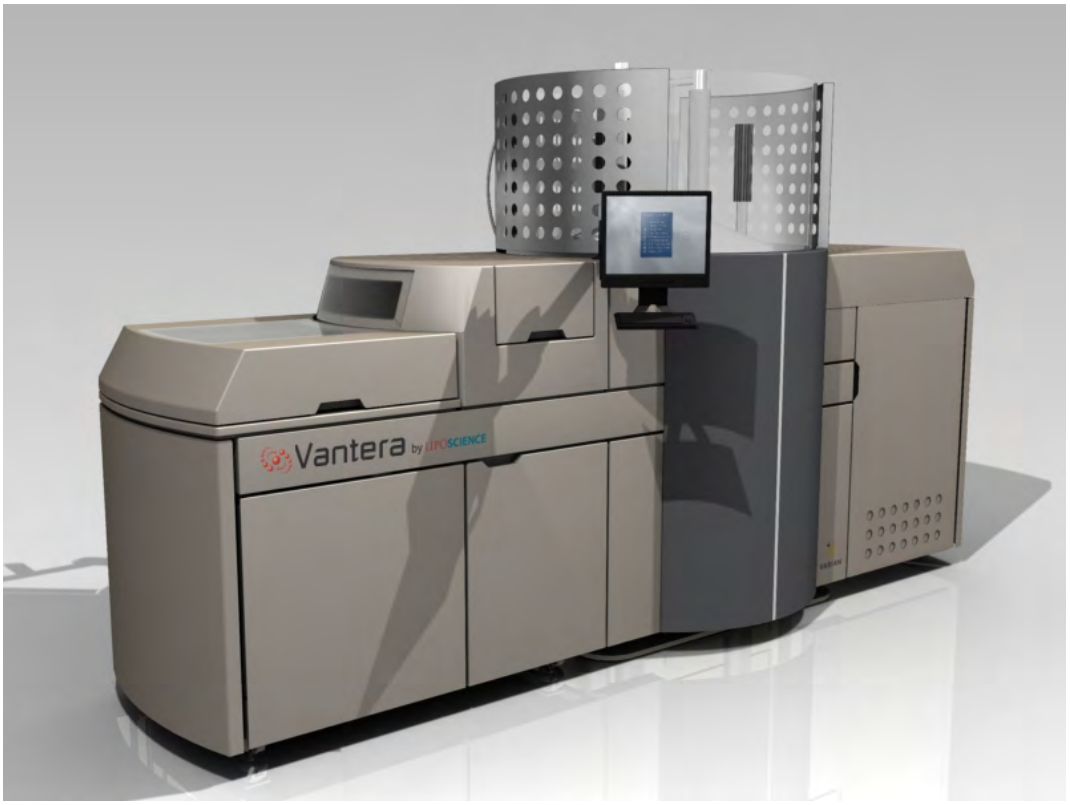
14.3 Vantera Clinical Analyzer User's Manual

User's Manual
Version 5.0
December 9, 2011
80-001-01-UM

Vantera® Clinical Analyzer

For In-vitro Diagnostic Use



LipoScience, Inc.
2500 Sumner Blvd.
Raleigh, NC 27616
Main: 877-547-6837 or 919-212-1999
Technical Assistance Center: 866-799-5297
www.liposcience.com

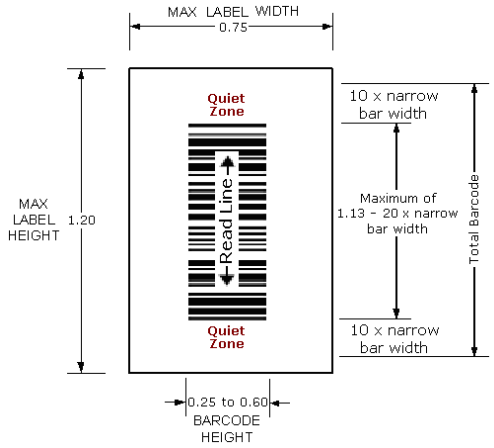
NMR LipoProfile® test is a registered trademark of LipoScience, Inc.

Vantera® Clinical Analyzer is a registered trademark of LipoScience, Inc.

FCC Part 15: This device complies with Part 15 of the FCC Rules. Operation is subject to the following two conditions: (1) this device may not cause harmful interference, and (2) this device must accept any interference received, including interference that may cause undesired operation.

ICES-003: This Class A digital apparatus complies with Canadian ICES-003. Cet appareil numérique de la classe A est conforme à la norme NMB-003 du Canada.

Contents



Summary of warnings and cautions

CAUTION

Cautions alert you to situations when failure to observe instructions could result in serious damage to equipment or loss of data.

WARNING

Warnings alert you to potentially hazardous situations that could result in serious injury or death to humans or animals, or significant property damage.

Observe the following precautions during operation of the instrument. Failure to comply with these warnings may result in instrument damage, injury, or death.

Intended use

WARNING: Follow all instructions provided by the manufacturer for the operation of this device.

User injury or impairment may result if the system is used in a manner not specified by manufacturer. Refer to “Statement of intended use” on page 1.

Technical assistance

WARNING: Contact the LipoScience Technical Assistance Center at 866-799-5297 if there is any system malfunction that you cannot resolve.

Equipment access

WARNING: In the event of a system failure, do not open or remove any user accessible covers until it is determined that the user is safe from moving parts.

CAUTION: Maintain a 3-ft unobstructed access area around the device.

Equipment damage may result if there is not adequate access to the mains power switch and to the liquid nitrogen and liquid helium fill valves.

Asphyxiation

WARNING: Leave the area immediately in the event of a magnet quench.

If the magnet should quench (a sudden release of extremely cold liquids or gasses from the top of the magnet), leave the area immediately. A sudden release of helium or nitrogen liquids or gases can rapidly displace oxygen in an enclosed space creating a possibility of asphyxiation. Do not return until the release of cryogens has stopped and the room has been ventilated so that oxygen level returns to normal.

WARNING: Ensure that the laboratory meets or exceeds minimum room size and ventilation requirements.

In the unlikely event of a magnet quench, the ventilation system will permit your safe evacuation from the laboratory.

WARNING: Do not remove the relief valves on the vent tubes.

Relief valves prevent air from entering the nitrogen and helium vent tubes. Air that enters the magnet contains moisture that can freeze, causing blockage of the vent tubes and possibly extensive damage to the magnet. It could also cause a quench. The relief valves should always be secured on the vent tubes, except when transferring nitrogen or helium.

CAUTION: Check helium and nitrogen gas flow meters daily.

Record the gas flow readings to confirm appropriate operating levels. The readings will vary somewhat because of changes in barometric pressure. If the readings for either gas should change abruptly, contact the Technical Assistance Center (TAC). Failure to correct the cause of abnormal readings could result in extensive equipment damage.

Biohazard exposure

WARNING: Assume that all specimens, control materials, waste fluids, leaks, and spills contain potentially infectious biological material.

Handle all specimens, control materials, and waste fluids in accordance with Universal Precautions, including the use of Personal Protective Equipment (PPE), as prescribed in package inserts and in accordance with your standard laboratory operating procedures. Clean and disinfect all leaks and spills.

Chemical exposure

WARNING: Observe all handling instructions on the manufacturer's package, including the use of Personal Protective Equipment (PPE), for all instrument fluids and cleaning agents.

Skin or eye contact with instrument fluids and cleaning agents may be hazardous.

Electrical shock

WARNING: Only qualified service personnel shall remove equipment covers or perform internal instrument adjustments.

Dangerous high voltages that can kill or injure exist inside the instrument.

WARNING: Do not insert any objects or tools into the instrument when a lower cover on the sample handler or NMR console is open, through an opening in a cover, or near electrical or electronic components such as the power supply.

The object may come in contact with dangerous high voltages that exist inside the instrument, which can kill or injure.

Pinch, crush, and puncture hazards

WARNING: Keep hands away from moving parts when access doors are open.

Injuries may result from moving parts. Operation of the instrument with the covers open is potentially hazardous and is not recommended. Keep body parts, hair, and clothing clear of all moving parts. The instrument automatically stops most motors as soon as a cover is opened. The exceptions are the load and unload areas, which continue to move racks when a cover is open. Also, there is limited movement of the metering arm (initiated by the user) to allow replacement of the sample probe tip.

Pinch hazards exist in the carousel area. Crush hazards exist in the load, unload, and carousel areas. Puncture hazards exist in the sample mixing area.

Laser exposure

WARNING: Laser radiation. Do not stare into beam.

The bar code readers in the load area, the carousel, and the bulk fluid areas are Class II lasers.

The following labels are located on the top, side, and bottom of the MS-3 FIS-0003 Reader:

Top

Side

Bottom

Approvals

This equipment is in compliance or approved by the following organizations:

- CDRH (Center for Devices & Radiological Health)
- UL (Underwriters Laboratories, Inc.)
- cUL (UL mark of Canada)
- FCC (Federal Communication Commission)
- CE Compliant
- BSMI (Bureau of Standards, Metrology and Inspection)

Warning and Caution Summary

This equipment has been tested and found to comply with the limits for a Class A digital device, pursuant to part 15 of the FCC Rules. These limits are designed to provide reasonable protection against harmful interference in a residential installation. This equipment generates, uses, and can radiate radio frequency energy, and, if not installed and used in accordance with the instructions, may cause harmful interference to radio communications. However, there is no guarantee that interference will not occur in a particular installation. If this equipment does cause harmful interference to radio or television reception, which can be determined by turning the equipment off and on, the user is encouraged to try to correct the interference by one or more of the following measures:

- Reorient or relocate the receiving antenna.
- Increase the separation between the equipment and receiver.
- Connect the equipment into an outlet on a circuit different from that to which the receiver is connected.
- Consult the dealer or an experienced radio/TV technician for help.
- For connection to a UL Listed direct plug-in power unit marked Class 2 and rated at 5VDC at 2 Amps or greater.

- European models must use a similarly rated Class I or Class II power supply that is certified to comply with standard for safety EN 60950.

WARNING

Use of controls, adjustments, or performance of procedures other than those specified herein may result in hazardous laser light radiation exposure.

WARNING

There are no user serviceable parts in the scanner. Opening the scanner voids the Micros-can Systems warranty and could expose the user to laser diode power of up to 7mW.

WARNING

The laser beam can be harmful to eyesight. Avoid eye contact with the laser beam. Never point the beam at other people, or in a direction where people may be passing.

Magnetic field exposure

WARNING: Persons with implanted or attached medical devices such as pacemakers and prosthetic parts must remain outside the 360° perimeter of the magnet enclosure. It is recommended that a person with a pacemaker NOT operate the system without the express approval of his or her physician.

The superconducting magnet system generates strong magnetic fields that can affect operation of some cardiac pacemakers or harm implanted or attached devices such as prosthetic parts, and metal blood vessel clips and clamps.

Pacemaker wearers should consult the user manual provided by the pacemaker manufacturer or contact the pacemaker manufacturer to determine the effect on a specific pacemaker. Pacemaker wearers should also always notify their physician and discuss the health risks of being in proximity to magnetic fields. Wearers of metal prosthetics and implants should contact their physician to determine if a danger exists.

WARNING: Keep metal objects outside the 10-gauss perimeter from the centerline of the magnet. This area includes a 2 ft, 360° perimeter from the magnet enclosure, the space between the floor and the bottom of the magnet, and the space within 4 ft above the magnet.

Although the magnet is heavily shielded, a residual magnetic field still exists outside of the magnet enclosure. This field is the strongest underneath and above the magnet. The residual magnetic field is still strong enough to attract lightweight objects containing steel, iron, or other ferromagnetic materials. Such materials must be kept outside of the covers to prevent them from being drawn in by the magnetic field. Objects drawn into the magnet bore may damage the magnet or other components. The greater the mass of the object, the more strongly the magnet attracts the object and the more damage that might be sustained.

Only nonferromagnetic materials—plastics, aluminum, wood, nonmagnetic stainless steel, etc.—should be used in the area around the magnet. If an

object is stuck to the magnet surface and cannot easily be removed by hand, contact the Technical Assistance Center (TAC) for assistance.

CAUTION: Keep magnetic media, ATM and credit cards, and watches outside the 360° perimeter of the magnet enclosure.

The strong magnetic field surrounding a superconducting magnet can erase magnetic media such as floppy disks and tapes. The field can also damage the strip of magnetic media found on credit cards, automatic teller machine (ATM) cards, and similar plastic cards. Many wrist and pocket watches are also susceptible to damage from intense magnetism.

Thermal exposure

WARNING: Avoid helium or nitrogen contact with any part of the body.

The Vantera Clinical Analyzer uses helium and nitrogen, which are supercooled gases. In their liquid forms or as escaping gases, as in the case of a quench, they can cause immediate frostbite injury if they come in contact with exposed skin. Never place your head or other body parts over the helium and nitrogen exit tubes on top of the magnet. If helium or nitrogen contacts the body, seek immediate medical attention, especially if the skin is blistered or the eyes are affected.

WARNING: The rotating magnet cover should be closed at all times in order to prevent the possible exposure to helium or nitrogen during a magnet quench.

In contact with the body, helium and nitrogen can cause an injury similar to a burn. Never place your head over the helium and nitrogen exit tubes on top of the magnet. If helium or nitrogen contacts the body, seek immediate medical attention, especially if the skin is blistered or the eyes are affected.

WARNING: You must wear proper Personal Protective Equipment (gloves, aprons, and face shields) while filling the nitrogen supply or working with the metal fittings on the magnet.

Direct contact of the skin with cold metal fittings during the nitrogen fill can cause the skin to freeze to the fittings resulting in serious injury.

Hazards from sharp objects and sharp edges

WARNING: Use extreme care when handling specimen racks and tubes, and when near sharp edges on the instrument. Dispose of all cracked or broken specimen tubes

Failure to use caution near sharp objects could result in injury.

Incorrect test results

CAUTION: Follow all instructions provided in the assay package inserts.

Failure to adhere to instructions provided in the assay package inserts, including specimen collection and processing, assay performance, and reporting may produce incorrect test results.

CAUTION: Do not use expired fluids.

Use of expired fluids can result in incorrect test results.

1 Introduction

Statement of intended use

The Vantera® Clinical Analyzer is an automated laboratory test analyzer which measures the 400 MHZ proton nuclear magnetic resonance (NMR) spectrum of clinical samples to produce signal amplitudes, converting these signal amplitudes to analyte concentration. The device includes a 400 MHz NMR spectrometer and an analysis server containing software to analyze digitized spectral data. This instrumentation is intended to be used with NMR based assays to detect multiple analytes from clinical samples by technologists trained in laboratory techniques, procedures and on the use of the analyzer.

WARNING

User injury or impairment may result if the system is used in a manner not specified by manufacturer.

System overview

Nuclear magnetic resonance

Nuclear magnetic resonance (NMR) technology has been in existence for more than 40 years. The Vantera Clinical Analyzer is the first to adapt this technology for use in an *in vitro* diagnostic analyzer.

In the Vantera Clinical Analyzer, the sample to be analyzed flows through system tubing into a glass flowcell located at the center of the NMR magnet. This magnet is constructed of a coil of superconducting wire immersed in liquid helium. The strong magnetic field at the center of this magnet aligns the magnetically polarized particles in the sample to this field. A radio frequency signal is transmitted into the sample. This signal causes the molecules in the sample to momentarily alter their position in the magnetic field. When they return to their original position, a very small “resonant” radio frequency signal is transmitted, which is detected by the NMR system. Analysis of this signal can then determine the size, number, and type of molecules in the sample. In most cases, this process is repeated several times during sample testing.

How the Vantera System processes specimens

The processing of specimens on the Vantera Clinical Analyzer starts with their placement on the system. The user places serum or plasma specimen tubes in racks, and then places the racks on the system. After reading the bar code on a specimen tube, the system schedules the test or tests to be performed.

Usually, the sample processing robotic arm starts the process by aspirating the diluent into a mixing cup. The arm then aspirates an aliquot of the specimen from the tube. The system dispenses the diluent and specimen

into a dilution station at a high rate, which causes them to mix. The fluidics system within the Vantera Clinical Analyzer creates a sample “train” that consists of a sequence of sample segments in the system tubing that are separated by air bubbles.

Once the sample train is constructed, it flows through the system tubing until the largest segment of the sample fills the glass flowcell at the center of the NMR magnet. The sample is then subjected to a series of NMR scans that returns signals to the NMR electronics for analysis. The results of these scans are used to determine the clinical results for the test or tests being performed. After analysis by the NMR, the system moves the sample to waste. Finally, the system rinses and flushes the fluidics system, including the flowcell, in preparation for the next test.

How the Vantera Clinical Analyzer is different

The Vantera Clinical Analyzer is very different from most laboratory analyzers, such as those that perform clinical chemistry or immunoassays. Unlike those systems, the Vantera Clinical Analyzer does not alter the sample being tested in any way. The system does not add test-specific reagents to cause a change in the sample, such as a change in color or fluorescence, for detection. Also, in most cases, separate NMR scans are not required for each test being performed on the sample. All the test results are generated from the NMR spectrum.

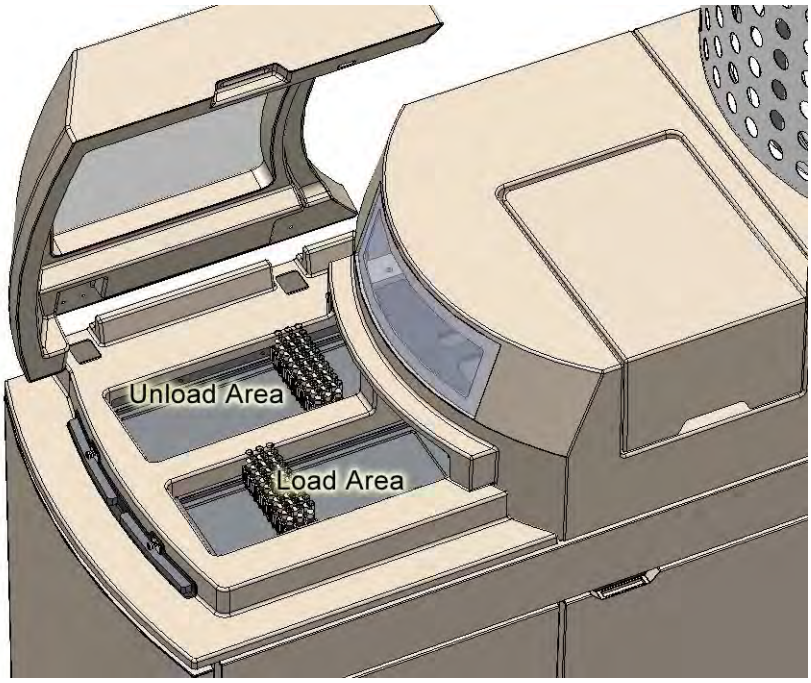
System components

Load, Transfer, and Unload Areas

The Load Area is the compartment where you place patient specimens, controls, and the NMR Reference Standard into the Clinical Analyzer for testing. You can access the Load Area by opening a cover. You must use one of the specimen tubes supported by the Vantera Clinical Analyzer. Supported tubes are listed in “Specifications” on page 85. Each specimen tube must have a Vantera readable bar code label. The NMR Reference Standard and control tubes provided by LipoScience have bar codes. The specimen tubes are placed in the Vantera racks with the bar code label visible through the slot in the side of the rack.

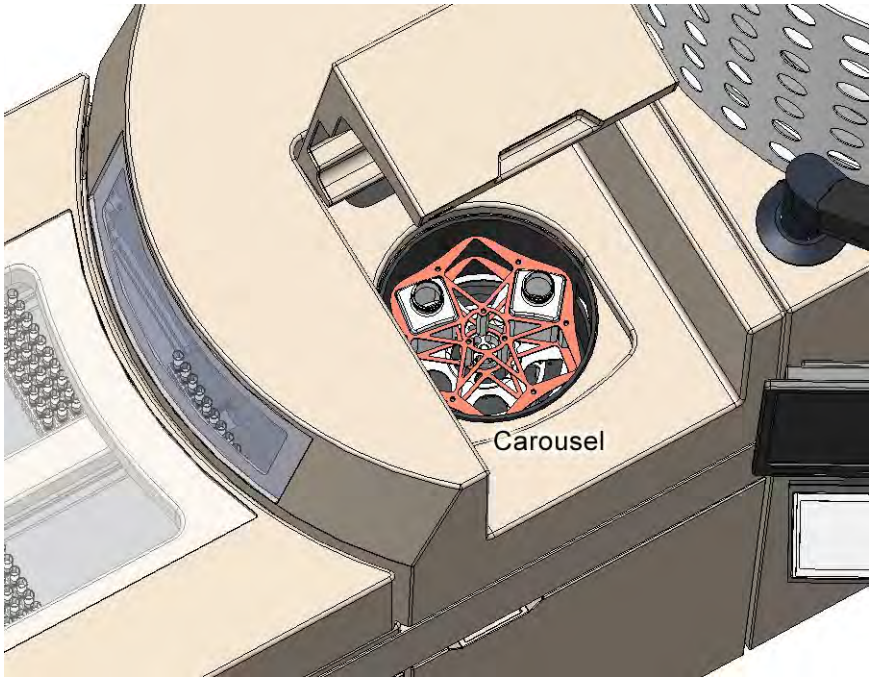
When the Vantera Clinical Analyzer is processing specimens, the rack is automatically moved into the Transfer Area where the system processes specimens one tube location at a time until all the tubes in the rack are processed. There is no access to the Transfer area to eliminate exposure to moving parts and biological materials.

When the last specimen is processed, the Vantera Clinical Analyzer moves the rack into the Unload Area where the rack can be removed. You can access the Unload Area by opening a cover.



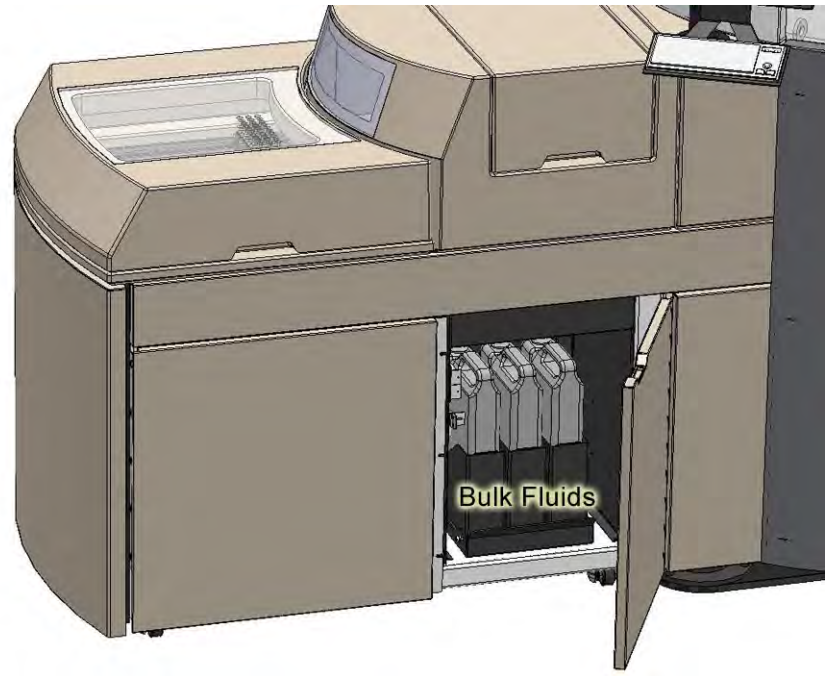
Carousel

The Carousel holds up to six separate system fluids. Each 250-ml bottle carries a bar code label that enables the Clinical Analyzer to determine the identity of the fluid in the bottle and the expiration date. During the sampling process, the system determines the amount of fluid in each container. The fluid level of each container is displayed in the Carousel status screen (refer to page 36).



Bulk fluid reservoirs

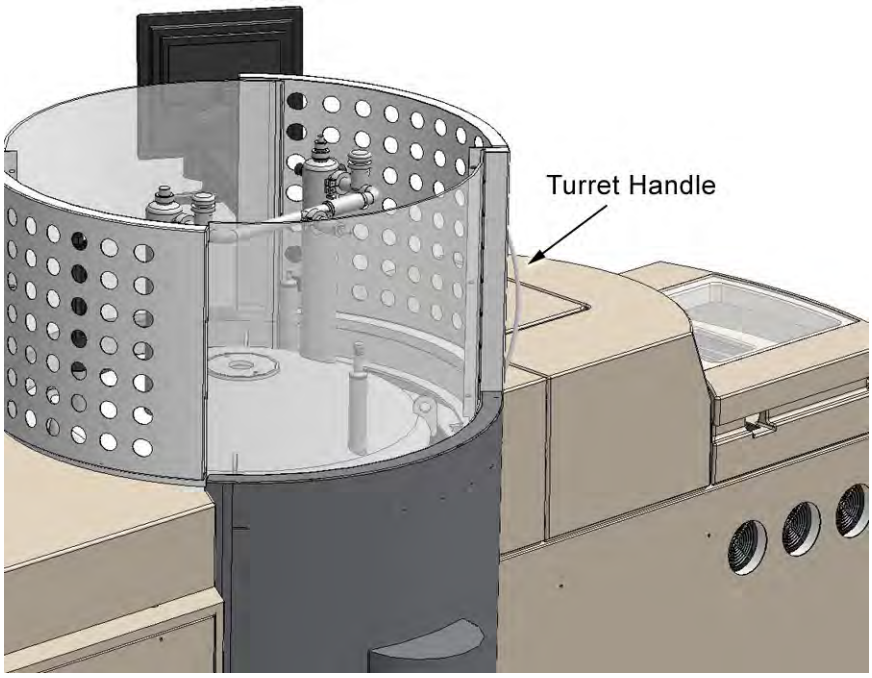
Bulk fluids are contained in the Bulk Fluids Area. There may be up to three bulk fluid containers, Rinse, Wash, and Waste, in this area. If your system is configured to use a laboratory drain, a Waste container is not used and might not be present.



Magnet

The NMR Magnet is contained in the magnet enclosure. The magnet turret door provides access to the Magnet for service and maintenance. A handle is provided at the rear of the system to open the Turret Door. It is recommended to access to the magnet from the rear of the instrument.

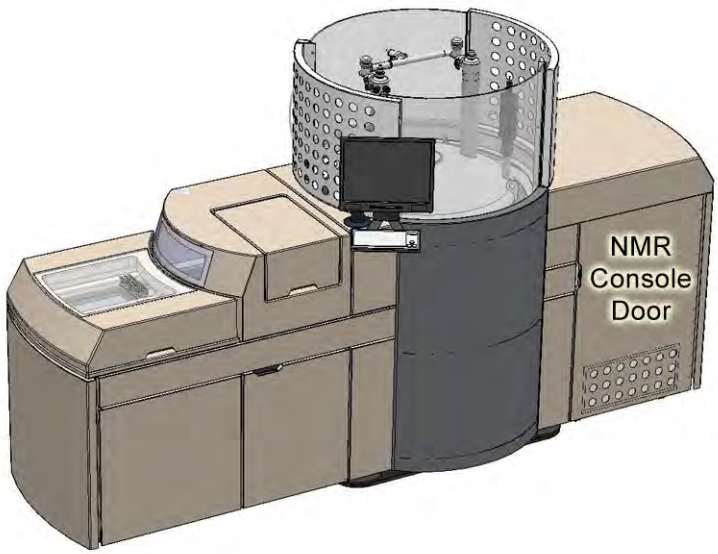
WARNING: The Magnet Turret Door should be closed at all times unless opened for maintenance or service.



NMR Console

The NMR Console is located in the cabinet behind the NMR Console door. It contains all the equipment to control the operation of the NMR magnet. There are no user operable items in the NMR Console. There is an air filter in the console that must be checked on a monthly basis. Refer to “Inspecting the NMR console door filter” on page 64.

Note: NMR Console door must be closed during normal operation.



User levels

There are three levels of user accounts: Basic, Expert, and Service. The Service user level is reserved for LipoScience service personnel and provides access to advanced features. The Basic or Expert level is assigned when the user account is created.

A Basic user has access only to a subset of system functions. An Expert user has access to all functions described in this User's Manual. Access to system functions is typically controlled by disabling, or graying out, menu buttons or specific screen controls. For example, if you are logged into the system as a Basic user, the Expert user level functions are grayed out on the screen. Note that access to some functions is also determined by the operational mode (see page 10) of the system. For example, the Settings button on the Main menu is grayed out for all users, regardless of user level, unless the system is in Standby or Stop mode.

The Vantera Clinical Analyzer functions by user level are shown in the following table.

Menu/Item	Basic	Expert	Service
Main Menu	X	X	X
Status Menu	X	X	X
Tube Rack Screen	X	X	X
Carousel Screen	X	X	X
Bulk Fluids Screen	X	X	X
Cryogen Screen	X	X	X
Temperatures Screen	X	X	X
Covers Screen	X	X	X
Results Screen	X	X	X
Logs Screen	X	X	X
Settings Menu	X	X	X
Default Worklist Settings Screen	X	X	X
Worklist Setup Screen		X	X
Alerts-Alarms Settings Screen		X	X
(Gray Button) Remote Access Settings			X
Printer Settings Screen	X	X	X
Accession Settings Screen		X	X
Bulk Fluids Settings Screen			X
Cryogen Settings Screen		X	X
My Information	X	X	X
HIPAA Settings Screen		X	X
Routine Maintenanace Screen	X	X	X
Manual Accessioning Screen	X	X	X
(Gray Button) Re-Test Settings			
User Settings Screen		X	X
Tools Menu	X	X	X
Clear Print Queue	X	X	X
Fluidics Menu	X	X	X
Rinse Flowcell	X	X	X
Mini-Prime		X	X
Prime		X	X
Evacuate Fluidics		X	X
Wash Fluidics		X	X
Calibrate Touch Screen		X	X
Initiate Remote Access		X	X
Sample Manager Menu	X	X	X
Clear Specimen Rack(s)	X	X	X
Change Sample Probe Tip		X	X
Re-Initialize		X	X
Data Archive	X	X	X

Switch User	X	X	X
Information	X	X	X
Shutdown	X	X	X

Graphical user interface

The upper section of the user interface has two major functions. The first indicates the instrument's current operating mode and enables the user to select another operating mode. The second is to inform the user of system status.

Operational modes

The user changes modes by touching the mode buttons at the top of the graphical user interface. When a mode change is requested by the user, the system checks to see if all conditions are met in order to transition to the requested mode. When these conditions are met, the system changes to the requested mode and the bar between the buttons and the main section of the screen turns a solid color: red (Stopped), yellow (Standby), blue (Ready), or green (Running).

Running–the system is currently processing specimens.

The system never automatically transitions to Running mode. The transition to Running mode requires user intervention.

Ready–the system is not currently processing specimens but is ready to begin processing.

The system transitions to Ready when all loaded specimen tubes have been tested and processed.

Standby–the system is not capable of processing specimens and might require attention by the user.

The user can transition to Standby mode by touching the Standby button.

The system can transition to Standby mode when:

- System initialization is successfully completed.
- The sample handler or carousel cover is opened when in Ready mode.
- The Rinse or Wash container (if present) is empty.
- The Waste container (if present) is full.
- The Rinse, Wash, or Waste container is removed when in Ready mode.
- The Wash fluid is expired.
- Diluent is not present or is expired.
- One or more of the system temperatures are out of range.
- Calibration of the NMR Subsystem is required.
- A clot was detected during sample preparation.

Stopped–the system is not capable of running specimens and requires significant attention or intervention by the user.

The user can change the mode to Stopped by touching the Stop button. The system prompts the user to confirm the action.

CAUTION: The user should only use the Stop button if there is a condition that could result in damage to the system or injury to the user.

The system can transition to Stopped mode if:

- The sample handler or carousel cover is opened when in Running mode.
- The Rinse, Wash, or Waste container is removed when in Running mode.
- The system detects a mechanical jam.
- A system temperature limit was exceeded.
- Communications to components within the system failed or an error was detected, such as with a pump or valve.
- The specimen bar code reader is not working.
- Communications are lost between any of the system computers.

System menus

Main menu–your starting point to access user functions. The Main menu enables you to display the Status, Settings, and Tools menus, to display information about your system, switch users and to shut down the system.

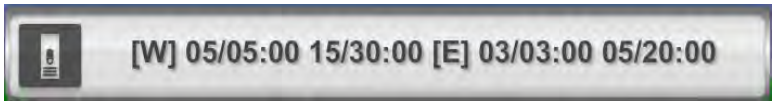
Sample Warning and Failures

The system utilizes NMR to detect if there has been a problem with the sample delivery, temperature, or magnetic drift. These errors may indicate that the system needs to be calibrated. The following parameters are used to indicate the need for re-calibration:

If a there are 5 consecutive samples with warnings; or 5 out of 15 samples with warnings

If there are 3 consecutive sample failures; or 15 out of 20 samples with failures.

If the instrument goes out of calibration because of warnings or failures; Go to the Tools Menu, Fluidics menu, and perform a Wash Fluidics(“Washing the fluidics system” on page 59), then a Mini-prime (“Performing a mini-prime of the fluidics system” on page 52).Once the mini-prime is complete, runs the system calibration (see page 27)



Status menu–enables you to view current system parameters.

Settings menu–enables you to perform user-definable system setup activities. Most features on the Settings menu are only accessible to an Expert user. Refer to the User Levels table on page 6.

Tools menu–enables you to perform activities that keep the system working properly.

Fluidics menu–enables you to perform certain tasks on the fluidics system.

Sample Manager menu–enables you to place the system in a state to clear sample racks or change the metering tip.

Breadcrumbs

The user interface provides a “breadcrumbs” feature at the bottom of each screen. The breadcrumbs serve two purposes: they provide a visual cue to indicate the location of the current screen with respect to the menu structure, and they provide an additional navigation aid.

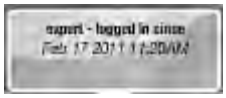
In the illustration above, the breadcrumb indicates the Carousel screen is displayed. The normal navigation to this screen is by touching Status from the Main menu, then Bulk Fluids from the Status menu. You can touch either Main Menu or Status Menu to display either of those screens.

Status icons

There are status icons and a clock in the lower-right corner of the screen.

Calibration–touch the icon to display the date and time of the last successful calibration. Touch again to close the message. The icon is red and crossed out if the system is out of calibration.

- Current user–touch the icon to display the user currently logged in and the date/time of that user’s login. Touch again to close the message.



- UPS–shows a plug icon when the system is running on line power. Shows a battery icon when the system is running on UPS power.
- Temperatures–the icon is gray when all monitored system temperatures are okay. The icon is red when any of the monitored system temperatures is outside its allowed limit. You can view the individual temperatures from the Temperatures status screen (refer to page 43).

- Remote connection active–the icon is present when a remote access connection is active. Touch the icon to display this message, then touch to disconnect the remote access session.

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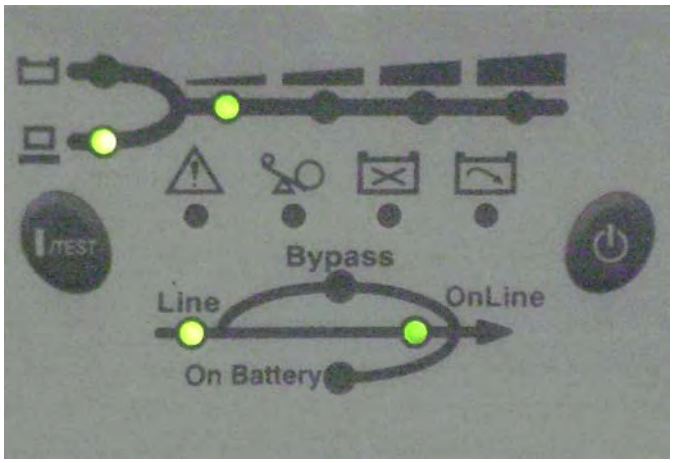
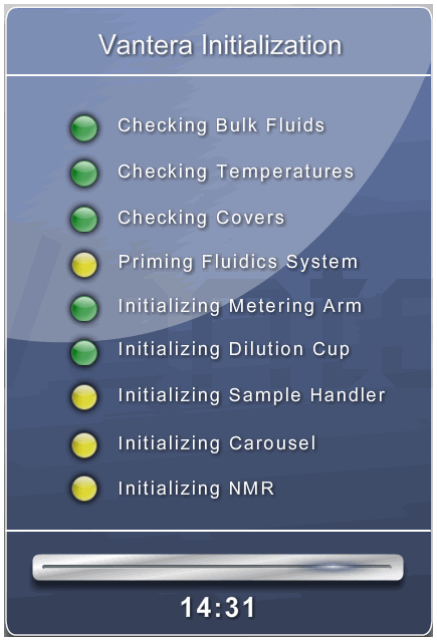
2 Starting up and shutting down the system

Starting up the Clinical Analyzer

- To start up the Vantera Clinical Analyzer, press and hold the TEST button on the UPS panel until a tone sounds, then release.



The Clinical Analyzer performs an orderly startup sequence. Part of this sequence includes checks of system conditions and functions as illustrated below. The system is allotted 15 minutes to complete a satisfactory initialization, as counted down by the timer at the bottom of the screen. Oftentimes, depending on existing temperatures, the sequence takes significantly less time than 15 minutes.



In the event of failure of any of the tests, or a failure of the system temperatures to reach target ranges, the system displays an alert, indicating

a need for user intervention, and is not capable of performing specimen testing until the fault is corrected.

Logging in

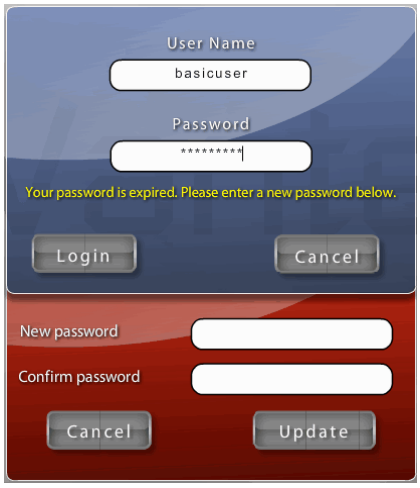
The Login screen appears after the Vantera Clinical Analyzer completes its initialization.

Note that your user name is not case-sensitive. For example, basicuser, BasicUser, and BASICUSER are equivalent user names. Passwords, however, are case-sensitive. For example, if your password is MyPassword, then mypassword or MYPASSWORD will not work.

To log in:

1. Type your User Name and press <Tab>.
2. Type your Password and touch Login.

NOTE: If your password has expired, you are prompted to change the password.

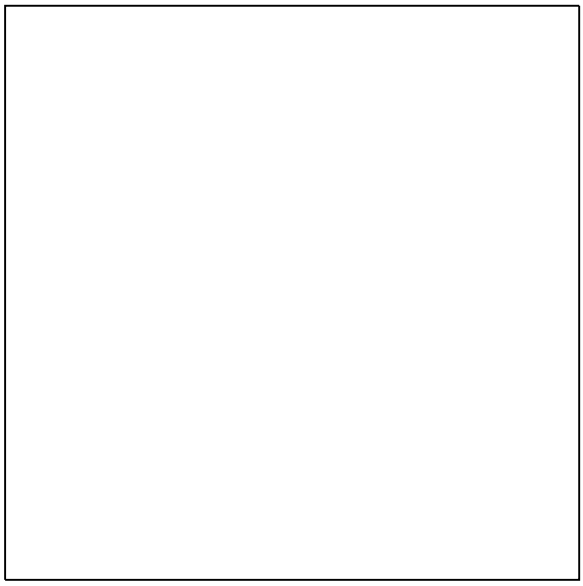


1. Type your new password.
2. Type the new password again to confirm.
3. Touch Update.

The Main menu appears.

To log in as a different user:

1. On the Main menu, touch Switch User.
   The Login screen appears.



2. Type your User Name and press <Tab>.
3. Type your Password and touch Login.
4. Pressing cancel will return you to the main menu.

Changing your password

You are prompted to enter a new password after your current password expires. Passwords must be from 4 to 12 characters long. You can use any combination of numbers and upper and lower case letters. Symbols are not allowed. Passwords are case-sensitive. For example, if you change your password to MyPassword, you cannot log in using mypassword or MYPASSWORD.

To change your password:

1. On the Main menu, touch Settings.

   The Settings menu appears.

2. Touch My Information.

   The My Information screen appears.

3. Touch Change Password.

4. Type your Old Password and press <Tab>.
5. Type your New Password and press <Tab>.
6. Type your password again in the Confirm Password field.

7. Touch Apply.

   Your new password is saved.

Normal shutdown

In a normal non-emergency situation, use the Shutdown function on the Main menu. You must be in an idle state (either stand by or stopped) to perform this function.

1. On the Main menu, touch Shutdown.

   You are prompted to confirm the shutdown of the system.

2. Touch Yes to finish the shutdown of the system.

   The system software performs an orderly shutdown of all computers and electronic equipment on the Vantera Clinical Analyzer.

Emergency stop

CAUTION: The user should only use the Stop button if there is an emergency condition that could result in damage to the system or injury to the user.

To perform an emergency stop of the Vantera Clinical Analyzer:

1. Touch the Stop button.

2. Touch Yes to confirm the immediate stop of the system.

All motors stop immediately, all sample processing stops, and the system transitions to Stop mode.

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Calibrating the NMR

It is possible that measurements from the NMR may change slightly over time. You should process a tube containing the NMR Reference Standard (calibrant) once per 8-hour shift. If the measurement for the calibrant sample differs from the previous calibration measurement, the system automatically adjusts the NMR magnet shimming to maintain the instrument in a calibrated state.

1. Place 1 ml of the NMR Reference Standard in a transfer tube. Recap NMR Reference Standard botle. Reference Standard transferred to a tube should only be used for day, and discarded after use.

2. Affix a bar code label that is supplied with the NMR Reference Standard. Place the tube firmly into an empty specimen rack with the bar code label visible through the opening in the rack.

   NOTE: During normal processing of samples, the system prepares a sample while the previous sample is in the flowcell. Since the calibration measurement takes more time than a normal sample measurement, it is recommended that you perform the calibration with the NMR Reference Standard tube as the only tube in the specimen rack.

3. Touch Run.

4. When the calibration is complete, the system returns to Ready.

   NOTE: If the calibration is unsuccessful, the system attempts to find another calibration tube in the current rack. If there is another calibration tube, the system repeats the calibration. If no calibration tubes are present, the system displays an alarm, and transitions to Standby.

5. If the calibration fails, perform Wash and a Mini-Prime and run calibration tube again.

6. If calibration continues to fail call Service

7. # Processing assay controls

WARNING: Assume that all specimens, control materials, waste fluids, leaks, and spills contain potentially infectious biological material.

Handle all specimens, control materials, and waste fluids in accordance with Universal Precautions, including the use of Personal Protective Equipment (PPE), as prescribed in package inserts and in accordance with your standard laboratory operating procedures, and disinfect all leaks and spills.

The assay controls provide quality assurance that the selected assay is providing accurate results for a number of concentrations. You should process the controls for each assay once per day, or in accordance with your laboratory procedures.

1. For each level of control material, place the appropriate amount into individual transfer tubes in accordance with the package inserts. Return unused control material to its appropriate storage condition.

2. Affix the corresponding bar code label supplied with the controls to each tube. Place the tubes firmly into an empty specimen rack with the bar code labels visible through the opening in the rack.

3. Touch Run.

   The system prepares a sample from each assay control tube.

Processing specimens

WARNING: Assume that all specimens, control materials, waste fluids, leaks, and spills contain potentially infectious biological material.

CAUTION: Do not pre-dilute samples unless instructed otherwise by the assay package insert.

Handle all specimens, control materials, and waste fluids in accordance with Universal Precautions, including the use of Personal Protective Equipment (PPE), as prescribed in package inserts and in accordance with your standard laboratory operating procedures. Clean and disinfect all leaks and spills.

Note: If running without LIS connectivity or manually accessioning, set-up the Default worklist (see page 48).

To start the processing of specimens:

1. Affix a unique accessing bar code label to each specimen tube.

   You can orient the label so that the printed number can be read from either the top of the tube to the bottom, or from the bottom to the top. Refer to “Specimen tube bar code label specifications” on page 86 for bar code labeling requirements.

2. Insert the specimen tubes into specimen tube racks.

   Be sure that all specimen tubes are firmly seated at the bottom of the rack and that the labels are clearly visible through the rack slot.

   You can load as many as ten tubes into the rack. However, it is not necessary to fully load specimen racks for processing.

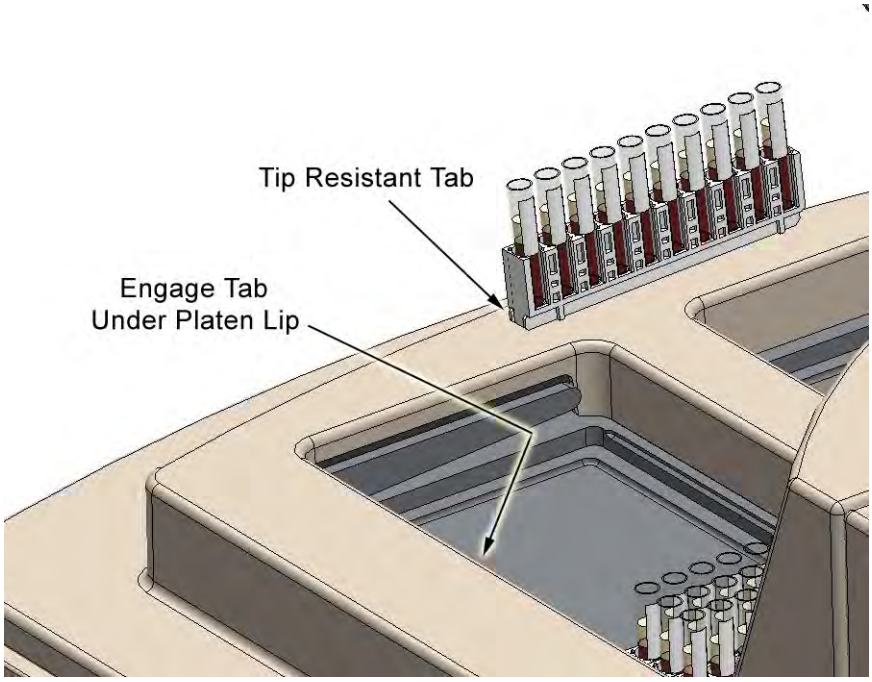
   NOTE: The Vantera Clinical Analyzer processes specimen tubes in the rack from location 10 to location 1.

3. Open the Load/Unload cover.

CAUTION: To ensure that all rack bar codes are read correctly, do not load any racks beyond the point indicated by the labeling in the load area.

4. Orient the rack so that the tip resistant tab is pointed toward the front of the system. Slide the rack into position in the Load Area of the platen. Make sure to engage the tab underneath the lip of the Load Area tray.

   You can load up to twenty specimen racks at one time. The Vantera Clinical Analyzer supports the ability to load and unload specimen racks while the system is processing specimens.



5. Close the Load/Unload cover.

6. Touch Run.

   After all of the specimens in a rack are processed, the system moves the rack to the Unload Area. These racks are now available for unloading by the user.

7. Open the Load/Unload cover.

8. Remove the specimen rack from the Vantera Clinical Analyzer and close the Load/Unload cover.

You can check the results of sample processing from the Results screen. Refer to “Viewing results” on page 45.

Processing specimens manually without an LIS

The manual accessioning feature enables you to continue processing specimens even when the connection to your LIS is not operational. When this occurs, the system allows you to enter the minimum patient and test information (bar code, patient date of birth, and assay to run). When the connection to your LIS is restored, you can sync the completed tests with the LIS by using the Resend to LIS function on the Results screen (refer to page 45.)

To process specimens using manual accessioning:

1. Place the system in Standby.
2. On the Main menu, touch Settings.

   The Settings menu appears.
3. Touch Manual Accessioning.

   The Manual Accessioning Settings screen appears. The screen initially shows a list of the tube bar codes that have already been accessioned.
4. Touch Add Barcode.

   The Patient Information page for the Manual Accessioning Settings screen appears.

5. Enter the bar code for the tube.

6. Select whether the tube is to be used again:
   - Select One Time if the tube will not be used again.
   - Select Recurring to retain the manual accessioning information you enter for future processing.

7. Enter the relevant information for the specimen on the Patient Information page. The Barcode and Patient DOB are required fields.

8. Enter Date and Time for collection and receipt. Select the assay(s) from the Available column and touch Add Assay. The assay(s) are moved to the Assigned column.

9. Touch Add Accession.

   The specimen tube is added to the database and can now be processed normally.

Repeat for each tube to be accessioned. Make sure that Manual Accession Settings is Enabled on the Accession Settings screen (refer to “Setting up accessioning” on page 78). Load the tubes on the system to process.

Recovering when the system detects a clot

The system utilizes a sophisticated clot detection feature designed to prevent the clogging of fluidics lines. If a clot is detected while trying to aspirate from a specimen tube, the system stops processing and attempts to return any aspirated specimen back to the tube. The system then wash the probe, displays a message about the detected clot, moves the probe to an accessible position, and transitions to Standby.

WARNING: Assume that all specimens, control materials, waste fluids, leaks, and spills contain potentially infectious biological material.

If a clot is detected:

- Ensure the use of proper personal protective equipment, and then wipe the probe with a lint free cloth saturated with a 10% bleach solution.
- If the outside of the probe appears to be covered with a gel that is difficult to remove:
  a. Clean with 10% bleach solution and/or alcohol prep pads as needed.
  b. When the outside of the probe is clean, remove and discard the probe, and replace with a spare. Refer to “Changing the sample probe tip” on page 69.
- If the probe is coated with a clot or other biological material:
  a. Wipe with a lint free cloth saturated with a 10% bleach solution.
  b. When the outside of the probe appears to be clean, wash the fluidics (“Washing the fluidics system” on page 59), and perform a mini-prime (“Performing a mini-prime of the fluidics system” on page 52).
  c. Continue running as normal.

NOTE: If a clot is detected on the next sample, contact LipoScience Service.

Transitioning the system to other modes

There is an order for the operational modes: from Stopped, to Standby, to Ready, and finally to Running.

- **Stopped**–the system is not capable of running specimens and requires attention or intervention by the user.
- **Standby**–the system is not capable of processing specimens and might require attention by the user.
- **Ready**–the system is not currently processing specimens but is ready to begin processing.
- **Running**–the system is currently processing specimens.

Under certain conditions, the system can automatically transition to a different mode without user intervention, but it can only transition to a “lower order” mode (for example, from Running to Ready). A transition to a “higher order” mode (for example, Standby to Ready) requires an action by the user. The user also might want to set the mode back to a lower order (for example Ready to Standby in order to change system settings).

A user transitions the system to Running mode in order to process specimen tubes. Refer to “Processing specimens” on page 29.

To transition to Ready mode:

- Touch the Ready button.

  The Ready Pending message appears until the Clinical Analyzer can complete the transition.

  When the transition is complete, the Ready message appears.

To transition to the Standby mode:

- Touch the Standby button.

  The Standby Pending message appears until the Clinical Analyzer can complete the transition. The system finishes the processing of any tests that are in progress.

  When the transition is complete, the Standby message appears.

A user should only transition the system to Stopped mode in the case of an emergency that could result in damage to the system or injury to the user. Refer to “Emergency stop” on page 25.

Auxiliary functions

In addition to processing specimens, the Vantera Clinical Analyzer provides auxiliary functions.

Clearing the specimen rack in the transfer area

Since the Vantera Clinical Analyzer does not provide easy access to the specimen rack in the transfer area, the system provides a function to move the rack into the unload area.

1. Place the system in Standby.

   NOTE: In order to preserve the specimen, the system finishes the processing of any tests that are in progress.

2. On the Main menu, touch Tools.

   The Tools menu appears.

3. Touch Sample Manager.

   The Sample Manager menu appears.

4. Touch Clear Specimen Rack(s).

   The rack is moved to the unload area. The “Clear Sample Rack: Complete” message appears when done.

Acknowledging alerts and alarms

To acknowledge an alert or an alarm:

- Touch OK on the alert or alarm message box.

To silence the audible alert or alarm tone:

- Touch the icon in the upper-right corner of the alarm message box.

Measuring the levels of the carousel fluids

The fluid levels for each bottle in the carousel are verified prior to the start of a run each time the Carousel Door and Carousel Lid are opened and / or removed and a RUN initiated. You can view the updated level information on the Carousel screen (refer to page 40).

4 Additional system functions

Checking the status of the analyzer

The Status menu provides access to a number of screens from which you can check detailed information about the condition of the Vantera Clinical Analyzer.

Viewing the current tube rack

The Vantera Clinical Analyzer provides the ability to monitor the status of specimen tubes as they are processed. To view the status of the current tube rack:

1. On the Main menu, touch Status.

   The Status menu appears.

2. Touch Tube Rack.

   The Tube Rack screen appears.

The bottom of the screen shows the contents of the current rack, the tube at the test position, the tube at the retest position, and the status of each tube whose bar code has been read. If there is a bar code affixed to the tube rack, the bar code appears on the rack graphic below the specimen tubes and also along the left side. If there is no bar code on the rack or if the bar code was not read successfully, NO READ appears on the graphic.

NOTE: The screen shows the specimen tubes in the same way that they are processed by the analyzer, from left to right. The system processes the left-most specimen tube first (position 10) and then proceeds to the right.

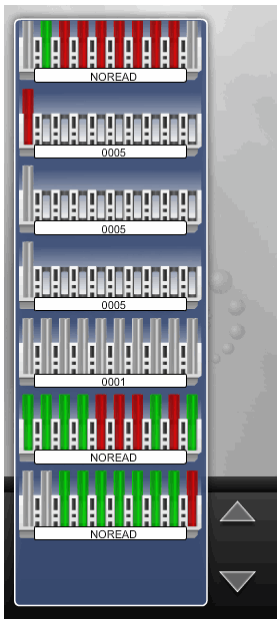
The Vantera Clinical Analyzer provides descriptive graphics and color codes indicating the state of each specimen tube. Each graphic tube label shows a label after the bar code reader has successfully read the bar code.

The color of the specimen tube indicates its status:

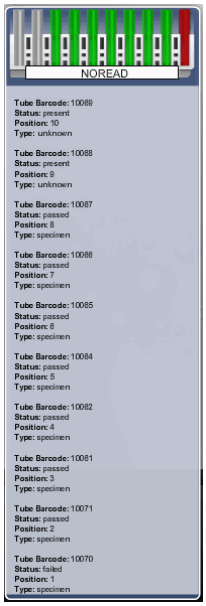
- No tube–the system determined that no tube exists at this location.
- Clear with a label–the system determined that there is a tube in this location and has read the bar code. Processing has not yet started.
- Clear with a NO READ label–the system was not able to read the bar code on this tube.
- Blue–the system started processing this specimen. The tube turns blue as soon as the system starts to aspirate any necessary materials.
- Green–the specimen tube was processed successfully. No additional processing will take place.
- Red–the processing of this tube failed.
- A black label with white lettering indicates the tube contains the NMR Reference Standard used for calibration.

You can get additional information about an individual specimen tube by touching a tube in the rack display. When selected, the additional information appears in the window at the top of the screen.

After each rack is complete, it is added to the racks on the left side of the screen. The most recent racks appear at the top.



Touch any rack to display the details of that rack.



Checking the carousel fluid levels

To view the status of the carousel:

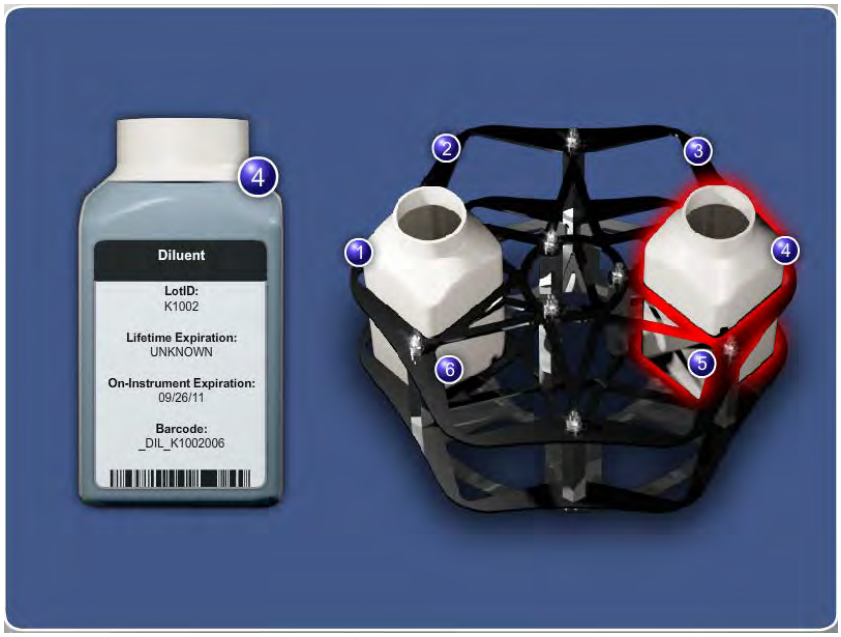
1. On the Main menu, touch Status.

   The Status menu appears.

2. Touch Carousel.

   The Carousel screen appears.

The screen shows the carousel and a graphic of the selected container.



The screen initially shows information for the container in position 1:

- carousel position
- contents of the container
- lot ID
- fluid and on-board expiration dates
- bar code
- Volume remaining

Touch another container in the carousel graphic to display information for that container.

To refresh the fluid level (after replacing a dilent bottle, for example), refer to “Measuring the levels of the carousel fluids” on page 36.

Checking bulk fluid levels

To view the status of the bulk fluid containers:

1. On the Main menu, touch Status.

   The Status menu appears.

2. Touch Bulk Fluids.

   The Bulk Fluids screen appears.

The top of the screen shows a graphic for each of the bulk fluid containers: System (Rinse), Wash, and Waste.

Note that the graphics are not accurate representations of the fluid levels. The graphics show only three levels, which are signified by colors, green, yellow, or red, which indicate fluid status. For Rinse and Wash, these colors are used:

- Green–full
- Yellow–almost empty (20% or less of full volume)
- Red–empty

For Waste:

- Green–empty
- Yellow–almost full (80% or more of full volume)
- Red–full

NOTE: In the case of Empty for Rinse and Wash, and Full for Waste, there is enough capacity to continue processing all specimens that have been started. After these specimens are fully processed, no additional specimens can be started and the system transitions to Standby.

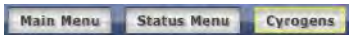
Additional information about each bulk fluid is shown in the window below each container.

The bottom of the screen shows information about each bulk fluid container:

- the fluid level
- the date and time the system software last checked the level
- for Wash, the bar code and expiration dates

Checking the cryogen levels

To view the cryogen levels:



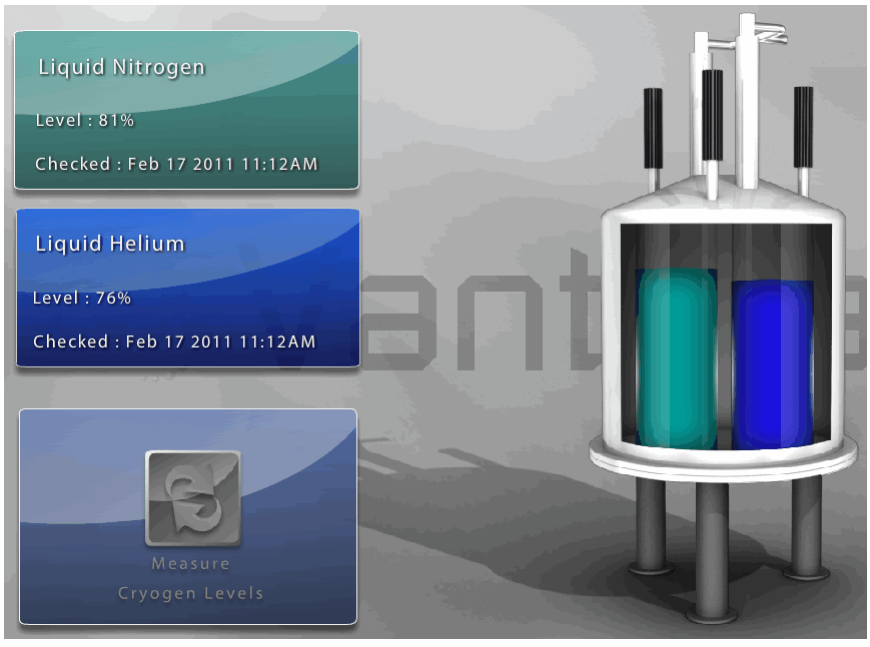
1. On the Main menu, touch Status.

   The Status menu appears.

2. Touch Cryogens.

   The Cryogens screen appears.

The graphic on the right of the screen shows the cryogen levels. The liquid nitrogen level is shown on the left and the liquid helium level is shown on the right.



The left and right sides of the screen shows information for each cryogen supply:

- cryogen level (percent full)
- the date the system software last checked the level

NOTE: The Measure Cryogen Levels button is enabled only for Expert users.

3. To initiate an immediate measurement of the cryogen levels, touch Measure Cryogen Levels.

NOTE: Measuring the cryogen levels consumes a small portion of each cryogen. It is recommended that users measure the levels no more than once per day. To set up the system to automatically measure the cryogen levels, refer to “Setting the cryogen monitoring time” on page 79.

Checking system temperatures

To view the current temperatures:

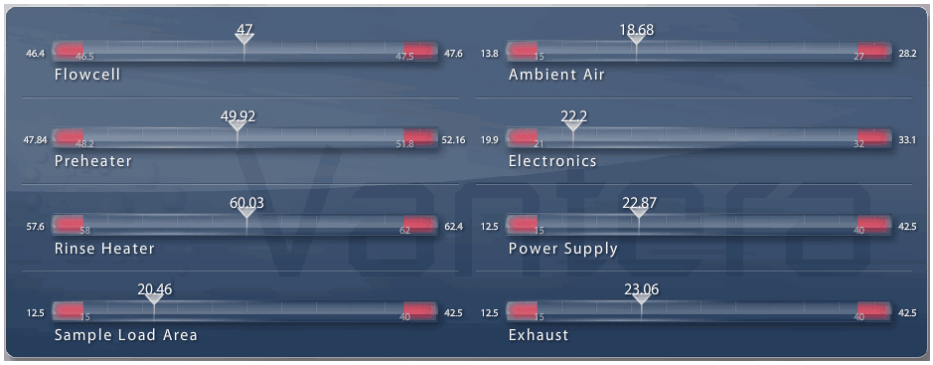
1. On the Main menu, touch Status.

   The Status menu appears.

2. Touch Temperatures.

   The Temperatures screen appears.

The screen shows a graphic for each temperature sensor in the system.



The diamond is indicates the current temperature. The blue area for each sensor indicates the acceptable temperature range for that sensor and the red areas indicate the ranges outside of acceptable temperature limits.

Checking system covers

The system monitors for doors and covers:

- Specimen load/unload door
- Metering arm door
- Carousel cover
- Bulk fluids door

The Covers status screen shows a graphic of the system and the location of the open cover or door.

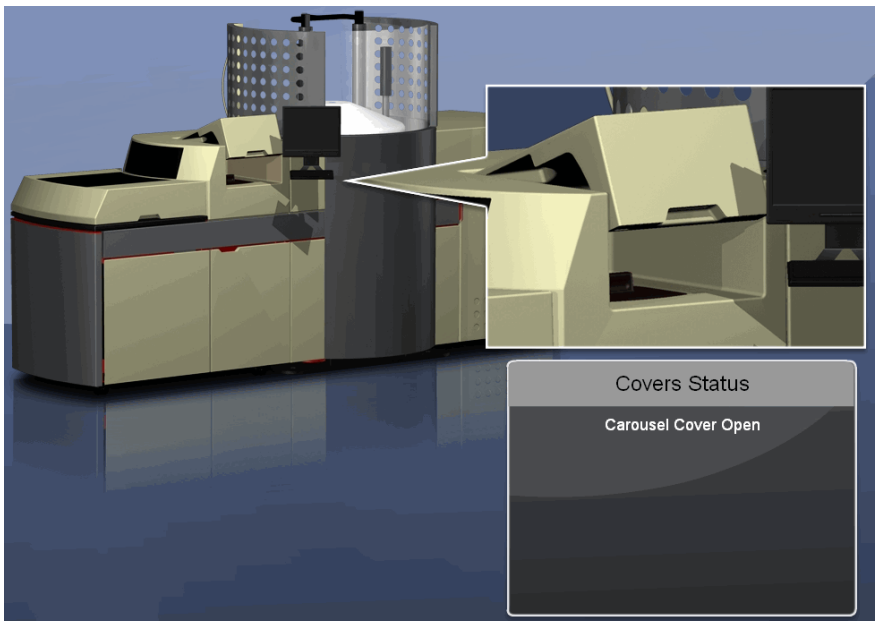
To view the system covers status:

1. On the Main menu, touch Status.

   The Status menu appears.

2. Touch Covers.

   The Covers screen appears. The Covers screen shows a graphic of the system and the location of the open cover or door.



Viewing results

To view specimen test results:

1. On the Main menu, touch Status.

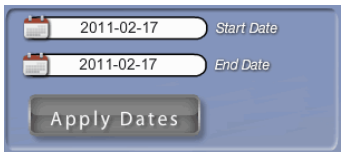
   The Status menu appears.

2. Touch Results.

   The Results screen appears.

The left side of the screen is initially blank. To display test results on the screen, you must use the status buttons to filter the requests you want to view. You can also use these in conjunction with the date filters.

- To filter the list to display only one status type, touch one of the buttons (Passed, Failed, Skipped, or In Progress) in the upper-left corner of the screen.



- To filter the list to show tests from a specific date or range of dates, touch the Start Date field.

  A calendar control appears.

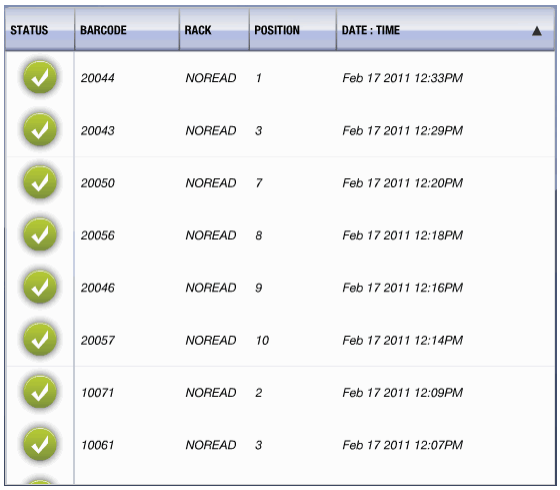
  Touch the date and touch the X to close the calendar.

  Repeat for the End Date field.

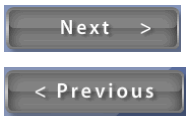
  Touch Apply Dates to enable the date range.

NOTE: The Results screen is not updated as the system continues to process samples. You must repeat the filtering actions each time you want to view additional test results.

The left side of the Results screen can display any tests that have been started. Each test displays its status (passed, failed, skipped, or in progress), the specimen tube and rack bar codes, position of tube in the rack and the date and time of the test.

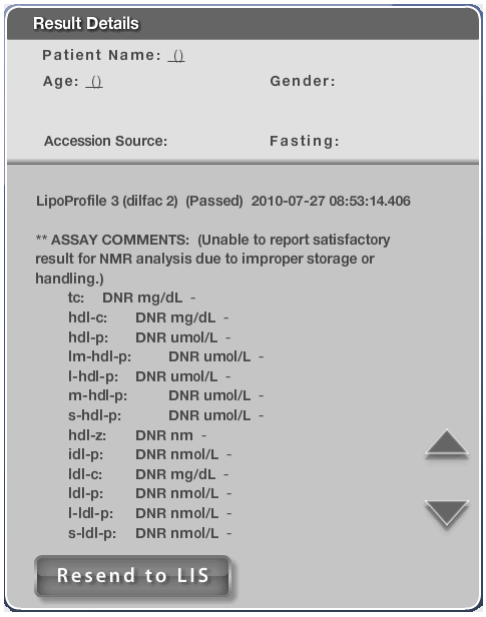


STATUS	BARCODE	RACK	POSITION	DATE : TIME
	20044	NOREAD	1	Feb 17 2011 12:33PM
	20043	NOREAD	3	Feb 17 2011 12:29PM
	20050	NOREAD	7	Feb 17 2011 12:20PM
	20056	NOREAD	8	Feb 17 2011 12:18PM
	20046	NOREAD	9	Feb 17 2011 12:16PM
	20057	NOREAD	10	Feb 17 2011 12:14PM
	10071	NOREAD	2	Feb 17 2011 12:09PM
	10061	NOREAD	3	Feb 17 2011 12:07PM



- To view the next page of processed specimen tubes, touch Next.
- To view the previous page of processed specimen tubes, touch Previous.
- To sort the list by Status, tube bar code, rack bar code, position or Date/Time, touch the appropriate column heading. To switch between ascending and descending order, touch the column heading again.

The right column of the screen displays patient information and test(s) results for the selected specimen. When the Results screen initially appears, the fields in this column are empty.



- To view the patient information and test results for a specific specimen, touch the specimen entry from the list on the left.

  If the specimen was skipped or the test failed, the Result Details provides a reason for the skip or failure to help you determine whether to reprocess the specimen.

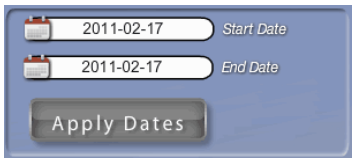
  NOTE: If the system is configured to hide the patient's private information, the Patient Name and Date of Birth fields are empty. Refer to "Showing or hiding patient private information" on page 80.
- If the connection to your LIS was not operational and you are using manual accessioning, you can sync test results to the LIS after the fact by using the Resend to LIS button.

- To print the result details for the test currently displayed, touch Print Record.

- To print a summary of all results, touch Print Range.

  NOTE: The printed results summary includes all pages of results. If necessary, filter out the results list using the status buttons (Passed, Failed, Skipped, In Progress) or the Date controls, then touch Print Range.

Viewing the event log



1. On the Main menu, touch Status.

   The Status menu appears.

2. Touch Logs.

   The Logs screen appears.

The Logs screen is initially blank. To display log entries, you must use the log type buttons to filter the entries you want to view. You can also use these in conjunction with the date filters.

- To sort the list by Type, User, Code, Information text, or Date and Time, touch the appropriate column heading. To switch between ascending and descending order, touch the column heading again.
- To filter the list to display only one status type, touch one of the buttons (Alarms, Alerts, Event, or Info) in the upper-left corner of the screen.
- To filter the list to show log entries from a specific date or range of dates, touch the Start Date field.

  A calendar control appears.

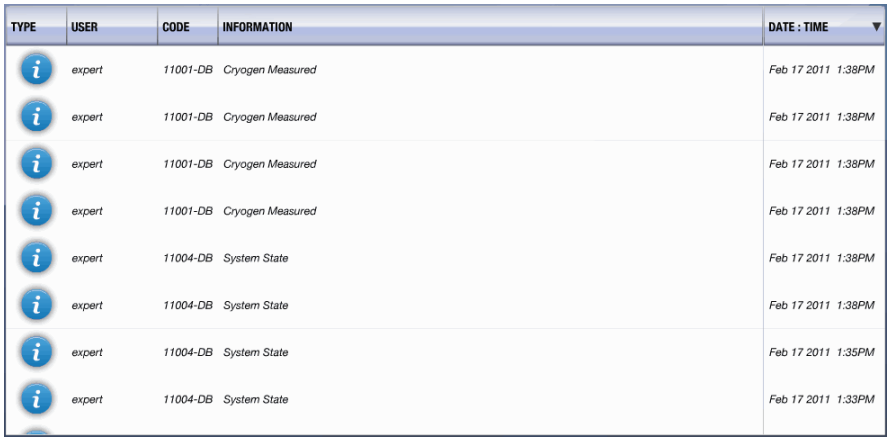
  Touch the date.

  Repeat for the End Date field.

  Touch Apply Dates to enable the date range.

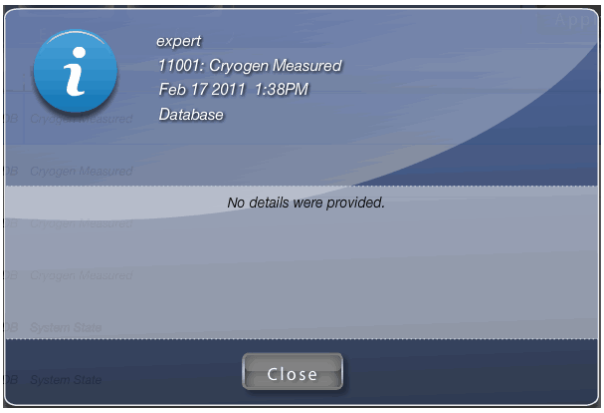
NOTE: The Logs screen is not updated as additional events occur. You must repeat the filtering actions each time you want to view additional log entries.

The screen displays a list of the event log. Initially, the most recent log entries are displayed first. Each entry includes the Type (Alarm, Alert, Event, Info), User logged in at the time of the entry, a numeric Code, Information text, and the Date/Time of the entry.



- To view detailed information for any entry, touch that entry.

  A pop-up window appears.



- To view the next page of log entries, touch Next.
- To view the previous page of log entries, touch Previous.
- Touch Close to dismiss the window.

Adding or removing assays from the default worklist

The default worklist is a set of one or more tests that are always performed on a sample instead of, or in addition to, the system's accession settings. The tests that are available for inclusion in the default worklist are set by an Expert user on the Worklist Setup screen (refer to "Selecting the assays available for the default worklist" on page 74).

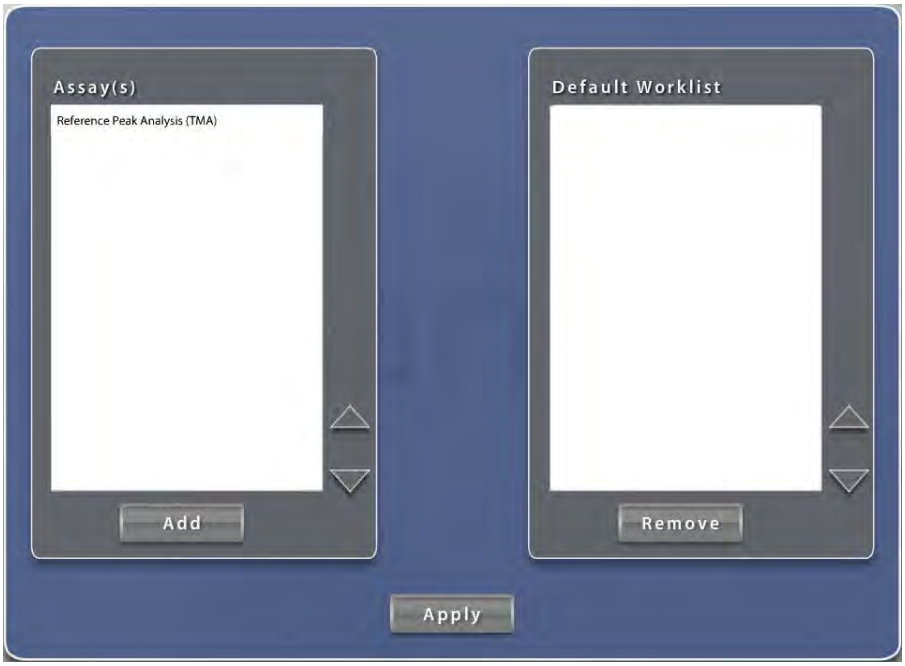
NOTE: The Default Worklist button is enabled only if the Default Worklist is Enabled on the Accession Settings screen (refer to "Setting up accessioning" on page 78).

To add an assay to the default worklist:

1. Place the system in Standby.
2. On the Main menu, touch Settings.

   The Settings menu appears.
3. Touch Default Worklist.

   The Default Worklist Settings screen appears.



4. To add an assay to the default worklist, select the assay name from the Assays list and touch Add.

   The assay name appears in the Default Worklist.

5. To remove an assay from the default worklist, select the assay name from the Default Worklist and touch Remove.

   The assay name is removed from the Default Worklist.

6. Touch Apply to save worklist settings.

Displaying information about your system

The system enables users to display software version information and provides access to on-line versions of the User's Manual.

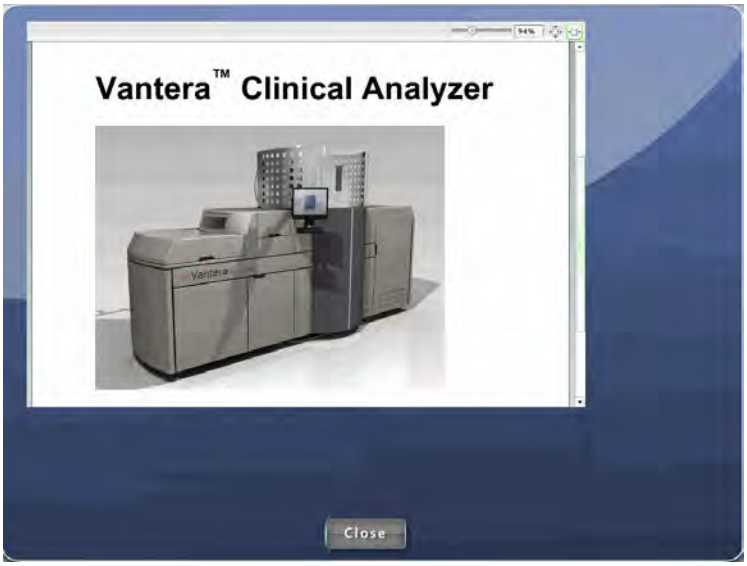
- On the Main menu, touch Information.

  The Information menu appears.

  The screen displays information about contacting LipoScience and about the versions of software installed on your system.

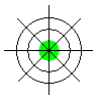
7. To display the User's Manual, touch the icon.

   The User's Manual is displayed on the screen.



Calibrating the touch screen



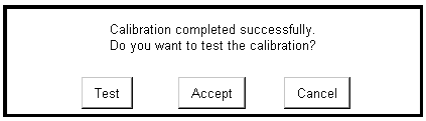
The system provides a tool to calibrate the behavior of the touch screen. Follow these steps if the touch screen does not perform as expected.

1. Place the system in Standby.
2. On the Main menu, touch Tools.

   The Tools menu appears.
3. Touch Calibrate Touch Screen.

   A white screen replaces the Vantera Clinical Analyzer GUI.
4. Follow the instructions on the screen. Touch the targets when prompted.

   When the calibration is complete, this message appears.



5. Touch Accept to save the calibration.
6. Touch OK to confirm and to return to the system.

Fluidics operations

Priming the fluidics system

A full prime operation assumes a dry fluidics system and is typically required anytime you replace a bulk fluids container or any other fluidics component, such as tubing or a pump. You must also prime the fluidics system anytime you evacuate the system. The priming function pumps Rinse through all the fluid lines and leaves fluid in the lines.





1. Place the system in Standby.
2. On the Main menu, touch Tools.

   The Tools menu appears.
3. Touch Fluidics.

   The Fluidics menu appears.
4. Touch Prime.

   The system primes the fluidics system. The Prime: Complete message appears when done.

Performing a mini-prime of the fluidics system

A mini-prime operation consists of a quick wash and rinse of the fluidics system. Perform a mini-prime of the fluidics system if you notice air bubbles in a fluidics line or after the system has been sitting idle for 4hours or more.





1. Place the system in Standby.
2. On the Main menu, touch Tools.

   The Tools menu appears.
3. Touch Fluidics.

   The Fluidics menu appears.
4. Touch Mini-Prime.

   The mini-prime operation begins. The Mini Prime: Complete message appears when done.

   The system performs a mini-prime of the fluidics system. The Mini-Prime: Complete message appears when done.

Evacuating the fluidics system

Evacuating the fluidics system removes all liquids from the system. Evacuate the system if there is a leak in the system or before replacing a fluidics component, such as tubing or a pump.





1. Place the system in Standby.
2. On the Main menu, touch Tools.

   The Tools menu appears.
3. Touch Fluidics.

   The Fluidics menu appears.
4. Touch Evacuate Fluidics.

   The system empties the fluidics system. The Evacuate: Complete message appears when done.

Rinsing the flowcell

To rinse the flowcell:

1. Touch the Standby button to place the system in Standby.
2. On the Main menu, touch Tools.

   The Tools menu appears.
3. Touch Fluidics.

   The Fluidics menu appears.
4. Touch Rinse Flowcell.

   The system rinses the flowcell. The Rinse Flowcell: Complete message appears when the rinse is completed.

Initiating a remote access session

The Vantera Clinical Analyzer is designed to enable remote troubleshooting and adjustment of system functions. If your Vantera Clinical Analyzer is in need of service, your LipoScience TAC representative may request a remote connection to your system. An Expert user can perform this procedure with the direction of a LipoScience TAC representative. Your TAC representative can troubleshoot and attempt to correct the error in your system. If the error cannot be corrected remotely, a TAC representative may be dispatched to your facility.

This feature is accessible only to an Expert user.

To initiate a remote access session with LipoScience TAC:

1. Place the system in Standby.
2. On the Main menu, touch Tools.

   The Tools menu appears.
3. Touch Remote Access.

   The background to the screen changes to indicate that the remote access is in progress.

   Do not use the system until notified by the TAC representative.
4. When TAC notifies you that remote access is no longer necessary, touch Click to Disconnect from the lower corner of the screen.

5 Maintenance

Maintenance schedule

Frequency	User	Task
Shift	Basic	1. Inspect the Vantera Clinical Analyzer. Refer to page 58. 2. Check the bulk fluid levels. Refer to page 41. 3. Wash the fluidics. Refer to page 59. 4. Perform a mini-prime. Refer to page 52. 4. Calibrate the NMR. Refer to page 27. 5. Process the assay controls. Refer to page 28.
Daily	Basic	Check and record the nitrogen and helium boil-off rates. Refer to page 66.
Weekly	Basic	1. Inspect the air condensate and particle filters. Refer to page 60. 2. Clean the load and unload areas and platens. Refer to page 62. 3. Empty and disinfect the rinse fluid container. Refer to page 62. 4. Inspect the NMR console filters. Clean as needed. Refer to page 64. 5. Perform Archive utility. Refer to page 70.
	Expert	Fill the liquid nitrogen tank. Refer to page 67.

List of consumables

Item	Mfr	U/M	Part Number
Wash Fluid	LipoScience		99-100-30
Rinse Fluid (deionized water)	Supplied by laboratory		n/a
Diluent I	LipoScience		99-200-30
NMR Reference Standard (calibrant)	LipoScience		99-300-30
Liquid Nitrogen	Supplied by laboratory		n/a

Scheduled maintenance logs

There is a blank log sheet at the end of this manual for maintenance that must be performed each shift, day, and week. The log contains the maintenance actions for one month. Duplicate the sheet as needed. Record and maintain the log in accordance with your lab procedures.

Basic user maintenance

Recording maintenance activities

The system provides the ability to record maintenance activities. You should record maintenance activities according to your local laboratory procedures.

To record a maintenance activity in the log:

1. On the Main menu, touch Settings.

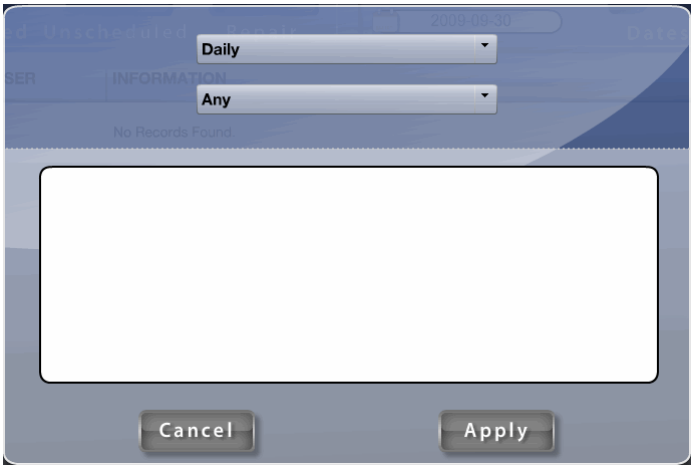
   The Settings menu appears.

2. Touch Routine Maintenance.

   The Routine Maintenance screen appears.

3. Touch Add.

   A pop-up window appears.



4. Select the activity type (Daily, Weekly, or Monthly).

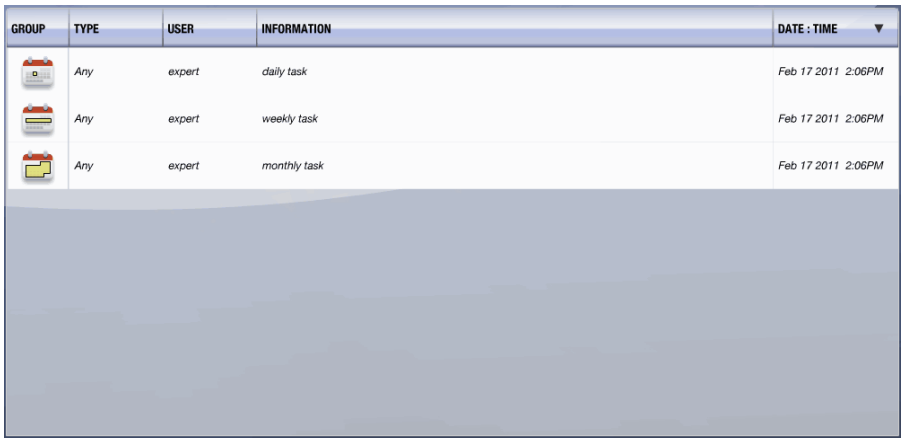
NOTE: The second drop-down list (Any) is reserved for future use.

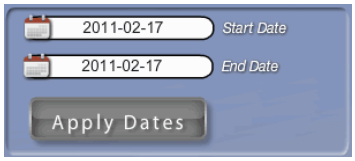
5. Type a short description of the maintenance performed.

6. Touch Apply.

The system saves the entry in the list.

The Routine Maintenance screen provides a list of all maintenance entries. Initially, the most recent entries are displayed first.





- To view the next page of log entries, touch Next.
- To view the previous page of log entries, touch Previous.
- To sort the list by Group, Type, User, Information text, or Date and Time, touch the appropriate column heading. To switch between ascending and descending order, touch the column heading again.
- To filter by Group, touch Monthly, Weekly, or Daily.
- To filter the list to show log entries from a specific date or range of dates, touch the Start Date field.

  A calendar control appears.

  Touch the date.

  Repeat for the End Date field.

  Touch Apply Dates.

Inspecting the Vantera Clinical Analyzer

WARNING: Assume that all specimens, control materials, waste fluids, leaks, and spills contain potentially infectious biological material.

Handle all specimens, control materials, and waste fluids in accordance with Universal Precautions, including the use of Personal Protective Equipment (PPE), as prescribed in package inserts and in accordance with your standard laboratory operating procedures. Clean and disinfect all leaks and spills.

Before using the Vantera Clinical Analyzer, perform an inspection of the device to ensure safe operation.

1. Place the system in Standby.
2. Check the Load and Unload Areas, the Carousel Area, and the Bulk Fluids Area for leaks or spills.

   Clean any spills. Refer to “Cleaning spills” on page 62. Report any apparent leaks to shift supervision.
3. If required at your site, record the activity in the maintenance log. Refer to “Recording maintenance activities” on page 56.

Washing the fluidics system

Washing the fluidics system pumps wash fluid through the system to remove any residual specimen particles from the fluidics tubing. After the tubing is washed, the tubing is flushed with rinse fluid. You should wash the fluidics system once per shift as part of the Shift Maintenance protocol.

Repeat this procedure if you encounter a clot, if there is degradation in performance (indicated by repeated failures), or after clearing a fluidics related alert.

NOTE: Washing the fluidics system requires several minutes to perform.

1. Place the system in Standby.
2. On the Main menu, touch Tools.

   The Tools menu appears.
3. Touch Fluidics.

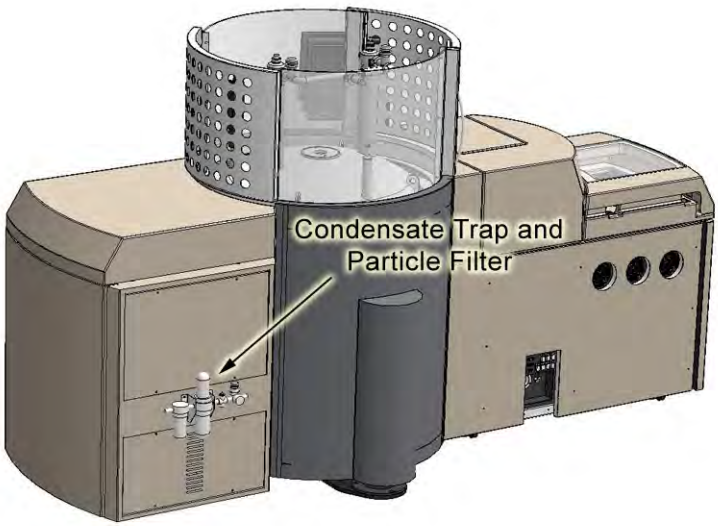
   The Fluidics menu appears.
4. Touch Wash Fluidics.

   The system washes and rinses the fluidics system. The Wash Fluidics: Complete message appears when the clear is done.
5. If required at your site, record the activity in the maintenance log. Refer to “Recording maintenance activities” on page 56.

Inspecting the air condensate and particle filters

A condensate and particle filter assembly is located on the rear of the system.

1. Check for liquid or particles in the compressed air trap. If liquid or particles are visible, contact the LipoScience Technical Assistance Center.



2. If required at your site, record the activity in the maintenance log. Refer to “Recording maintenance activities” on page 56.

Preparing bleach solution

WARNING: Observe all handling instructions on the manufacturer's package, including the use of Personal Protective Equipment (PPE), for all instrument fluids and cleaning agents.

Skin or eye contact with instrument fluids and cleaning agents may be hazardous.

Use the bleach solution as a decontamination fluid to clean spills on the device.

1. Measure 90ml deionized (DI) water into a graduated cylinder.
2. Measure 10ml of household bleach into a container using a disposable pipette or a graduated cylinder.
3. Add the household bleach to the DI water.
4. Mix thoroughly and vigorously for at least one minute with a pipette or a stir bar and mixing plate.
5. Label the container in accordance with local practice.
6. Store the bleach solution at 2°C to 30°C.
7. Return the household bleach to storage area.

Cleaning spills

WARNING: Assume that all samples, waste fluids, and leaks and spills contain potentially infectious biological material.

Handle all specimens, control materials, and waste fluids in accordance with Universal Precautions, including the use of Personal Protective Equipment (PPE), as prescribed in package inserts and in accordance with your standard laboratory operating procedures. Clean and disinfect all leaks and spills.

WARNING: Observe all handling instructions on the manufacturer's package, including the use of Personal Protective Equipment (PPE), for all instrument fluids and cleaning agents.

Skin or eye contact with bleach solution may be hazardous.

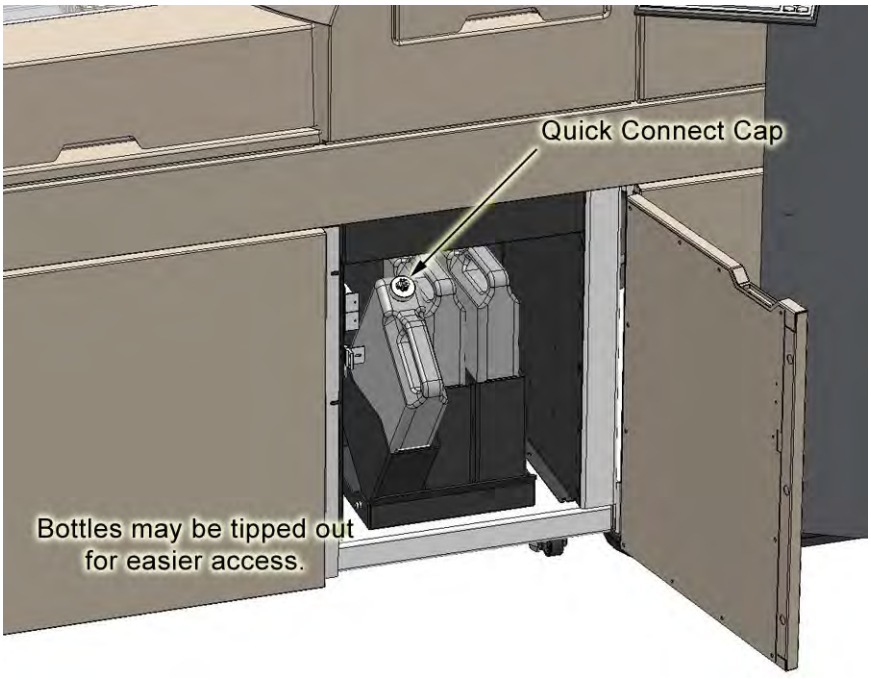
1. Place the system in Standby.
2. If necessary, remove any specimen tube racks from the Load and Unload Areas, or diluent bottles from the Carousel.
3. Spray or soak a disposable wipe with bleach solution (page 61). Wipe the spilled liquid and dispose of the wipe in accordance with your laboratory procedures.
4. Wipe the surface where the spill was removed with the bleach solution, and allow the fluid to sit for 20 minutes.
5. Wipe the bleach solution from the surface using a disposable wipe dampened with tap water.
6. If required at your site, record the activity in the maintenance log. Refer to "Recording maintenance activities" on page 56.

Emptying and disinfecting the rinse fluid container

WARNING: Observe all handling instructions on the manufacturer's package, including the use of Personal Protective Equipment (PPE), for all instrument fluids and cleaning agents.

Skin or eye contact with cleaning agents may be hazardous.

1. Place the system in Standby.
2. Open the bulk fluid door.



3. Remove the supply tube from the rinse fluid container by pressing the metal quick connect on the cap assembly. (You can tip the container forward for easier access.)
4. Refill another clean, dry rinse fluid container.
5. Place the container in the bulk fluid area and insert the supply tube.
6. Perform a prime of the fluidics system.

   Refer to “Priming the fluidics system” on page 51.
7. Empty the rinse fluid from the container that you removed.
8. Fill the container with deionized (DI) water and shake vigorously.
9. Empty the entire contents of the container and rinse thoroughly with fresh DI water.
10. Store the empty container until the next scheduled cleaning.
11. If required at your site, record the activity in the maintenance log. Refer to “Recording maintenance activities” on page 56.

Emptying the waste fluid container

WARNING: Assume that all specimens, control materials, waste fluids, leaks, and spills contain potentially infectious biological material.

WARNING: Observe all handling instructions on the manufacturer's package, including the use of Personal Protective Equipment (PPE), for all instrument fluids and cleaning agents.

Skin or eye contact with cleaning agents may be hazardous.

1. Fill the extra empty waste fluid container with 40 ml of household bleach.

2. Place the system in Standby.
3. Open the bulk fluid door.
4. Remove the supply tube from the waste fluid container by pressing the metal quick connect on the cap assembly. (You can tip the container forward for easier access.)
5. Place the empty container (with bleach) in the bulk fluid area and insert the supply tube.
6. Empty the waste fluid from the container that you removed in accordance with your standard laboratory procedures.
7. Add 10 ml of bleach and fill the container with tap water. Shake vigorously.
8. Empty the entire contents of the container and rinse thoroughly with fresh tap water.
9. Store the empty container until the next scheduled cleaning.
10. If required at your site, record the activity in the maintenance log. Refer to "Recording maintenance activities" on page 56.

Inspecting the NMR console door filter

WARNING: Do not insert any objects into the instrument when a lower cover on the NMR console is open.

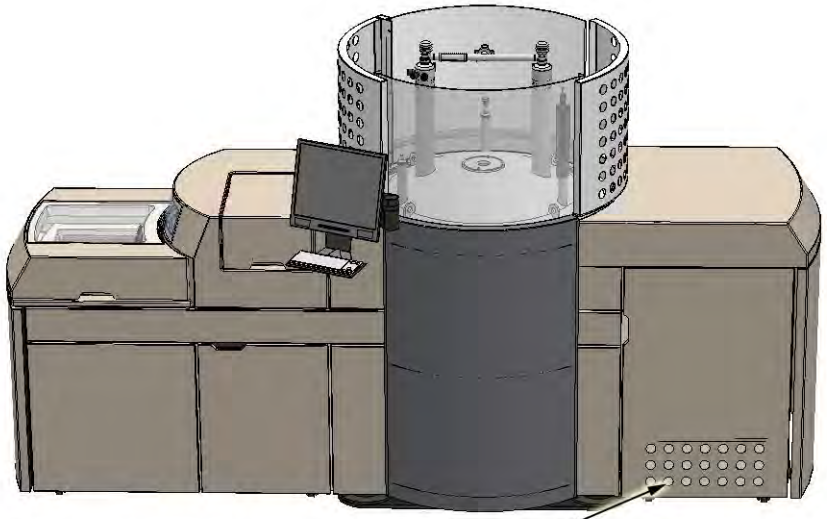
The object may come in contact with dangerous high voltages that exist inside the instrument, which can kill or injure.

The filter is on the inside of the NMR console front door. Check the filter for dust and dirt buildup. If necessary, remove and clean the filter:

1. Remove the dirty filter from the filter frame in the panel.

2. Clean the dirty filter with mild detergent and water. Allow the filter to dry completely.

3. Replace the filter in the filter frame.



4. If required at your site, record the activity in the maintenance log. Refer to “Recording maintenance activities” on page 56.

Recording the cryogen boil-off rate

The nitrogen and helium boil-off gauges are located on the top of the magnet.

Nitrogen

Read the nitrogen boil-off rate each day and record the value in your scheduled maintenance log. If required at your site, record the activity in the maintenance log. Refer to “Recording maintenance activities” on page 56.

Helium

Read the helium boil-off rate each week and record the value in your scheduled maintenance log. If required at your site, record the activity in the maintenance log. Refer to “Recording maintenance activities” on page 56.

Expert user maintenance

Replenishing the nitrogen supply

WARNING: Avoid helium or nitrogen contact with any part of the body.

In contact with the body, helium and nitrogen can cause an injury similar to a burn. Never place your head over the helium and nitrogen exit tubes on top of the magnet. If helium or nitrogen contacts the body, seek immediate medical attention, especially if the skin is blistered or the eyes are affected.

WARNING: You must wear proper Personal Protective Equipment (gloves, aprons, and face shields) while filling the nitrogen supply or working with the metal fittings on the magnet.

Direct contact of the skin with cold metal fittings during the nitrogen fill can cause the skin to freeze to the fittings resulting in serious injury.

NOTE: Replenishing the liquid helium is only performed by LipoScience Service.

1. Place the system in Standby.
2. Turn off the compressed air supply to the anti-vibration legs. Open console door and turn anti-vibration air regulator counter clockwise until the pressure reading is below 20 PSI.
3. Remove the cover from the nitrogen fill and vent ports (shown below).

4. Open the nitrogen supply valve for several seconds to bleed air from the tank hose, then close the supply valve.

5. Connect the nitrogen tank hose to the fill port, and tubing to vent port.

6. Open the nitrogen supply valve to fill the NMR with nitrogen.

   Monitor the nitrogen supply indicator until the supply is full (F). If the vent tube starts to spit small amounts of liquid, the supply is full.

7. Close the nitrogen supply valve and remove the tank hose from the nitrogen fill port.

8. Replace the nitrogen fill and vent port covers.

9. Restore compressed air to the anti-vibration legs. Open console door and turn the anti-vibration leg regulator clockwise until the gauge reads 70 PSI.

10. If required at your site, record the activity in the maintenance log. Refer to “Recording maintenance activities” on page 56.

NOTE: Wait approximately 20 minutes before calibrating or processing samples. This period provides time for the magnet to stabilize after the nitrogen fill.

Changing the sample probe tip

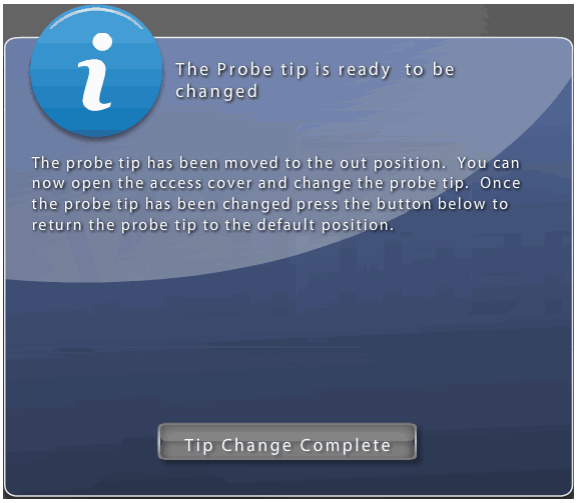
Change the sample probe tip if the tip becomes clogged or visibly bent.

1. Place the system in Standby.
2. On the Main menu, touch Tools.

   The Tools menu appears.
3. Touch Sample Manager.

   The Sample Manager menu appears.
4. Touch Change Sample Probe Tip.

   The system moves the probe to the carousel area and then displays this message.



5. Open the carousel cover to access the sample probe.
6. Unscrew the plastic fitting to loosen and remove the probe tip.
7. Install the replacement tip and secure with the plastic fitting.
8. Close carousel cover.

9. Touch Tip Change Complete.
10. If required at your site, record the activity in the maintenance log. Refer to “Recording maintenance activities” on page 56.

Archiving data

Archive data weekly as part of your maintanence practices. This will prevent data building up in the database which could affect software performance.

1. Place the system in Standby.
2. On the Main menu, touch Tools.
3. Press the Archive data button

6 Setup and configuration

User accounts

This feature is accessible only to an Expert user.

To set up a new user account:

1. Place the system in Standby.

2. On the Main menu, touch Settings.

   The Settings menu appears.

3. Touch Users.

   The Users screen appears.

4. Touch Add User.

   The User Information appears on the right side of the screen.

5. Type the User Name.

   User names must be from 6 to 12 characters long, in any combination of letters and numbers. User names are not case-sensitive.

6. Type the password of the user.

   Passwords must be from 4 to 12 characters long, in any combination of numbers and upper and lower case letters. Passwords are case-sensitive.

7. Type the password again to confirm.

8. Select the User Role (Basic or Expert).

9. Touch Apply.

The new user name is saved and is listed on the left side of the screen.

To activate, deactivate, or delete a user, or change the user's level:

1. Place the system in Standby.
2. On the Main menu, touch Settings.

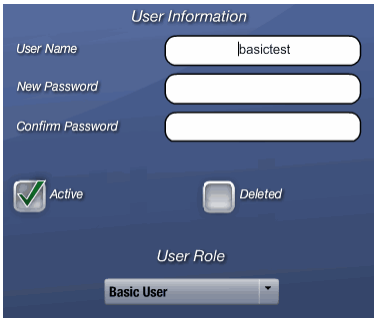
   The Settings menu appears.
3. Touch Users.

   The Users screen appears. A list of the existing users is on the left side of the screen.

USER ▲	ROLE	CREATED	EXPIRES	ACTIVE	DELETED
basicuser	Basic User	2011-02-16	2011-02-23	YES	NO
basictest	Basic User	2011-02-17	2011-02-24	YES	NO

4. Select the user whose account you want to modify.

   The information for that user appears on the right side of the screen.



5. To change the user level, select Basic or Expert.
6. To activate or deactivate the user, check or uncheck the Active box.
7. To delete the user, check the Deleted box.

8. Touch Apply.

The changes are saved and are listed on the left side of the screen.

You can also set the length of time, from the time of user creation, before passwords expire. This setting applies to all system users.

To set the password expiration time for all users in the system.

1. Place the system in Standby.

2. On the Main menu, touch Settings.

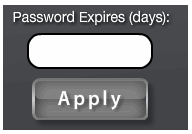
   The Settings menu appears.

3. Touch Users.

   The Users screen appears.

4. Touch Password Expiration.

   The Password Expires field appears.



5. Enter a value from 1 to 26 (weeks) or enter 0 to set the password expiration value to indefinite. Touch Apply.

The system displays the new expiration date in the Expires column for each user.

System setup

The Settings menu includes a number of setup functions that are available to an Expert user to configure the system.

Selecting the assays available for the default worklist

The default worklist is a set of tests that are always performed on a sample (if Run Default Worklist Also is checked on the Accessioning Settings screen) even if the test is not ordered by the LIS. The Worklist Setup screen enables an expert user to select the assays that a basic user is allowed to place in the default worklist.

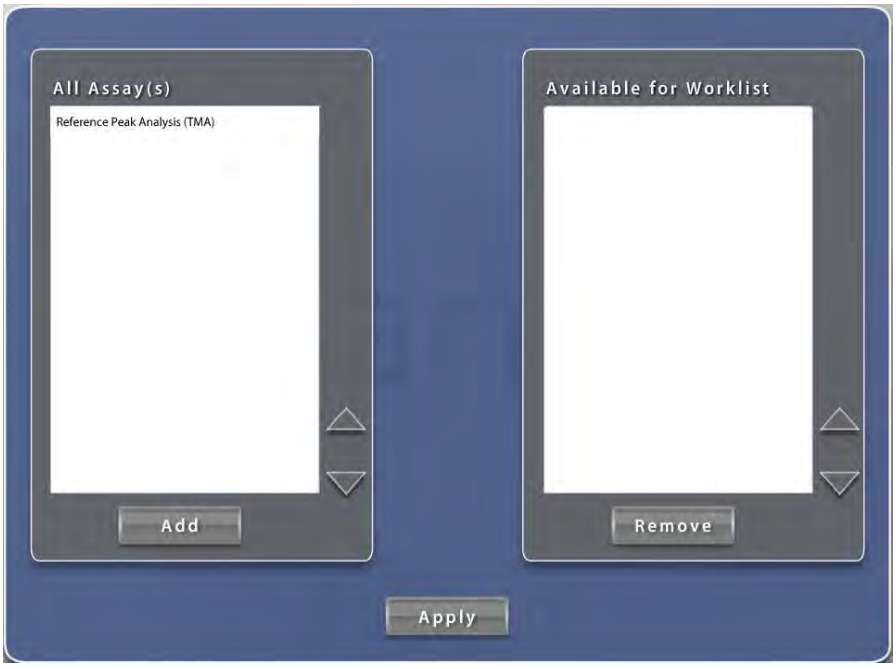
This feature is accessible only to an Expert user.

To define the assays that are available on the Default Worklist screen.

1. Place the system in Standby.
2. On the Main menu, touch Settings.

   The Settings menu appears.
3. Touch Worklist Setup.

   The Worklist Setup screen appears.



4. To make an assay available for inclusion on the default worklist, select the assay name from All Assays and touch Add.

   The assay name appears in the Available for Worklist list.

5. To remove an assay from the list available for the default worklist, select the assay name from Available for Worklist and touch Remove.

   The assay name is removed from the Available for Worklist list.

6. Touch Apply to save worklist settings.

Setting up alarms and alerts

This feature is accessible only to an Expert user.

To set up alarms and alerts:

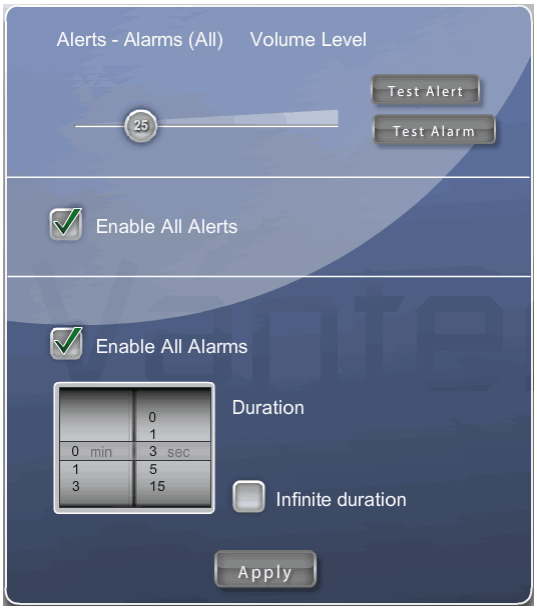
1. Place the system in Standby.

2. On the Main menu, touch Settings.

   The Settings menu appears.

3. Touch Alerts - Alarms.

   The Alerts - Alarms Settings screen appears.



4. Touch and drag the Volume Level slider to adjust the alarm and alert volume. Touch Test Alert or Test Alarm to hear the new volume.

5. Set Enable All Alerts to the desired state:
   - When checked, all alerts are indicated by a tone at the volume you selected above.
   - When unchecked, alerts are not indicated by an audible tone.

6. Set Enable All Alarms to the desired state:
   - When checked, all alarms are indicated by a tone at the volume you selected above.
   - When unchecked, alarms are not indicated by an audible tone.

7. Touch and drag the Duration thumbwheels to adjust the time the alarm tone is sounded, or check Infinite duration to set the alarm to sound until it is dismissed by the user.

8. Touch Apply to save the alarm and alert setup.

Setting up the printer

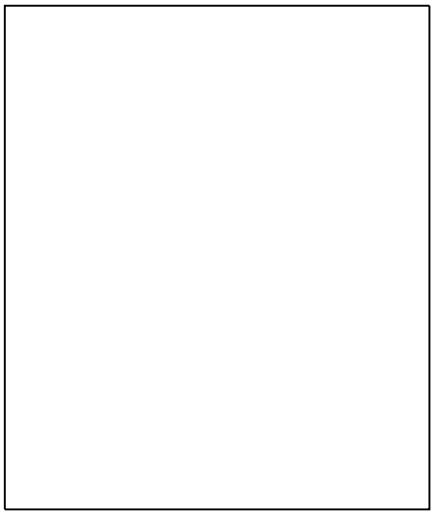
To set up a printer so that you can print test results:

1. On the Main menu, touch Settings.

   The Settings menu appears.

2. Touch Printer.

   The Printer Settings screen appears.



3. Select how the printer is connected to the system. If you select Network Printer, enter the IP address of the printer.

4. To test the selected printer, touch Print Test Page.
5. Touch Apply to save the printer setup.

Setting up accessioning

This feature is accessible only to an Expert user.

To set up your system accessioning:

1. Place the system in Standby.
2. On the Main menu, touch Settings.

   The Settings menu appears.
3. Touch Accession.

   The Accession Settings screen appears.

4. In the LIS Settings section, check Enabled if you want the LIS to create the worklist for each specimen. Check Run Default Worklist Also if you want to run the tests included on the default worklist in addition to any specified by the worklist from the LIS.
5. In the Manual Accession Settings section, check Enabled if you want the user to enter accessioning information manually for each specimen. Check Run Default Worklist Also if you want to run the tests included on the default worklist in addition to any the user might manually specify.
6. In the Default Worklist section, check Enabled to be able to use the default worklist in either of the steps above.

   Refer to “Adding or removing assays from the default worklist” on page 48 for information about setting up the default worklist.

7. Click Apply to save the accessioning setup.

Setting the cryogen monitoring time

This feature is accessible only to an Expert user.

To specify the time of day that the system reads the liquid nitrogen and liquid helium levels:

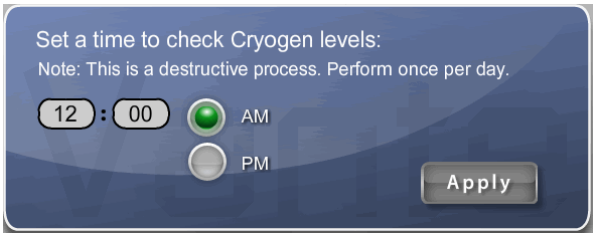
1. Place the system in Standby.

2. On the Main menu, touch Settings.

   The Settings menu appears.

3. Touch Cryogen.

   The Cryogen Settings screen appears.



4. Specify the time of day.

5. Touch Apply to save the cryogen level measurement time.

Showing or hiding patient private information

This feature is accessible only to an Expert user.

To enable or disable patient private information (patient name and date of birth) from appearing on the Results screen and on prints from that screen:

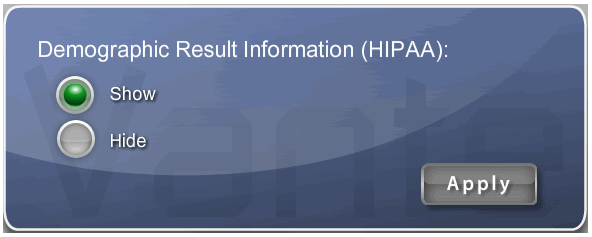
1. Place the system in Standby.

2. On the Main menu, touch Settings.

   The Settings menu appears.

3. Touch HIPAA.

   The HIPAA Settings screen appears.



4. Select Show or Hide.

5. Touch Apply to save the HIPAA setup.

7 Glossary

accessioning
The process by which a unique identifier (accession number) for an individual sample is obtained. Accessioning usually involves data entry of client number, tests ordered for the sample, and any known demographic information for the sample. Typically, bar code labels corresponding to the accession number are generated by the LIS and attached to the specimen tube. For situations where the LIS is not available, tubes can be accessioned manually.

alarm
A system message informing the user that there is a condition that requires user intervention to continue using the system.

alert
A system message informing the user of a specific event or condition. An alert does not require user intervention to continue to use the system.

aliquot
A specified volume of sample transferred to a separate container that inherits the identifying information for the sample. An aliquot can be diluted.

aspirate
The withdrawal of fluid by the system from a specimen tube or a system fluid bottle.

basic user
The lowest user level that allows access to a subset of the complete system functions. Basic users can run specimens and check the status of the system.

calibration
Act of comparing an instrument's measuring accuracy to a known standard. There are two types of calibration used with the analyzer. NMR calibration compares the result from a sample using the NMR Reference Standard and adjust (shims) the magnet accordingly. Touch screen calibration ensures expected behavior of the touch screen.

carousel
The compartment on the top of the Vantera Clinical Analyzer that houses up to six separate 250-ml diluent fluid containers.

cryogen
A substance to produce extremely low temperatures. The Vantera Clinical Analyzer uses two cryogens: liquid nitrogen and liquid helium.

demographic information
The identifying information relating to a sample. Demographic information might include some or all of the following types of data: study site, investigator, subject number, visit, draw date/time, subject initials, subject name (usually not in clinical research study), subject date of birth, subject sex, and fasting status.

diluent
A solution used to dilute a sample.

expert user
An expert user has access to all functions described in this User's Manual.

flowcell
A glass vessel located at the center of the NMR magnet in which measurements of the sample are taken.

load area
The compartment where you place specimen racks for testing.

mini-prime
A system operation that purges air from the fluidics lines by pumping rinse fluid through the lines. A mini-prime is a shorter version of the full prime operation.

NMR
Acronym for Nuclear Magnetic Resonance

NMR LipoProfile® Test
The *NMR LipoProfile* Test is an advanced cardiovascular diagnostic test that uses Nuclear Magnetic Resonance (NMR) spectroscopy to uniquely provide rapid, simultaneous, and direct measurement of lipoproteins. See the package insert for details.

NMR Reference Standard
The calibrant used by the Vantera Clinical Analyzer. The NMR Reference Standard is sodium trimethylacetate hydrate (TMA).

order
Designation that a specific test is to be performed on samples in a particular study. Multiple tests may be ordered for samples in a study.

pending
The temporary state that indicates the system is attempting to transition to a different operational state. For example, Stop Pending.

personal protective equipment (PPE)
Equipment worn or used by workers to protect themselves from exposure to hazardous materials or conditions; provides a barrier between individuals and hazardous elements.

plasma
The liquid part of blood, as distinguished from the suspended material.

prime
A system operation that purges air from the fluidics lines by pumping rinse fluid through the lines.

probe
The small tube used to prepare and mix samples to be tested.

quench
A sudden release of extremely cold liquids or gasses from the top of the magnet. If a quench occurs, leave the area immediately. Sudden release of helium or nitrogen liquids or gases can rapidly displace oxygen in an enclosed space creating a possibility of asphyxiation. Do not return until the release of cryogens has stopped and the room has been ventilated so that oxygen level returns to normal.

ready
The operational state when the system is not currently processing specimens but is ready to begin processing.

running
The operational state when the system is currently processing specimens

sample
An aliquot from a specimen with added Diluent I.

serum
The liquid part of blood, as distinguished from the suspended material, after coagulation.

service user
The user level reserved for LipoScience service personnel that provides access to advanced features.

shimming
The process the system uses during calibration to compensate for slight drifting of the NMR magnet over time.

specimen
Undiluted body fluid.

specimen tube
Container for a specimen. Usually has specimen-identifying information affixed via a bar coded label.

standby
The operational mode where the system is not capable of processing specimens and might require attention by the user.

stopped
The operational mode where the system is not capable of running specimens and requires significant attention or intervention by the user.

TAC
The Technical Assistance Center at LipoScience.

transfer area
The area from which the system aspirates liquid from a specimen tube.

unload area
The area where tested specimen racks are moved so they can be removed from the Vantera Clinical Analyzer.

UPS

Acronym for uninterruptible power source. The UPS provides automatic, temporary battery backup in the event of loss of power, which enables the orderly shutdown of the Clinical Analyzer.

worklist

The list of tests sent by the LIS for each specimen.

Appendices

Specifications

Specimen Types	Undiluted serum, plasma
Aspiration Volume per Test	150 µl
On-board Sample Capacity	Up to 200 specimens in (20) Vantera 10 x 1 tube racks
Supported Specimen Tubes (Uncapped)	12mm x 75mm 13mm x 75mm 13mm x 100mm 16mm x 100mm
Assay Fluid Capacity	Up to six - 250ml bar coded bottles
Bulk Fluid Capacity	Two – 5L bottles – 1 wash (supplied by LipoScience) and 1 rinse – de-ionized water (refilled by user)
Waste Capacity	One – 5L bottle
Required Cryogens	Liquid nitrogen (refilled by user) Liquid helium (refilled by LipoScience Service)
Certifications	UL
Room Temperature	63°F to 75°F (17°C to 24°C)
Humidity	20% – 60% RH
Altitude	Not Specified
Laboratory Size (Length x Width x Height)	16.00 ‘ x 16.00 ‘ x 9.00’ minimum (487.68 x 487.68 x 274.32 cm minimum)
Ventilation	45 m^3 / min, minimum
Size (Length x Width x Height)	126.00” x 49.00” x by 71.00” (320.04 x 124.46 x 180.34 cm)
Weight	2496 lb (1132.17 kgs)
Service Access Perimeter	3 ft. (91.44 cm) unobstructed perimeter around the system with a minimum 4 ft. (121.92 cm) path to the system
Voltage	200 – 240 VAC The Vantera Clinical Analyzer should be plugged directly into a UPS, which is in turn plugged directly into facility power. Facility power must meet all building codes to ensure proper grounding of the device.
Current	16 Amps
Frequency	60 Hz
Power Connection	Wall outlet, Hubbel Twist-Lok
LIS Support	ASTM 1381 1394 Supported
Connections	Ethernet connections USB printer port RS-232 serial port for UPS; RS-232 serial port for LIS
Waste Drain (Optional)	Drain should be unobstructed and capable of handling a minimum of 16 liters per hour. The drain is required to be at floor level. The drain line should be securely placed into the drain to prevent accidental removal. Laboratories should refer to local wastewater requirements to ensure that there are no special drain requirements.
Laboratory Compressed Air	90-100 psi, 20 L/min minimum Requires ¼-inch male NPT connector at the wall
Filtered Air Supply	Comply with ISO8573-1, Class 4

Specimen tube bar code label specifications

The specimen tube bar code labels shall be encoded in one of the following bar code symbologies: Code39, Code128, Codabar or Interleaved 2 of 5. The specimen tube bar code character string length shall not exceed 16 characters for Code39, 49 characters for Code 128, or 37 characters for Codabar. The characters in a specimen tube bar code will be limited to upper and lower case alphabetic (a-z, A-Z), numeric (0-9), and an underscore (_).

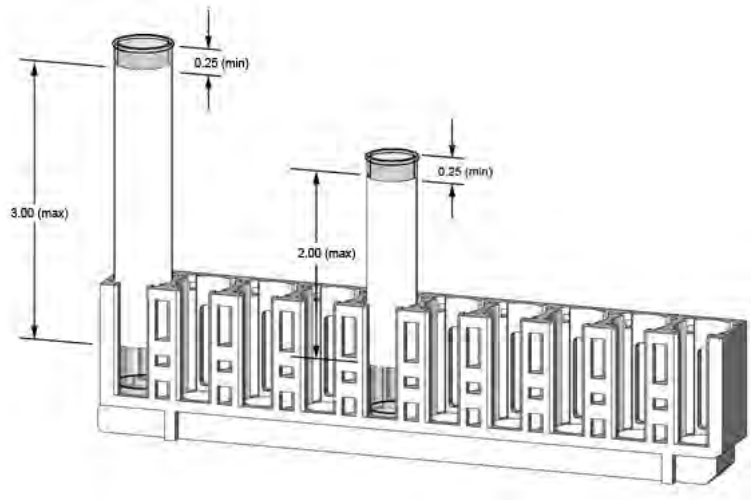
The Quiet Zone shall be at least 10 times the narrow bar width of the bar code.

The bar code color scheme shall be black lines on white background.

The specimen tube bar code label shall be located vertically on the side of the tube perpendicular to the rack. The specimen tube bar code label decode string will be a unique identifier assigned by the user.

The specimen tube bar code reader shall be capable of reading a bar code on a specimen tube and placed in the rack with the bar code centered in the rack opening within a rotational tolerance of ±15°.

The specimen tube bar code label when affixed to the specimen tube shall be between 0.25 inches and 1.2 inches from the top of the tube as shown below.

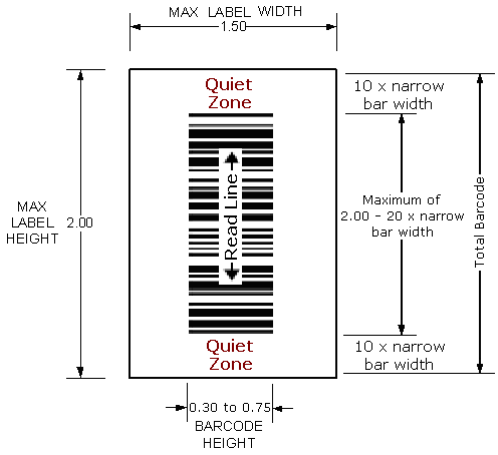


An example of a specimen tube bar code label is shown below.

75 mm specimen tubes

The specimen tube bar code width, including Quiet Zone, shall be no greater than 2.00 ± 0.40 inches along the tube length. The specimen tube bar code height shall be between 0.30 and 0.75 inches.

The specimen tube label width shall be no greater than 1.50 inches along the tube length. The specimen tube label height shall be no greater than 2.00 ± 0.40 inches.



100 mm specimen tubes

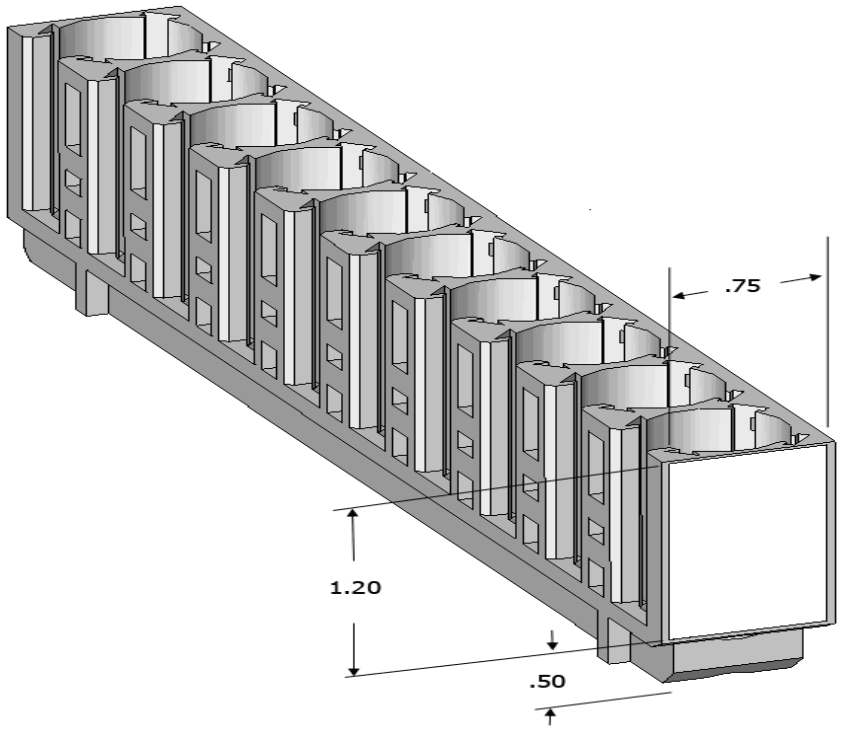
The specimen tube bar code width, including Quiet Zone, shall be no greater than 3.00 inches along the tube length. The specimen tube bar code height shall be between 0.30 and 0.75 inches.

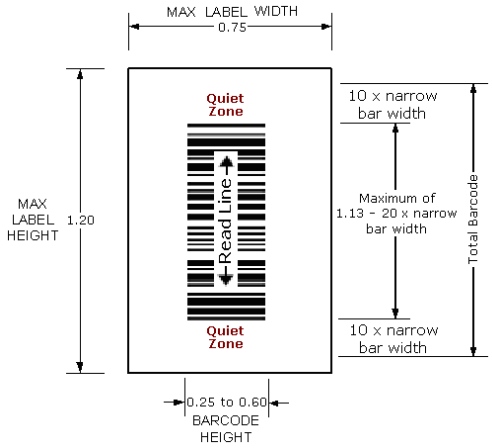
The specimen tube label width shall not exceed 1.50 inches. The specimen tube label height shall not exceed 3.00 inches.

Sample Rack Barcodes

The rack barcode labels are encoded with the Codabar symbology.

The rack barcode width, including Quiet Zone, is no greater than 1.20 ± 0.10 inches. The rack barcode height is between 0.25 ± 0.10 to 0.60 ± 0.10 inches, the barcode label is located on the end of the rack (position #10 side). The rack barcode label width will not exceed 0.75 ± 0.10 inches, and the rack barcode label height will not exceed 1.20 ± 0.10 inches as shown below.





LIS Interface Specification

The Vantera Clinical Analyzer is an instrument that conveys assays based on Nuclear Magnetic Resonance (NMR) technology to the clinical laboratory. It operates as an integrated resource within the clinical laboratory and requires an LIS interface to receive patient and patient order information, and to report results. This document describes the hardware and software interface that is necessary to provide that information flow. The LIS design specification is apportioned to this document from the *Numera Software Design Specification*, 62-001-01-0109.

Reference Documents

To the point they are referenced herein, the following documents form a part of this interface specification.

Title	Document ID
Standard Specification for Low-level Protocol to Transfer Messages Between Clinical Laboratory Instruments and Computer Systems. (This document was formerly known as ASTM E1381-02 and is available for order online at www.clsi.org.)	NCCLS LIS1-A
Specification for Transferring Information Between Clinical Instruments and Computer Systems; Approved Standard – Second Edition. (This document is a revision of the former ASTM E1394-97 and is available for order online at www.clsi.org.)	NCCLS LIS2-A2

Definitions

Terms, acronyms, and descriptions used in this document that are important to understanding the technical contents.

Table 1 - Definitions

Term	Description
CTS	Clear to Send
DCE	Data Communications Equipment
DSR	Data Set Ready
DTE	Data Terminal Equipment
DTR	Data Terminal Ready
HDL	High-Density Lipoprotein
LDL	Low-Density Lipoprotein
LIS	Laboratory Information System
LS	LipoScience
NMR	Nuclear Magnetic Resonance
RTS	Request to Send
Vantera	NMR Clinical Analyzer

INTERFACE SPECIFICATION

Interfacing specifications for the Vantera Clinical Analyzer are described in this section. Following an overview, the description proceeds in a bottom-up manner from hardware connectors and cabling, through low level software protocols, and concluding with an application layer protocol description.

Overview

Within the clinical laboratory, the Vantera Clinical Analyzer implements a Query Bi-Directional Interface as described in *Interfacing the Clinical Laboratory*. The diagram below summarizes information flow.

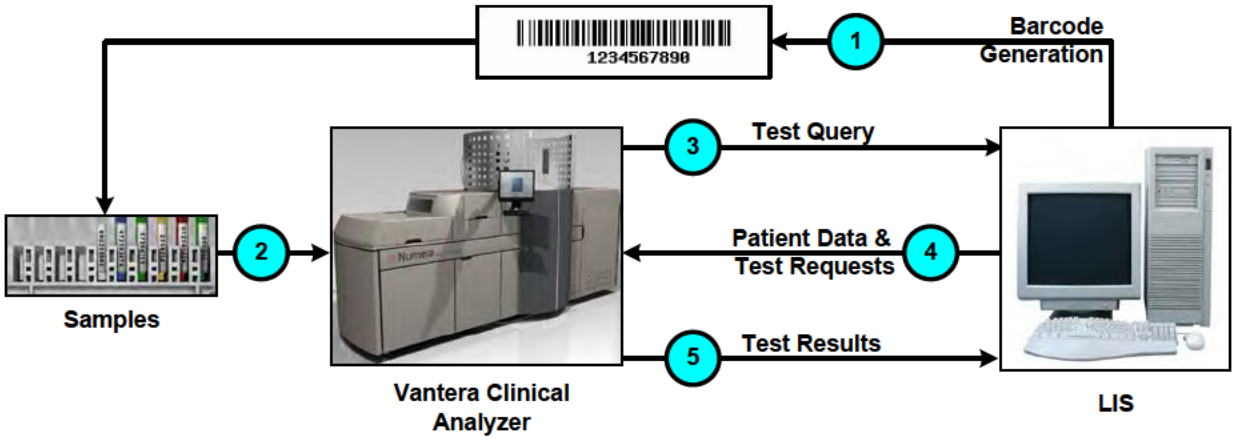


Figure 1 – Client-Server Data Flow

The table below provides details for the labeled information flow identified in the figure above.

Table 2 – Vantera-LIS Data Flow Description

ID	Name	Description
1	Barcode Generation	The LIS or other information system (e.g., HIS) generates a barcode that enables the LIS to uniquely identify the subject patient sample
2	Sample Load	The barcode is applied to the patient sample tube and loaded into the Vantera Clinical Analyzer by the clinical operator
3	Test Query	The Vantera Clinical Analyzer reads the barcode and issues a test query that contains the patient sample barcode information
4	LIS Response	The LIS returns information that contains patient demographic data and clinical tests associated with the patient sample
5	Test Results	The Vantera Clinical Analyzer executes the tests on the patient sample and returns the results

Mechanical and Electrical Interfaces

The Vantera Clinical Analyzer presents a hardware interface identified as a serial port. The physical characteristics of this interface and cabling are presented herein.

Serial Connector (EIA-232)

The table below summarizes the mechanical and electrical characteristics of the serial connection. Bolded items within an option list indicate the preferred or default value.

Table 3 – Serial Communication Hardware Summary

Item	Specification or Option
Mechanical	9-pin D male with pin assignments per EIA-574
Electrical Format	EIA-232 DTE emulation
Baud rate	300, 1200, 2400, 4800, **9600**, 19200, 38200, 57600, 115200
Data bits	8
Parity	Odd, Even, or **None**
Framing (stop bits)	**1** or 2
Flow Control	**None**, Hardware, Xon/Xoff

Serial Cabling

The interface cable is supplied by the user and no specific cabling configuration is prescribed by the Vantera Clinical Analyzer. In order to maintain the electrical signal characteristics defined by EIA-232, a cable length of no more than 50 feet is recommended. The precise configuration between the Vantera Clinical Analyzer and the LIS depends on four factors:

1. The selected flow control (none, hardware or Xon/Xoff)
2. Whether the LIS emulates a DTE or DCE device (the Vantera Clinical Analyzer emulates DTE)
3. Whether the Vantera Clinical Analyzer and the LIS will use on-line indicators (DSR and DTR)
4. The connector type used by the LIS (DE-9 (DB-9) or DB-25)

The following table and subsequent figures help to describe the influences of the four factors listed above on cable design and selection. For some background information and examples of common configurations, refer to Section 0.

Table 4 – Cable Selection Influences

Factor	Influence
Flow control	Hardware flow control requires that the RTS and CTS signals be connected between the Vantera Clinical Analyzer and the LIS. Hardware flow control signals may be routed so that they loop back at the local connector. Loop-back wiring side-steps actual hardware-based flow control but enables systems that require hardware flow control to work with those that do not have it. Since the Vantera Clinical Analyzer is flexible, it is likely that the diagram on the left side of Figure 5 will prevail for the Vantera Clinical Analyzer interfaces where flow control is required.
DTE or DCE	Communicating with devices of the same type requires incorporation of a null modem. The transmit and receive lines must be appropriately routed Null modem connections are shown in Figure 6.
On-line Indication	The DSR and DTR may be used to establish and terminate connections. Presence of these signals provides assurance to the Vantera Clinical Analyzer and the LIS that the connection status is alive and well. If the DSR signal de-asserts while the Vantera system is transmitting, the Vantera Clinical Analyzer interprets this as an error condition and will not attempt further communication until the DSR signal is again detected.
DE-9 or DB-25	Figure 4 and Table 14 above provide a mapping between the two connector types.

Software Layers

The figure below portrays the Vantera Clinical Analyzer communication hierarchy with software layers represented as non-shaded boxes and hardware layers as shaded boxes. The LIS2-A2 Application Layer Protocol and the LIS1-A Low-Level Protocol layers define the system software interface behavior to the LIS. Each of these layers is described in subsequent subsections. Note that the TCP/IP Driver and Network Adaptor depicted in the diagram is not implemented by the Vantera Clinical Analyzer at this time.

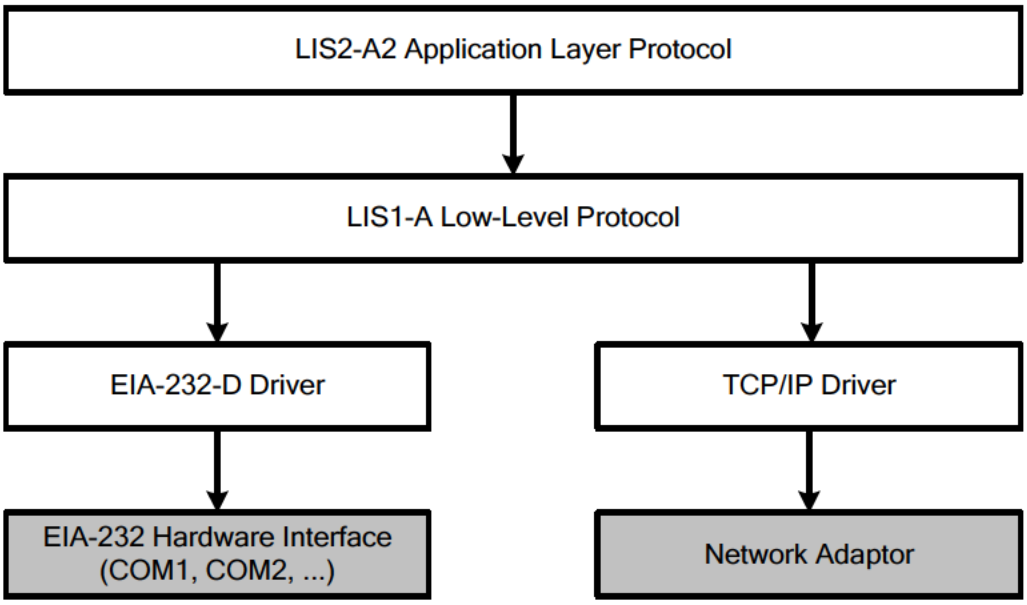


Figure 2 – Vantera Clinical Analyzer Software Layers

LIS1-A Low-Level Protocol

The Vantera Clinical Analyzer implements the LIS1-A data link protocol for both the serial and network connections. LIS1-A was formerly known as ASTM E1381-02 and is equivalent to that document. The lower layer software is responsible for data link connection and release, data delimiting and synchronism, sequential control, error detection, and error recovery. The LIS1-A document forms a part of this specification and the associated technical information is not repeated herein. It is assumed that the LIS interface implementer will have access to and be familiar with the contents of LIS1-A.

Configuration Parameters

The table below identifies configurable items that impact the Vantera Clinical Analyzer LIS1-A protocol behavior. The default values are in accordance with the nominal or minimal values as specified in the LIS1-A standard. Refer to Section 6 and Figure A1.1 of the LIS1-A standard for information that describes the effect of the configuration parameters.

Table 5 – LIS1-A Configuration Parameters

Item	Description	Range	Default
Frame Length	Maximum number of characters in a frame	247 to 64000	247
Busy Timer	Length of time that the Vantera Clinical Analyzer will wait after a NAK is received in response to an ENQ before sending another ENQ	Adjustable	10 sec
Contention Timer	Length of time that Vantera Clinical Analyzer will wait after an ENQ is received in response to an ENQ before sending another ENQ	Adjustable	1 sec
Post Interrupt Wait	Length of time that Vantera Clinical Analyzer will wait after a send interrupt is received before entering the link establishment phase if the receiver does not send a message	Adjustable	15 sec
Frame Retry	Number of times a frame send is attempted before proceeding to the termination phase	Adjustable	6
Establishment Sender Timeout	Length of time that a sender waits for a reply during the establishment phase	Adjustable	15 sec
Establishment Receiver Timeout	Length of time that a receiver waits for an ENQ after contention is detected during establishment phase	Adjustable	20 sec
Transfer Send Timeout	Length of time that a sender waits for a reply during the transfer phase	Adjustable	15 sec
Transfer Receive Timeout	Length of time that a receiver waits for a frame or <EOT> during the transfer phase	Adjustable	30 sec

LIS2-A2 Application Layer Protocol

The Vantera Clinical Analyzer implements the LIS2-A2 at the application layer. LIS2-A2 has evolved from ASTM E1394-02 and is largely equivalent to that document. Information contained within LIS2-A2 forms a part of the Vantera Clinical Analyzer interface specification and is not repeated herein. It is assumed that the LIS interface implementer will have access to and be familiar with the contents of LIS2-A2.

LIS1 and LIS2 both employ a transmission error detection and recovery strategy. The strategy within LIS1 can make it very difficult to successfully implement the strategy within LIS2. To enable both strategies to work, the Vantera Clinical Analyzer transmitted data enforces a rule that no LIS1 frame contains more than one record segment. Data link frames contain data that belongs to one and only one message. All frames containing a <CR> (the record delimiter) within their data content will have that <CR> as the last character of their data content, and that frame will end with an <ETX> (end frame).

The Vantera Clinical Analyzer utilization of LIS2 is described by individual record type within subsequent subsections. A common table format is used to summarize utilization information. Columns in the table have the following meaning:

Table 6 - LIS2-02 Record Table Column Legend

Column Name	Description
ID	Numeric identifier of the sequential order of the field in the record
LIS2	LIS2-A2 paragraph number associated with the field
ASTM	ASTM E1394 paragraph number associated with the field

Column Name	Description
Name	Name of the field
Max	Maximum field length
Rx	Describes what the Vantera Clinical Analyzer expects or how it will treat a field when a message containing the record is received from the LIS
Tx	Describes what the LIS should expect in messages transmitted by the Vantera Clinical Analyzer that contain the record

Fields that are omitted from a record table are not used by the Vantera Clinical Analyzer and may be filled in or left blank at the discretion of the LIS. The LIS should not expect to process any value from a field that is not supported by the Vantera Clinical Analyzer. Fields excluded from the description table are not supported.

Message Header Record

The message header record is the first record of a transmission and is a level 0 record. It must be followed at some point by message terminator record before ending the message.

Table 7 - Message Header Record Utilization

ID	LIS2	ASTM	Name	Max	Rx	Tx
1	6.1	7.1.1	Record type	1	'H'	'H'
2	6.2	7.1.2	Delimiter definition	4	The Vantera Clinical Analyzer accepts and interprets the messages in accordance the delimiter definition	The Vantera Clinical Analyzer uses delimiters "|\^&|"
5	6.5	7.1.5	Sender name or ID	6	Not used	"Vantera"
13	6.13	7.1.13	Version number	7	Not used, assumed to be LIS2-A2 or equivalent	"LIS2-A2"
14	6.14	7.1.14	Message date/time	14	Not used	Message date/time

Patient Information Record

Patient records are at level 1 in the message hierarchy. It is expected that the LIS response to a test query will contain a single patient record. The Vantera Clinical Analyzer test result messages will contain a single patient information record.

Table 8 – Patient Information Record Utilization

ID	LIS2	ASTM	Name	Max	Rx	Tx
1	7.1	8.1.1	Record type	1	'P'	'P'
2	7.2	8.1.2	Sequence number	1	'1'	'1'
4	7.4	8.1.4	Laboratory assigned patient ID	--	Laboratory assigned patient ID	Laboratory assigned patient ID
8	7.8	8.1.8	Birth date	8	Patient birth	Null
9	7.9	8.1.9	Patient sex	1	Patient gender: 'M' - Male 'F' - Female 'U' - Unknown	Null
21	7.21	8.1.21	Patient's diet	1	'Fasting status for report 'F' – Fasting 'N' – Not fasting	Null

					‘U’ - Unknown	

Test Order Record

Test order records are at level 2 in the message hierarchy. The LIS response to a test query may result in a response that has many orders for an individual patient. The Vantera Clinical Analyzer will process all order records for a patient and accept those that it can fulfill. The Vantera Clinical Analyzer test result messages will contain a single test order record.

The Vantera Clinical Analyzer is responsible for parsing through the test order records associated with a patient and determining which orders it can fulfill. The Vantera Clinical Analyzer uses the Manufacturer’s Code (component 4) of the Universal Test ID field to determine the test type. The Vantera Clinical Analyzer currently supports the LipoProfile test, which is identified by the Manufacturer’s Code value of “LipoProfile”.

The Vantera Clinical Analyzer will indicate the relative success or failure of the order processing in the Report Types field. If the Vantera Clinical Analyzer encounters a condition that prevents successful processing, it will return an 'X' in the Report Types field and include comment records to describe the abnormal condition.

Table 9 – Test Order Record Utilization

ID	LIS2	ASTM	Name	Max	Rx	Tx
1	8.4.1	9.4.1	Record type	1	'O'	'O'
2	8.4.2	9.4.2	Sequence number	--	Valid sequence value	Valid sequence value
3	8.4.3	9.4.3	Specimen ID	--	Specimen barcode	Specimen barcode
5	8.4.5	9.4.5	Universal test ID	--	See Appendix B	See Appendix B
8	8.4.8	9.4.8	Specimen collection date and time	14	Specimen collection date and time	Null
15	8.4.15	9.4.15	Specimen received date and time	14	Specimen received date and time	Null
26	8.4.16	9.4.26	Report Types	--	Not used	Conveys report type 'F' - Final 'X' – Not done

Result Record

Result records are at level 3 in the message hierarchy. The Vantera Clinical Analyzer will transmit a result record upon assay analysis completion. Result records may not be included if the Vantera Clinical Analyzer detects an abnormal condition. In this case, the Vantera Clinical Analyzer will set the Report Types field of the order record to 'X' and describe the condition one or more comment records. Result records are not expected to be received by The Vantera Clinical Analyzer and are ignored.

The Manufacturer's Code (part 4) of the Universal Test ID field is used to convey the name of a specific result. The LipoProfile test generates many results that are reported to the LIS. Therefore, there are many result records generated by a single order for a LipoProfile.

Table 10 – Result Record Utilization

ID	LIS2	ASTM	Name	Max	Rx	Tx
1	9.1	10.1.1	Record type	1	Not used	'R'
2	9.2	10.1.2	Sequence number	--	Not used	Valid sequence value
3	9.3	10.1.3	Universal test ID	--	Not used	See Appendix B
4	9.4	10.1.4	Data/Measurement Value	--	Not used	Numeric value of the result type
5	9.5	10.1.5	Units	--	Not used	Units of the data value

Comment Record

Comment records in messages received by the Vantera Clinical Analyzer can appear at any level in the message hierarchy. The Vantera Clinical Analyzer ignores all comment records. The Vantera Clinical Analyzer may transmit one or more comment records immediately following an order

record to which the comment applies. The Vantera Clinical Analyzer uses comment records to convey textual analysis information that should be associated with an order and be treated as part of the test results.

Table 11 – Comment Record Utilization

ID	LIS2	ASTM	Name	Max	Rx	Tx
1	10.1	11.1.1	Record type	1	Not used	'C'
2	10.2	11.1.2	Sequence number	--	Not used	Valid sequence value
3	10.3	11.1.3	Comment source	1	Not used	'I'
4	10.4	11.1.4	Comment text	--	Not used	Comment text for use on test result report
5	10.5	11.1.5	Comment Type	--	Not used	'I'

Request Information Record

The Request Information record is sent by the Vantera Clinical Analyzer to request information about a single patient sample. Request information records received from the LIS are ignored by the Vantera Clinical Analyzer.

Table 12 – Request Information Record Utilization

ID	LIS2	ASTM	Name	Max	Rx	Tx
1	11.1	12.1.1	Record type	1	Not used	'Q'
2	11.2	12.1.2	Sequence number	--	Not used	Valid sequence value
3	11.3	12.1.3	Starting range ID	--	Not used	Specimen barcode in the 2nd component of the field
13	11.13	12.1.13	Request information status	1	Not used	'O' – orders and demographics only

Message Terminator Record

Message terminator records appear at the end of a message. If the patient sample identified by the Vantera Clinical Analyzer does not exist, the LIS should respond with an empty data frame (a message consisting of only a header and terminator record) with the termination code field of the termination record set to 'I'.

Table 13 – Message Terminator Record Utilization

ID	LIS2	ASTM	Name	Max	Rx	Tx
1	12.1	13.1.1	Record type	1	'L'	'L'
2	12.2	13.1.2	Sequence number	1	'1'	'1'
3	12.3	13.1.3	Termination code	1	'I' – no information 'N' or null - Normal	Not used

Scientific Record

Scientific records are not used by the Vantera Clinical Analyzer.

EXAMPLE MESSAGE SEQUENCES

This section contains example message sequences between the Vantera Clinical Analyzer and the LIS. Sections herein describe specific events that motivate a message transaction along with an example of the specific message contents that would be communicated.

Connection Establishment Sequence

The connection sequence depends on the interface type. For both types of connections, the link connection rules of LIS1-A apply as described in Section 6 of that document and in the state transition diagram in the Appendix of LIS1-A.

For the network interface, the LIS1-A connection sequence is preceded by the typical TCP/IP socket establishment calls. The LIS should establish a listening socket on an established port interface known to the Vantera Clinical Analyzer. The Vantera Clinical Analyzer will connect to that socket and the LIS will accept the connection. Data flow then continues in accordance with LIS1-A.

Test Query Message Sequence

The following sequence diagram depicts the time-ordered flow of information between the Vantera Clinical Analyzer and the LIS. A symbolic portrayal of this sequence is provided in Figure 3.

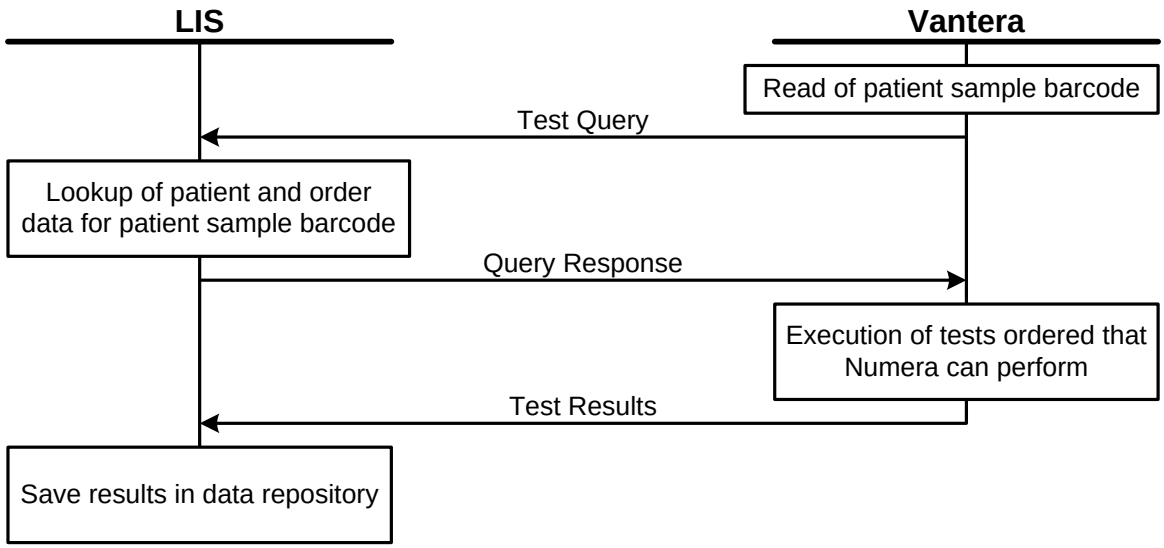


Figure 3 – Test Query Message Sequence

Normal Message Sequence

The following is an example of the test query message sequence. Bold text indicates that the message is sent by the Vantera Clinical Analyzer to the LIS. Non-bold text indicates that the message is being sent by the LIS to the Vantera Clinical Analyzer. The example messages reflect the minimal required data content. More content may be added to any message but may be ignored by the receiving system.

The examples exclude LIS1-A transmission control characters and focuses on the application layer. Carriage return and line feed characters are shown in between records of the message for formatting and readability within this document. The designated record separator for LIS2-A2 is just the carriage return character (decimal 13).

```
H|\^&|||Vantera|||||||LIS2-A2|20060627121500
Q|1|^12345678
L|1

H|\^&
P|1||H002123|| ||19570618|M||||||||||||F
O|1|99042718||^^^NA\^^^K\^^^CL|||||||||||||||||||O
O|2|12345678||NMR LipoProfile 3|||20060606|||||||20060606|||||||
L|1|N

H|\^&|||Vantera|||||||LIS2-A2|20060627121501
P|1||H002123
O|1|12345678||NMR LipoProfile 3|||||||||||||||||||F
C|1|I|103|I
R|1|tc|DNR|mg/dL
R|2|hdl-c|DNR|mg/dL
R|3|hdl-p|DNR|umol/L
R|4|lm-hdl-p|DNR|umol/L
R|5|l-hdl-p|DNR|umol/L
R|6|m-hdl-p|DNR|umol/L
R|7|s-hdl-p|DNR|umol/L
R|8|hdl-z|DNR|nm
R|9|idl-p|DNR|nmol/L
R|10|ldl-c|DNR|mg/dL
R|11|ldl-p|DNR|nmol/L
R|12|l-ldl-p|DNR|nmol/L
R|13|s-ldl-p|DNR|nmol/L
R|14|ldl-z|DNR|nm
R|15|tg|DNR|mg/dL
R|16|vl-ldl-p|DNR|nmol/L
R|17|vldl-p|49.8|nmol/L
C|1|I|8017|I
R|18|vldl-tg|DNR|mg/dL
R|19|lm-vldl-p|DNR|nmol/L
R|20|l-vldl-p|DNR|nmol/L
R|21|m-vldl-p|DNR|nmol/L
R|22|s-vldl-p|DNR|nmol/L
R|23|vldl-z|DNR|nm
L|1
```

No Order Response

The no order response message is sent by the LIS in response to the test query message when the identified patient sample is undefined. The following message sequence occurs.

```
H|\^&|||Vantera|||||||LIS2-A2|20060627121500
Q|1|^12345678
```

```
L|1


H|\^&
L|1|I
```

No Result Response

The no result response message is sent by the Vantera Clinical Analyzer when an abnormal condition prevents successful result generation.

```
H|\^&|||Vantera|||||||LIS2-A2|20060627121500
Q|1|^12345678
L|1

H|\^&
P|1||H002123|| ||19570618|M||||||||||||F
O|1|99042718||^^^NA\^^^K\^^^CL||||||||||||||||||||O
O|2|12345678||NMR LipoProfile 3|||20060606|||||||20060606|||||||
L|1|N


H|\^&|||Vantera|||||||LIS2-A2|20060627121501
P|1||H002123
O|1|12345678||NMR LipoProfile 3|||||||||||||||||||||X
C|1|I|103^Insufficient patient sample in tube.|I
L|1
```

Appendix A – SERIAL CABLE WIRING INFORMATION

The following information is provided to assist in the definition of an appropriate cable wiring based on the flexibility offered by the Vantera Clinical Analyzer serial interface. The information herein should be used in conjunction with section 0 to determine the appropriate serial cable.

The figure below shows the pin assignments for DE-9 and DB-25 connectors. The male connectors are shown to the left of the associated female connectors.

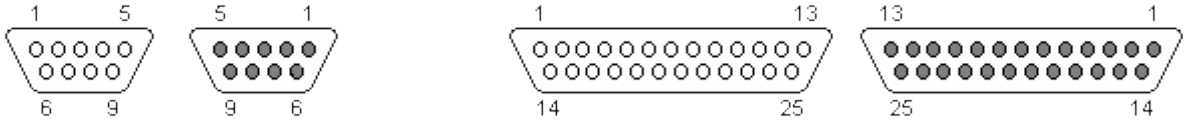


Figure 4 – DE-9 and DB-25 Pin Assignments

The table below identifies DE-9 and DB-25 pin utilization common for EIA-232.

Table 14 - DE-9 and DB-25 Pin Utilization

DB-25	DE-9	EIA	Acronym	Signal Name	Description
1	X	AA	CD	Protective Ground	Protective Ground
2	3	BA	TxD	Transmitted Data	Transmitted Data
3	2	BB	RxD	Received Data	Received Data
4	7	CA	RTS	Request To Send	Request To Send
5	8	CB	CTS	Clear To Send	Clear To Send
6	6	CC	DSR	Data Set ready	Data Set ready
7	5	AB	GND	Common Ground	Common Ground
8	1	CF	CD	Carrier Detect	Carrier Detect
20	4	CD	DTR	Data Terminal Ready	Data Terminal Ready
22	9	CE	RI	Ring Indicator	Ring Indicator

The figures below describe common cabling configurations based on the options above. Figure 5 depicts the appropriate cable wiring where the LIS emulates a DCE while Figure 6 depicts the appropriate cable wiring where the LIS emulates a DTE.

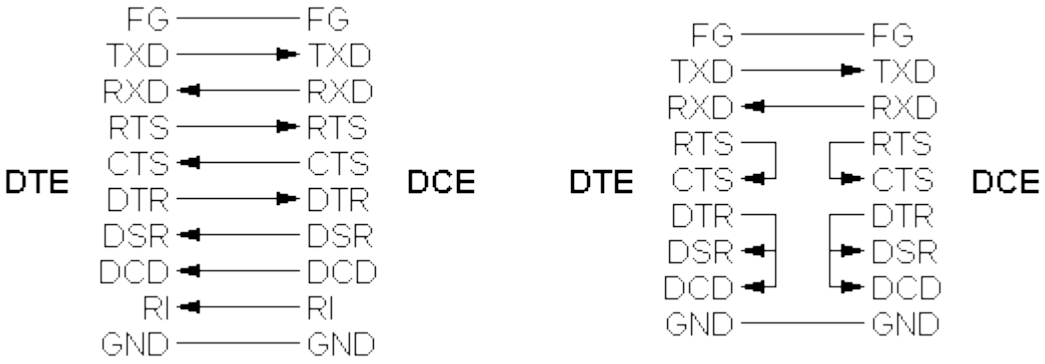


Figure 5 – Serial Port Handshaking Connections

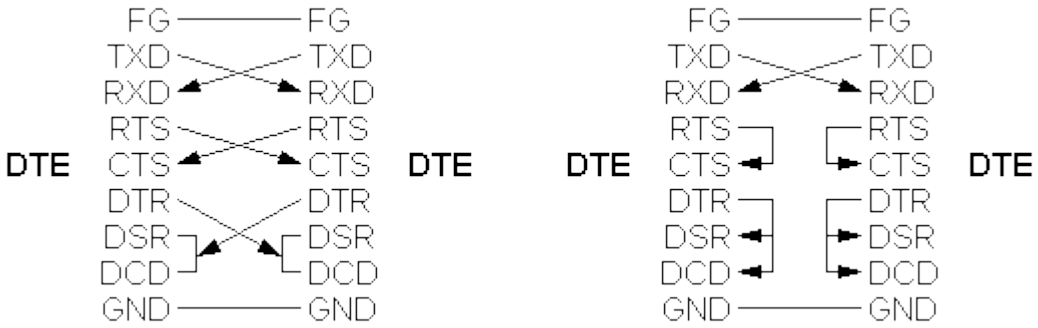


Figure 6 – Serial Port Null Modem Connections

Appendix B – Universal Test ID Definition

The following information is provided to define the Universal Test ID used in Order and Result records for assays available on the Vantera platform.

Table 15 – Order Record Universal Test ID

Assay	Universal Test ID
NMR LipoProfile	LipoProfile4

Table 16 – Result Record Universal Test ID

Assay	Result	Universal Test ID
NMR LipoProfile	Total Cholesterol by NMR	tc
	HDL Cholesterol by NMR	hdl-c
	HDL Particles	hld-p
	Large/Medium HDL Particles	lm-hdl-p
	Large HDL Particles	l-hdl-p
	Medium HDL Particles	m-hdl-p
	Small LDL particles	s-hdl-p
	HDL Size	hdl-z
	IDL Particles	idl-p
	LDL Cholesterol by NMR	ldl-c
	LDL Particles	ldl-p
	Large LDL particles	l-ldl-p
	Small LDL particles	s-ldl-p
	LDL Size	ldl-z
	Triglycerides by NMR	tg
	VLDL/LDL Particles	vl-ldl-p
	VLDL Particles	vldl-p
	VLDL Triglcerides	vldl-tg
	Large/Medium VLDL Particles	lm-vldl-p
	Large VLDL Particles	l-vldl-p
	Medium VLDL Particles	m-vldl-p
	Small VLDL Particles	s-vldl-p
	VLDL Size	vldl-z

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Scheduled maintenance log

INSTRUMENT NAME: Vantera Clinical Analyzer	
MANUFACTURER: LipoScience/Varian	
MODEL:	**SERIAL NUMBER:**

Month:
Reviewed by: _____ **Date:** _____

Scheduled Maintenance Steps Indicate Pass (**P**) or Fail (**F**). Failures must be resolved prior to running specimens.	**User's Manual Reference (page)**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**31**
First Shift																																
Inspect specimen handling and carousel areas, and area adjacent to the system	58																															
Check bulk fluid levels	41																															
Wash fluidics	59																															
Peform mini-prime	52																															
Run NMR Reference Standard	27																															
Run LipoProfile Level I and II Controls	28																															
Second Shift																																
Inspect specimen handling and carousel areas, and area adjacent to the system	58																															
Check bulk fluid levels	41																															
Wash fluidics	59																															
Peform mini-prime	52																															
Run NMR Reference Standard	27																															
Run LipoProfile Level I and II Controls	28																															
Third Shift																																
Inspect specimen handling and carousel areas, and area adjacent to the system	58																															
Check bulk fluid levels	41																															
Wash fluidics	59																															
Peform mini-prime	52																															
Run NMR Reference Standard	27																															
Run LipoProfile Level I and II Controls	28																															
Daily																																
Perform shift maintenance	(this table)																															
Check and record nitrogen boil-off rate	66																															
Weekly																																
Inspect air condensate and particle filters	60																															
Clean specimen platens	62																															
Empty and disinfect rinse fluid container	62																															
Recharge liquid nitrogen	67																															
Inspect and clean NMR console filters	64																															
Check and record helium boil-off rate	66																															
Fill the nitrogen tank	67																															
Perform Database Maintenance	76																															

Initials:	**Date:**	**Corrective Action:**	

Section 15: Sterilization and Shelf-life

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15.1 System Consumable Shelf-life

The proposed device and its consumables are not subject to sterilization procedures/processes. However, system consumables have a specified shelf-life. A summary of shelf-life is provided in Table 15-1.

Table 15-1: System Consumable Shelf-life

Consumables	Shelf-Life (months)	Extension
Reference Standard (TMA)	12	N/A
Diluent 1	18	N/A
WASH	6*	12

*Shelf life will be extended as data becomes available.

Section 16: Biocompatibility

Material Certification - The proposed device is not subjected to Biocompatibility Testing.

Section 17: Software

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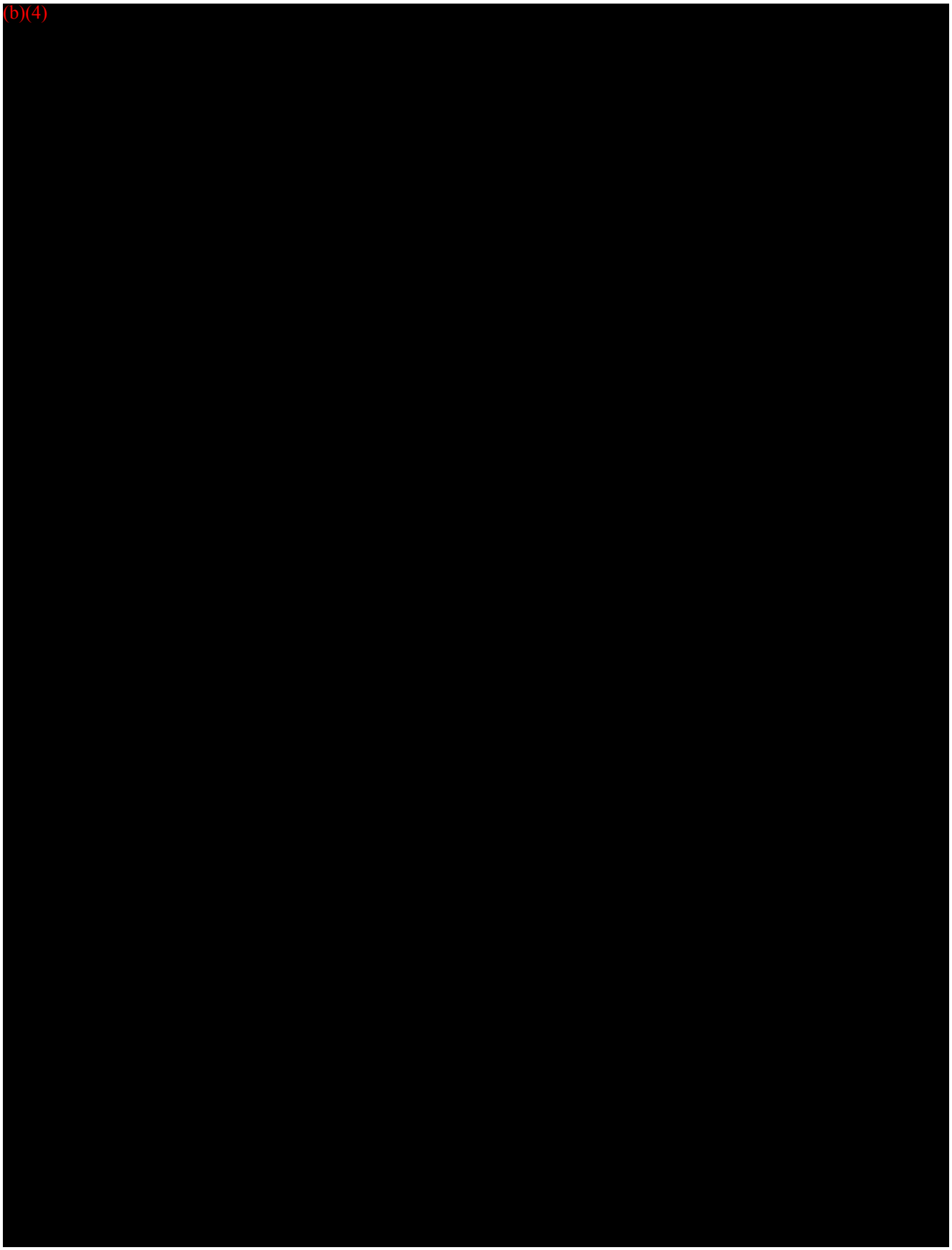

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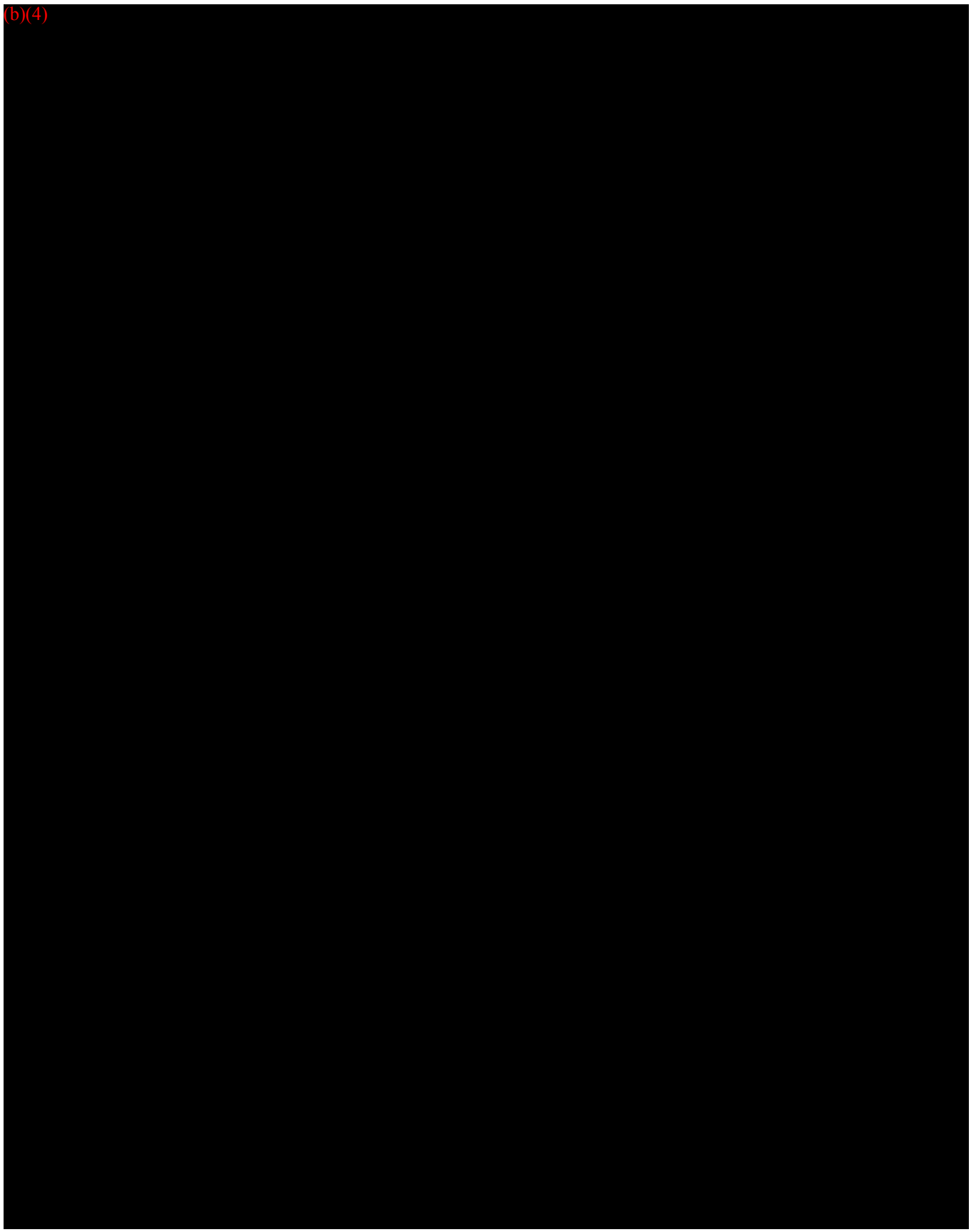

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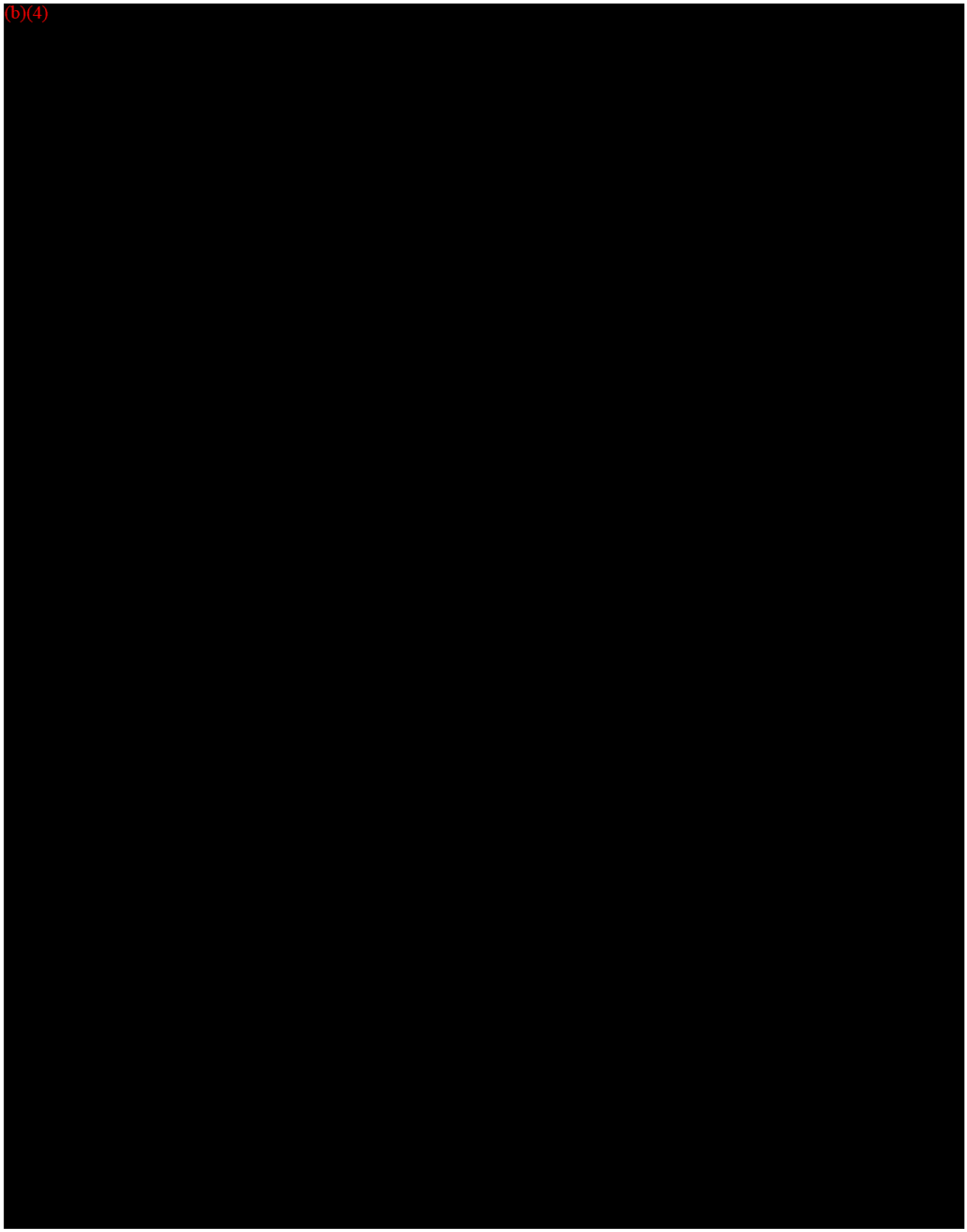

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Attachment 2:
Risk Management Procedure - (b)(4) [redacted]

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Attachment 3:
Numera Risk Analysis Matrix – (b)(4) [redacted]

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Attachment 4:
Vantera Design Failure Modes Effects and Criticality Analysis

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Approvals

Signature denotes the individual has read, understands, and agrees with the content of this document.

Title	Signature	Date
Director, Program Management (Author)	David Bryant	12.07.11
Director, Product Qualification (Reviewer, approver)	Yuan Xu	12/8/11
Director, Quality Management Systems (Reviewer, approver)	Sonya Baker	12/08/2011
Regulatory Affairs Manager (Reviewer, approver)	Suzette Warner	12/8/11
Director, Engineering (Reviewer, approver)	Thomas Givens	12/08/2011

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Attachment 5:
Vantera System Safety Risk Summary Report - (b)(4) [redacted]

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Attachment 6:
Vantera Master Verification and Validation Plan - (b)(4)

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Attachment 7:
Numera Product Requirements Document – (b)(4) [redacted]

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Attachment 8:
Software Requirements Specification for LipoScience Vantera Clinical Analyzer – (b)(4)

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Attachment 9:
Vantera Assay requirements

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Approvals

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[redacted]

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Attachment 10:
Numera Software Design Specification – (b)(4) [redacted]

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Attachment 11:
Numera System Traceability Matrix – (b)(4) [redacted]

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Attachment 12:
Numera Software Configuration Management Plan -
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Attachment 13:
Vantera Verification Summary Report – (b)(4) [redacted]

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Attachment 14:
Vantera System Validation Summary Report – (b)(4) [redacted]

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Section 18: Electromagnetic Compatibility and Electrical Safety

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18.1 Introduction

Testing to the IEC Standard, *IEC 61010-1: Safety requirements for electrical equipment for measurement, control, and laboratory use, Part 1: General requirements: 200, 2nd Edition,* was contracted out to (b)(4) As a result of the testing performed, an Informative Report was issued by (b)(4).

18.2 Summary of Testing

Table 18-1 provides a list of tests performed by (b)(4) A detailed report of the testing can be found in **Attachment 1.**

Table 18-1: Summary of Testing

Tests Performed	Test Clause
(b)(4)	

ATTACHMENT 1

Attachment 1: Test Report IEC 61010-1: Safety requirements for electrical for electrical equipment for measurement, control, and laboratory use

Part 1: General requirements

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Section 19: Performance – Bench Testing (Analytical Performance)

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Section 19 – Performance Testing – Bench Attachments

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Section 20: Performance Testing – Animal

No animal performance testing was performed with the proposed device. Therefore this section is not applicable.

Section 21: Performance Testing - Clinical

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Attachment 2: IRB Approval

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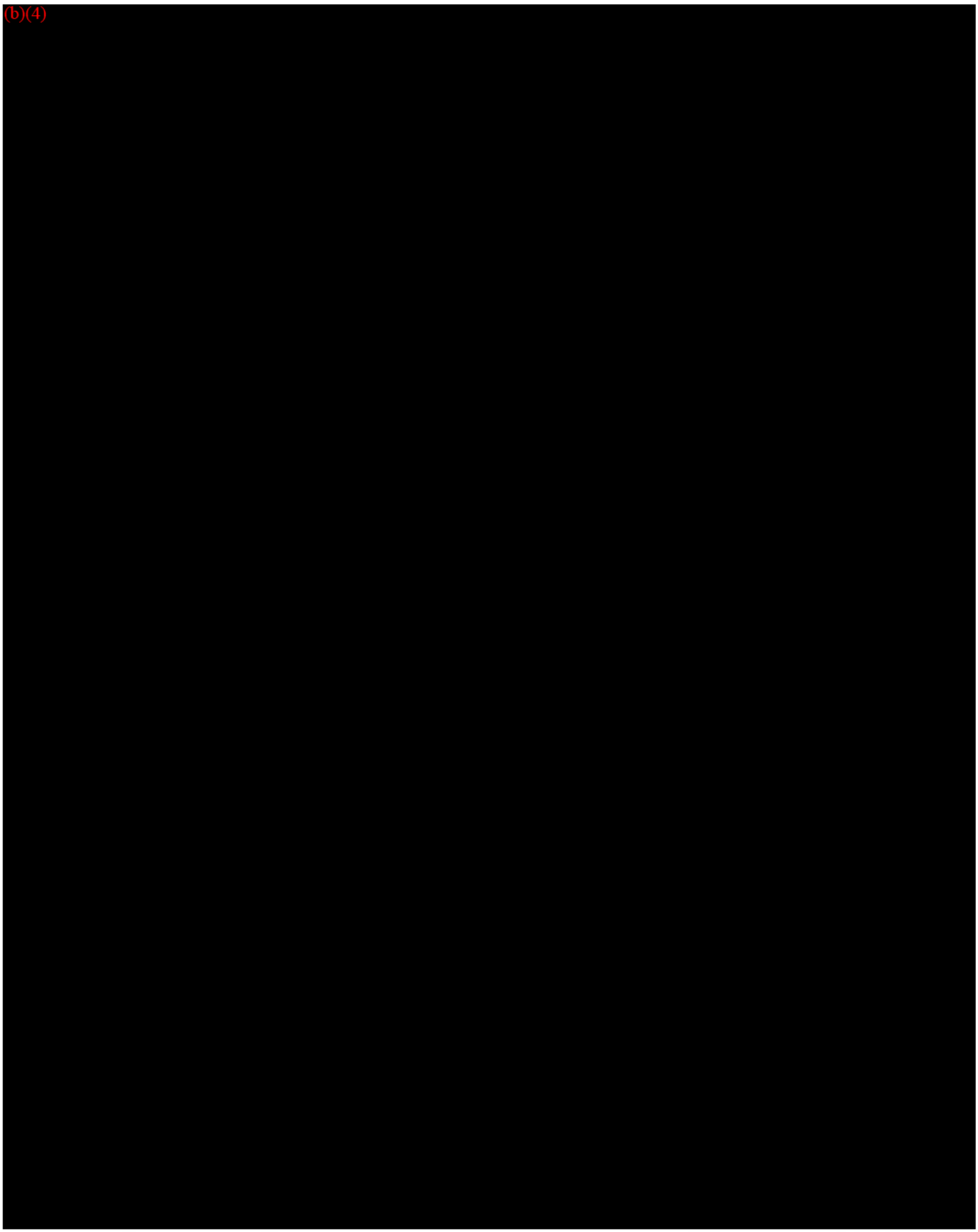


Section 22: Other
Glossary

The following terms are defined according to their usage at LipoScience.

TERMS	DESCRIPTION
Acceptance Criteria	The criteria a software product must meet to successfully complete a test phase or to achieve delivery requirements.
Autosampler (Sample Handler)	Instrumentation that manages test samples and performs the automation for the aspiration and delivery of samples to the NMR probe.
CaEDTA	An anti-coagulation agent found in plasma tubes.
CAP	College of American Pathologists
CLIA	Clinical Laboratory Improvement Amendments Act
NMR Console	An upright case which houses the controlling mechanisms for equipment.
COTS	Acronym for Commercial –Off-The-Shelf, an application or packaged software used in developing, or incorporated into, the software released.
CRB	The Change Review Board (CRB) is the group of Departmental representatives responsible for the review, acceptance, cancellation, or rejection of changes.
Curve Fit	The process of constructing a curve, that has the **best fit** to a series of data points, possibly subject to constraints
Data Analysis Software	Software which analyzes spectra to produce values for LDL-P, HDL-C and Triglycerides
Deconvolution	The process by which the encoded information is extracted-giving the amplitudes of the subclass signal parts that make up the mixture whole.
Digitized Specimen	A digital representation of a specimen. In the context of NMR spectroscopy, the NMR spectra recorded from a specimen constitute a digitized specimen and can be stored indefinitely via electronic media. Unlike a physical specimen frozen for long-term storage, the digitized specimen does not change over time and its future use is not limited by the existence of a finite specimen volume.
Diluent	A solution used to dilute a specimen; Any liquid or solid material used to dilute or carry an active ingredient.
Directed Testing	Testing in which a specific change implemented is verified to have been implemented correctly. Does not require a written protocol.
ECN	The Engineering Change Notice is the output of Lipo.mde for creating, Implementing and Monitoring change.
Failure Modes, Effects, and Critical Analysis (FMECA)	A procedure by which each potential failure mode in a system is analyzed to determine the results or effects on the system and to classify failure modes according to severity.

TERMS	DESCRIPTION
Functional Testing	Testing in which software components are verified to meet relevant requirements defined in the Software Requirements Specification. Requires a written protocol.
Hardware	A term used to describe the computer CPU and its peripheral equipment such as printers, workstations, disk/tape/CD drives, input/output equipment, communication equipment, etc.
Integration Testing	Testing in which the complete system is verified to meet relevant requirements defined in the Software Requirements Specification. Requires a written protocol.
In Vitro	Occurring outside the living body and in an artificial environment.
LIS	Acronym for Laboratory Information System.
Mean	Statistical calculation utilized to determine the average of control samples. Mean is calculated by dividing the sum of all values by the total number of values.
NMR	Acronym for Nuclear Magnetic Resonance.
***NMR LipoProfile*® test**	The *NMR LipoProfile*® test is an advanced cardiovascular diagnostic test that uses Nuclear Magnetic Resonance (NMR) spectroscopy to uniquely provide rapid, simultaneous, and direct measurement of LDL-P, HDL-C and Triglycerides.
NMR Profiler	Name given to the NMR instruments used by LipoScience to produce *NMR LipoProfile*® test results. Device cleared by FDA as K063841.
Numera	The Vantera® Clinical Analyzer was initially labeled as Numera. Older documents may still utilize the earlier name. References to the Vantera system and the Numera system are identical in their meaning.
Off-the-Shelf	A product that is commercially and publicly available.
Plasma	The fluid part of blood cells as distinguished from suspended material.
Reproducibility	Closeness of agreement between the results of measurements when operating conditions are varied.
Rack Definition File	A file (filename *.csv) describing the contents of a unique Gilson rack; the position, name (accession), and dilution factor of each specimen contained in the unique Gilson rack. Produced by the Rack Reader as an input to automating the Bruker NMR.
Requirements	(1) A condition or capability needed by a user to solve a problem or achieve an objective. (2) A condition or capability that must be met or possessed by a system or system component to satisfy a contract, standard, specification, or other formally imposed documents. (3) A documented representation of a condition or capability as in (1) or (2).
Sample	An aliquot of plasma or serum from a specimen (source tube) used for a specific testing process.

TERMS	DESCRIPTION
Signal Acquisition	The process by which an audio frequency is received and transformed from analog to digital to be stored in the computer as FIDs.
Signal Generation	The process by which radio frequency signal is generated, amplified and mixed with reference signals at the detector, resulting in an audio frequency.
Signal Processing	Is the compilation of all scans stored as FIDS which represents the range of chemical shift values.
Software Validation	Confirmation by examination and provision of objective evidence that software specifications conform to user needs and intended uses, and that the particular requirements implemented through the software can be consistently fulfilled. For the purposes of this document, design level validation is that portion of the software validation that takes place in parts of the software life cycle before the software is delivered to the end user.
Specimen	Plasma, serum, urine, etc. specimen drawn (obtained) from a patient (study subject) at a specified date and time. Contained in a single specimen tube.
Spectrum	The numerical raw NMR data acquired for a specimen.
SRS	Acronym for Software Requirements Specification.
TE_a	Acronym for Total Allowable Error.
TMA	Sodium Trimethylacetate Hydrate.
Traceability matrix	Reference system whereby any project requirements, can be traced forward or backwards through the various phases of the project life-cycle.
V&V	Verification and Validation
Validation	Objective evidence that system specifications conform to the user needs and intended uses, and that the particular requirements implemented through the system can be consistently fulfilled.
Vantera	LipoScience's second generation NMR clinical analyzer.
Verification	The process of providing objective evidence that the software and its associated products conform to specified requirements.

Food and Drug Administration
Office of Device Evaluation &
Office of In Vitro Diagnostics

COVER SHEET MEMORANDUM

From: Reviewer Name Elizabeth O'Keffe

Subject: 510(k) Number K113830

To: The Record

Please list CTS decision code TH

☐ Refused to accept (Note: this is considered the first review cycle, See Screening Checklist http://eroom.fda.gov/eRoomReg/Files/CDRH3/CDRHPremarketNotification510kProgram/0_5631/Screening%20Checklist%207%202%2007.doc)

☒ Hold (Additional Information or Telephone Hold).

☐ Final Decision (SE, SE with Limitations, NSE (select code below), Withdrawn, etc.).

Not Substantially Equivalent (NSE) Codes

☐	NO	NSE for lack of predicate
☐	NI	NSE for new intended use
☐	NQ	NSE for new technology that raises new questions of safety and effectiveness
☐	NP	NSE for lack of performance data
☐	NM	NSE requires PMA
☐	NS	NSE no response
☐	NH	NSE for another reason

Please complete the following for a final clearance decision (i.e., SE, SE with Limitations, etc.):		YES	NO
Indications for Use Page	*Attach IFU*		
510(k) Summary /510(k) Statement	*Attach Summary*		
Truthful and Accurate Statement.	*Must be present for a Final Decision*		
Is the device Class III?			
If yes, does firm include Class III Summary?	*Must be present for a Final Decision*		
Does firm reference standards? (If yes, please attach form from http://www.fda.gov/opacom/morechoices/fdaforms/FDA-3654.pdf)			
Is this a combination product? (Please specify category _____, see http://eroom.fda.gov/eRoomReg/Files/CDRH3/CDRHPremarketNotification510kProgram/0_413b/COMBINATION%20PRODUCT%20ALGORITHM%20(REVISED%203-12-03).DOC			
Is this a reprocessed single use device? (Guidance for Industry and FDA Staff – MDUFMA - Validation Data in 510(k)s for Reprocessed Single-Use Medical Devices, http://www.fda.gov/cdrh/ode/guidance/1216.html)			
Is this device intended for pediatric use only?			
Is this a prescription device? (If both prescription & OTC, check both boxes.)			
Did the application include a completed FORM FDA 3674, Certification with Requirements of ClinicalTrials.gov Data Bank?			
Is clinical data necessary to support the review of this 510(k)?			
For United States-based clinical studies **only**: Did the application include a completed FORM FDA 3674, *Certification with Requirements of ClinicalTrials.gov Data Bank*? (If study was conducted in the United States, and FORM FDA 3674 was not included or incomplete, then applicant must be contacted to obtain completed form.)			
Does this device include an Animal Tissue Source?			
All Pediatric Patients age<=21			

Neonate/Newborn (Birth to 28 days)			
Infant (29 days -< 2 years old)			
Child (2 years -< 12 years old)			
Adolescent (12 years -< 18 years old)			
Transitional Adolescent A (18 - <21 years old) Special considerations are being given to this group, different from adults age ≥ 21 (different device design or testing, different protocol procedures, etc.)			
Transitional Adolescent B (18 -<= 21; No special considerations compared to adults => 21 years old)			
Nanotechnology			
Is this device subject to the Tracking Regulation? (Medical Device Tracking Guidance, http://www.fda.gov/cdrh/comp/guidance/169.html)	*Contact OC.*		

Regulation Number **Class*** **Product Code**

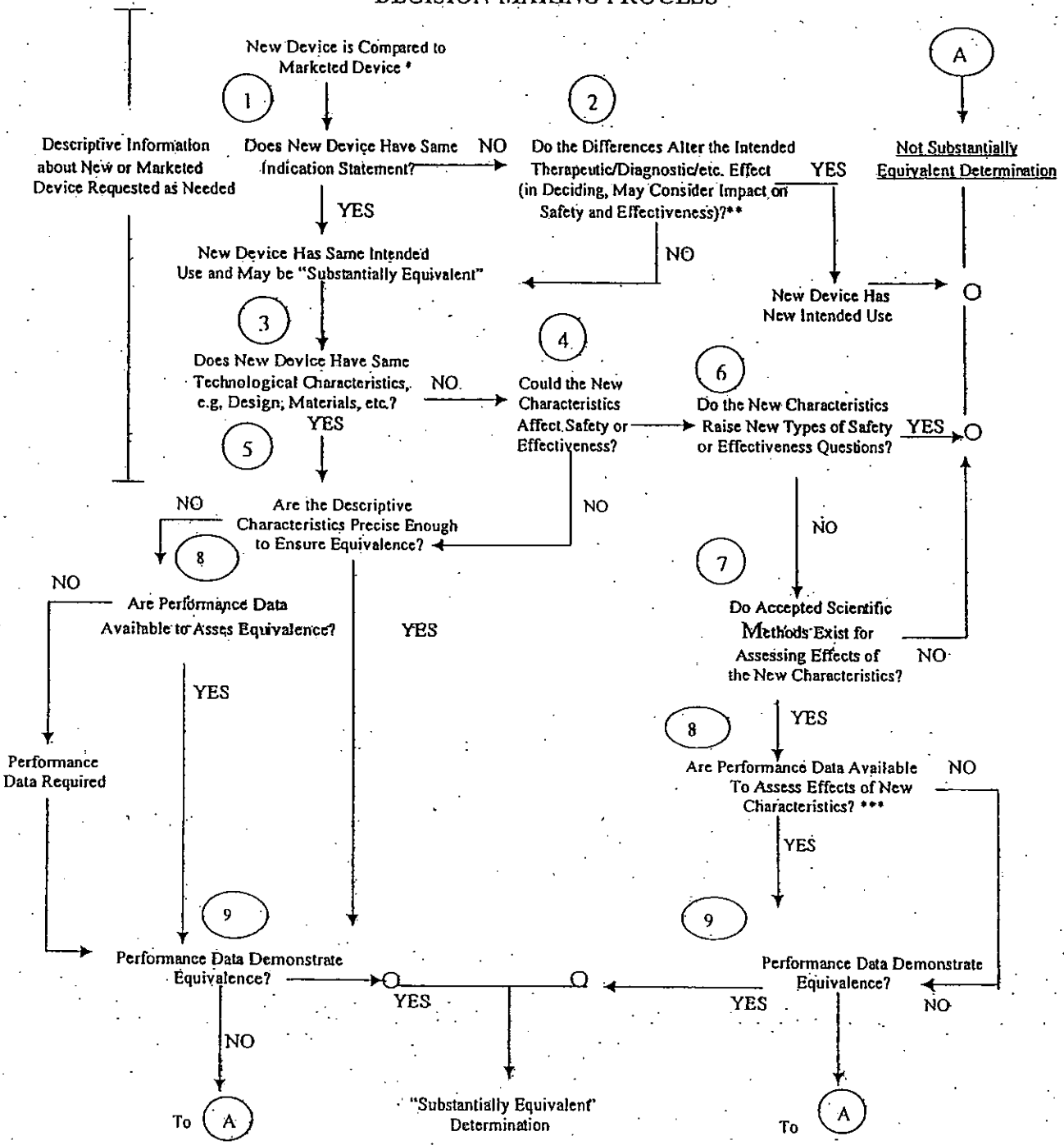
(*If unclassified, see 510(k) Staff)

Additional Product Codes:

Review: _____ DCTD 2/24/12
(Branch Chief) (Branch Code) (Date)

Final Review: _____
(Division Director) (Date)

510(k) "SUBSTANTIAL EQUIVALENCE" DECISION-MAKING PROCESS



* 510(k) Submissions compare new devices to marketed devices. FDA requests additional information if the relationship between marketed and "predicate" (pre-Amendments or reclassified post-Amendments) devices is unclear.

** This decision is normally based on descriptive information alone, but limited testing information is sometimes required.

*** Data maybe in the 510(k), other 510(k)s, the Center's classification files, or the literature.

To: The RECORD

From: Elizabeth O'Keeffe, Scientific Reviewer, CDRH, OIVD, DCTD

Date: February 24, 2012

Subject: Submission On Hold

I recommend that the submission be on hold pending responses to the issues listed on the following pages.

Elizabeth O'Keeffe
Scientific Reviewer

O'Keeffe, Elizabeth

From: O'Keeffe, Elizabeth
Sent: Friday, February 24, 2012 2:59 PM
To: 'Suzette Warner'
Subject: k113830 hold letter
Attachments: Deficiency Letter k113830.pdf

Hi Suzette,

Here is the hold letter that I spoke with you briefly about. Please let me know if you have any questions regarding any of the listed deficiencies, and when you would like to set up a teleconference to discuss both the deficiencies in the hold letter and the CLIA categorization that we discussed. You automatically have 30 days to respond to the hold letter, and if you would like more time you can request an extension of up to 180 days from the document mail center. Again don't hesitate to contact me with any questions, and I look forward to working with you on your submission. Have a great weekend!

~Elizabeth

Elizabeth O'Keeffe, Ph.D.
Scientific Reviewer

Food and Drug Administration
10903 New Hampshire Avenue
WO66, 3627
Silver Spring, MD 20993-0002

301-796-1567
elizabeth.okeeffe@fda.hhs.gov

Liposcience
c/o Suzette warner
2500 Summer Blvd.
Rakeigh, NC 27616

Re: k113830
Trade/Device Name: NMR LipoProfile® test on Vantera® Clinical Analyzer
Dated: 23 December, 2011
Received: 27 December, 2011

Dear Ms. Warner:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above. At this time we cannot determine if the device is substantially equivalent to a legally marketed predicate device due to several deficiencies in the submitted 510(k). This letter is to inform you that submission k113830 has been placed on telephone hold. Please note that additional deficiencies may be identified either as the submission undergoes further review or based upon your response to the listed deficiencies. To complete the review of your submission, we require responses to the following issues:

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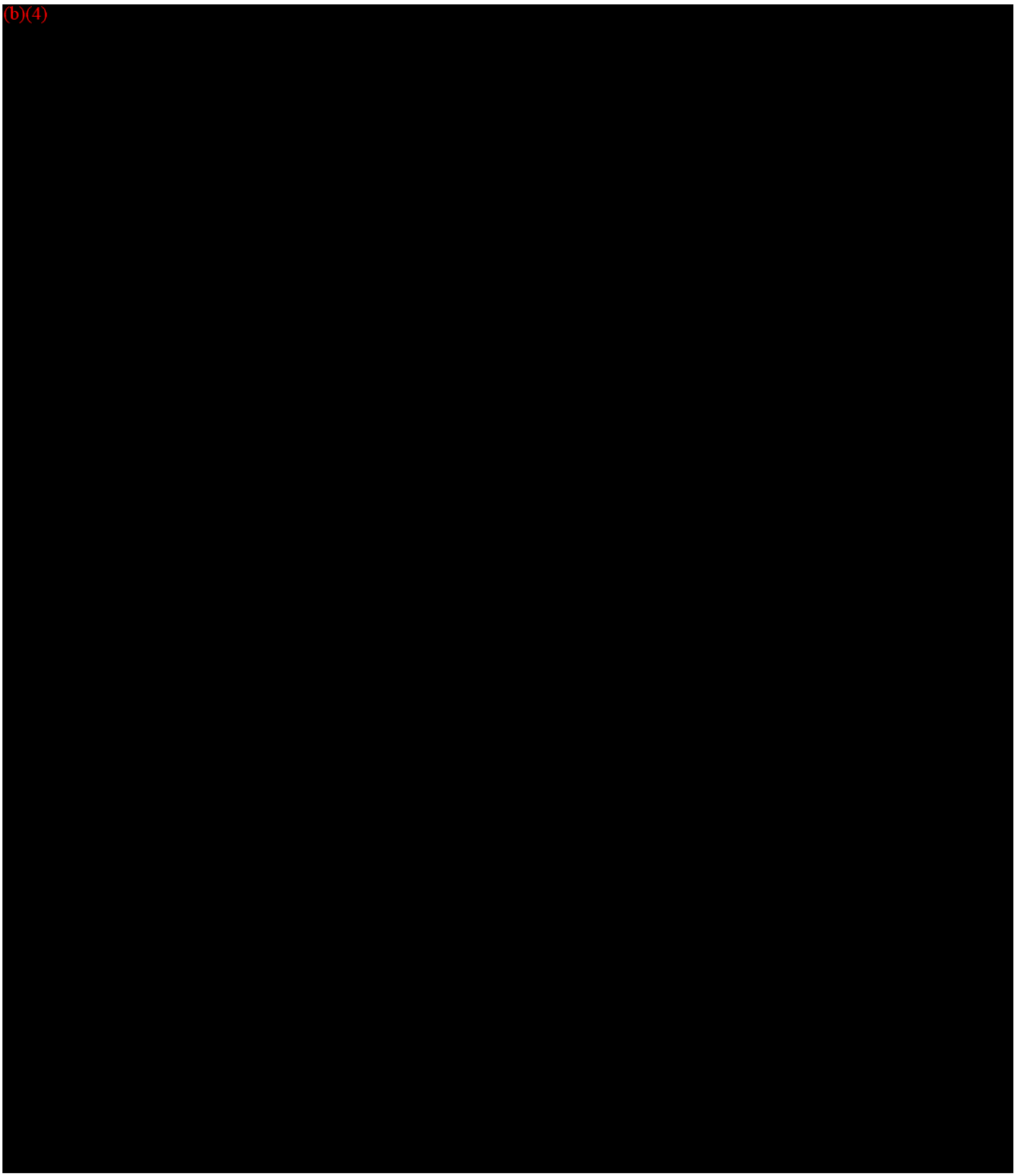

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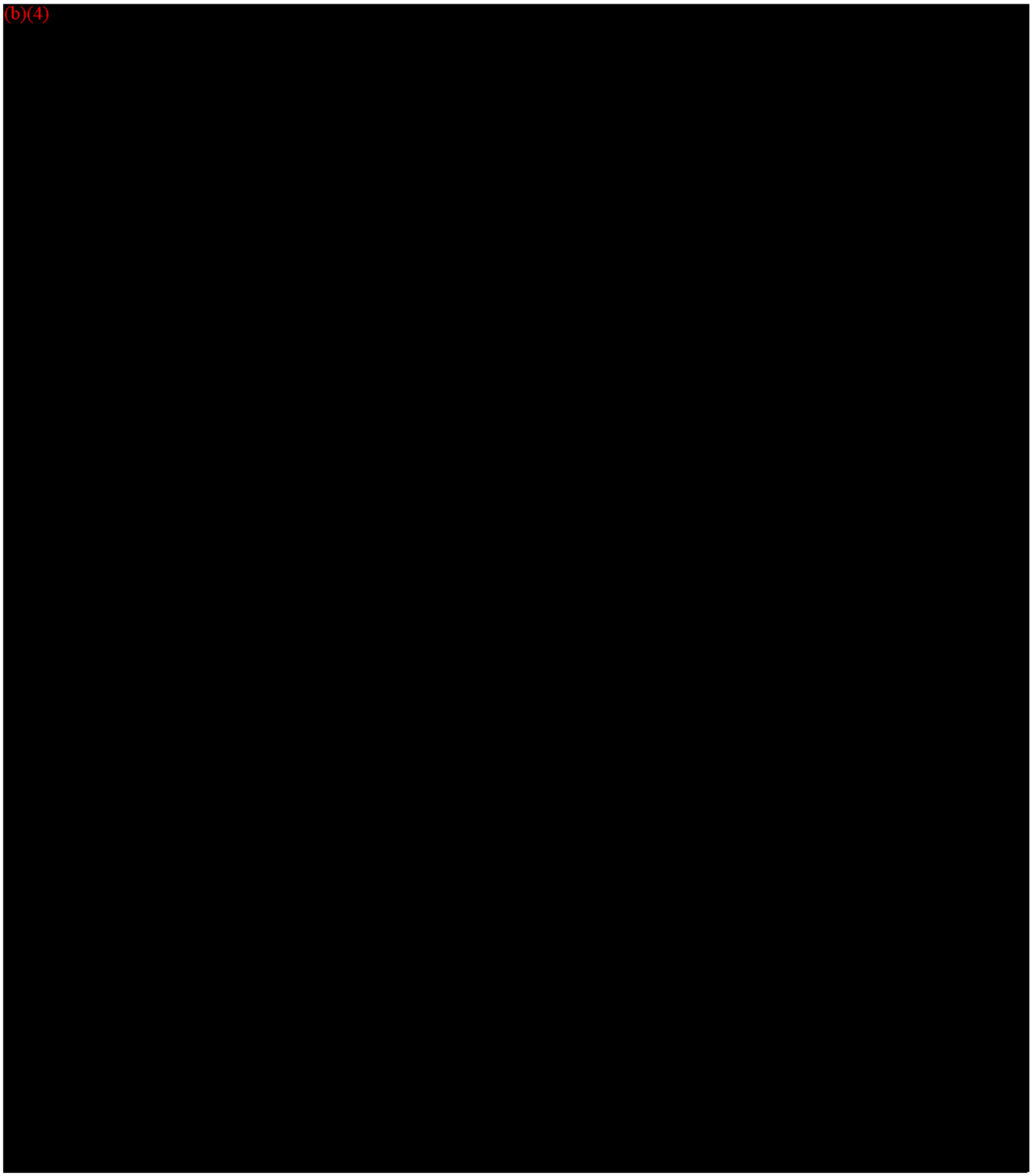

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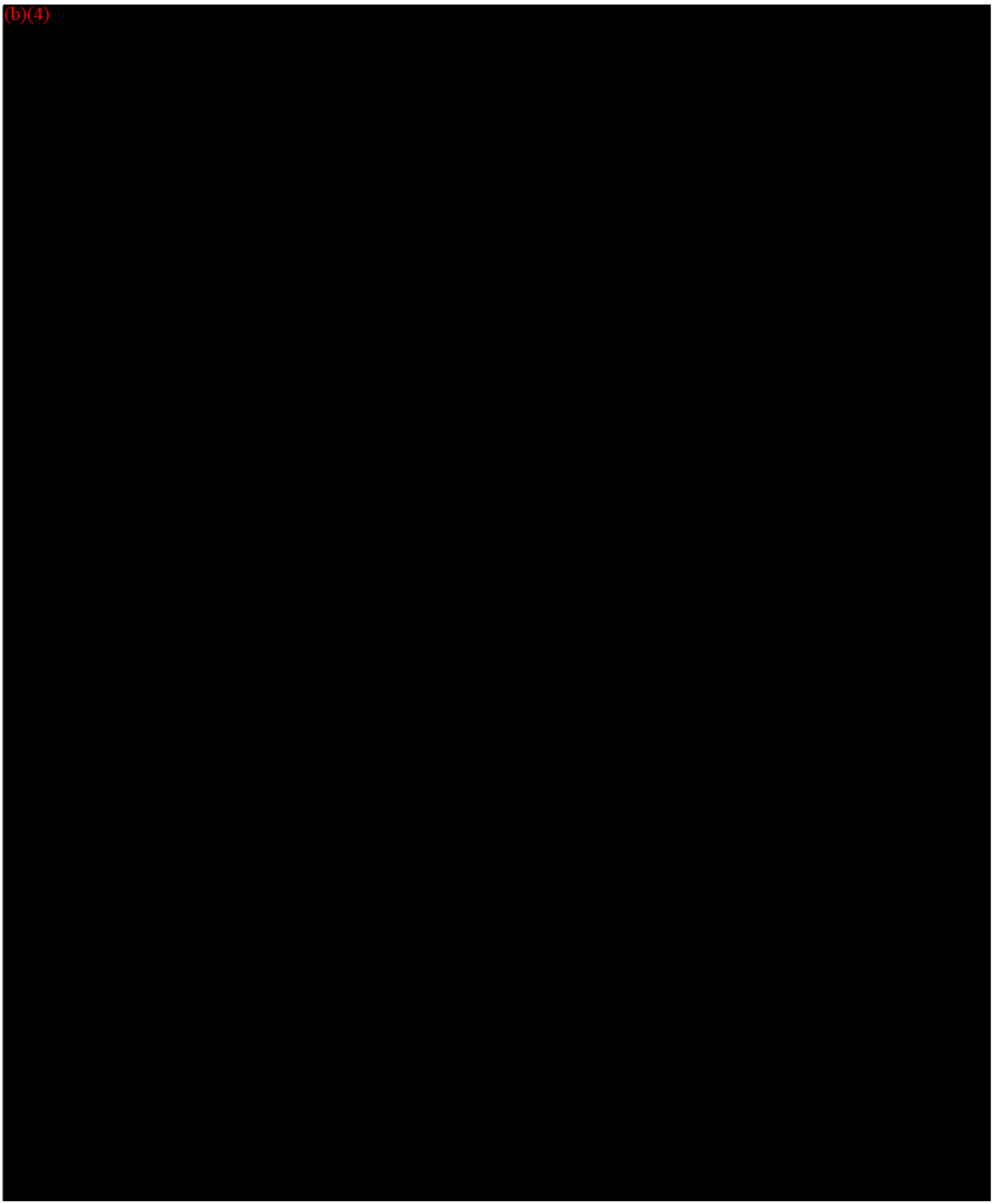

(b)(4)

The above identified deficiencies represent the issues that we believe need to be resolved before our review of your 510(k) submission can be successfully completed. In developing the deficiencies, we carefully considered the statutory criteria as defined in Section 513(i) of the Federal Food, Drug, and Cosmetic Act for determining substantial equivalence of your device.

Based upon your response to these items, additional studies and changes to the labeling may be needed. Please remember to send a new Truth and Accuracy Statement along with your response. And please feel free to contact me with any questions regarding the above deficiencies.

You may not market this device until you have provided adequate information described above and required by 21 CFR 807.87(l), and you have received a letter from FDA allowing you to do so. If you market the device without conforming to these requirements, you will be in violation of the Federal Food, Drug, and Cosmetic Act (Act). You may, however, distribute this device for investigational purposes to obtain clinical data if needed to establish substantial equivalence. Clinical investigations of this device must be conducted in accordance with the investigational device exemption (IDE) regulations.

If the information, or a request for an extension of time, is not received within 30 days, we will consider your premarket notification to be withdrawn and your submission will be deleted from our system. If you submit the requested information after 30 days it will be considered and processed as a new 510(k) (21 CFR 807.87(1)); therefore, all information previously submitted must be resubmitted so that your new 510(k) is complete. Please note our guidance document entitled, "Guidance for Industry and FDA Staff FDA and Industry Actions on Premarket Notification (510(k)) Submissions: Effect on FDA Review Clock and Performance Assessment". If the submitter does submit a written request for an extension, FDA will permit the 510(k) to remain on hold for up to a maximum of 180 days from the date of the additional information request.

The requested information, or a request for an extension of time, should reference your above 510(k) number and should be submitted in duplicate to:

Food and Drug Administration Center for Devices and
Radiological Health

Document Mail Center
10903 New Hampshire Avenue
WO66, 5510
Silver Spring, MD 20993-0002

Sincerely yours,

Dr. Elizabeth O'Keeffe
Scientific Reviewer

Office of *In Vitro* Diagnostic Device Evaluation and Safety
Center for Devices and Radiological Health
Food and Drug Administration
10903 New Hampshire Avenue
WO66, 5510
Silver Spring, MD 20993-0002
301-796-1567
elizabeth.okeeffe@fda.hhs.gov

O'Keeffe, Elizabeth

From: Suzette Warner [suzette.warner@liposcience.com]
Sent: Thursday, February 23, 2012 9:42 AM
To: O'Keeffe, Elizabeth
Subject: Greiner - Vacuette Tube

Dr. O'Keeffe
Here is the pre-market notification for the Greiner Tube.

http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm?ID=116033

Suzette M. Warner
Regulatory Affairs, Manager
O: 919-256-1326
Cell: 919-357-7801
LIPOSCIENCE
2500 Sumner Boulevard
Raleigh, NC 27616
Main: 877-547-6837

"It is not necessary to do extraordinary things to get extraordinary results."
Warren Buffett

(b)(4)

[redacted]

Elizabeth O'Keeffe, Ph.D.
Scientific Reviewer

Food and Drug Administration
10903 New Hampshire Avenue
WO66, 3627
Silver Spring, MD 20993-0002

301-796-1567
elizabeth.okeeffe@fda.hhs.gov

From: Suzette Warner [mailto:suzette.warner@liposcience.com]
Sent: Monday, February 06, 2012 2:47 PM
To: O'Keeffe, Elizabeth
Subject: CLIA Categorization

Dr. O'Keeffe
The group here have gone through the process of assessing the criteria for CLIA Categorization and we are having a hard time with the decision whether the platform is a HIGH or MEDIUM complexity. Could you provide some feedback as to what is the more appropriate categorization?

http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/IVDRegulatoryAssistance/ucm124208.htm

Regards
Suzette

Suzette M. Warner
Regulatory Affairs, Manager
O: 919-256-1326
Cell: 919-357-7801
LIPOSCIENCE
2500 Sumner Boulevard
Raleigh, NC 27616
Main: 877-547-6837

"It is not necessary to do extraordinary things to get extraordinary results."
Warren Buffett

(b)(4)

[redacted]

concerned that you may not have received it.

Regards
Suzette

From: Suzette Warner
Sent: Wednesday, February 01, 2012 2:51 PM
To: 'elizabeth.okeeffe@fda.hhs.gov'
Subject: K113830 - Vantera Clinical Analyzer

Good Day Elizabeth
As we discussed over the phone, here is the electronic copy of the Vantera Clinical Analyzer submission.

If you have further issues or in need of clarification please let me know.

Regards
Suzette

Suzette M. Warner
Regulatory Affairs, Manager
O: 919-256-1326
Cell: 919-357-7801
LIPOSCIENCE
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Warren Buffett

K113830/S1 V1

DEPARTMENT OF HEALTH & HUMAN SERVICES
Food and Drug Administration

10903 New Hampshire Avenue
Silver Spring, MD 20993

LipoScience, Inc.
c/o Suzette Warner
2500 Sumner Boulevard
Raleigh, NC 27616

AUG 30 2012

Re: k113830
Trade Name: Vantera® Clinical Analyzer; NMR LipoProfile® test on Vantera Clinical Analyzer
Regulation Number: 21 CFR §862.2570
Regulation Name: Instrumentation for clinical multiplex test systems
Regulatory Class: Class II
Product Codes: NSU, MRR, LBS, CDT
Dated: July 27, 2012
Received: July 30, 2012

Dear Ms. Warner:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to such additional controls. Existing major regulations affecting your device can be found in Title 21, Code of Federal Regulations (CFR), Parts 800 to 895. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Parts 801 and 809); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); and good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820).

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801), please contact the Office of In Vitro Diagnostic Device Evaluation and Safety at (301) 796-5450. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding postmarket surveillance, please contact CDRH's Office of Surveillance and Biometric's (OSB's) Division of Postmarket Surveillance at (301) 796-5760. For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm for the CDRH's Office of Surveillance and Biometrics/Division of Postmarket Surveillance...

You may obtain other general information on your responsibilities under the Act from the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (301) 796-5680 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm

Sincerely yours,

Courtney H. Lias, Ph.D.
Director
Division of Chemistry and Toxicology Devices
Office of *In Vitro* Diagnostic Device
Evaluation and Safety
Center for Devices and Radiological Health

Enclosure

Indication for Use

510(k) Number (if known): K113830

Device Name: Vantera® Clinical Analyzer

Indications for Use:

The Vantera® Clinical Analyzer is an automated laboratory test analyzer which measures the 400 MHz proton nuclear magnetic resonance (NMR) spectrum of clinical samples to produce signal amplitudes, converting these signal amplitudes to analyte concentration. The device includes a 400 MHz NMR spectrometer and software to analyze digitized spectral data. This instrumentation is intended to be used with NMR based assays to detect multiple analytes from clinical samples.

Prescription Use __X__ And/Or Over the Counter Use ____.
(21 CFR Part 801 Subpart D) (21 CFR Part 801 Subpart C)

(PLEASE DO NOT WRITE BELOW THIS LINE; CONTINUE ON ANOTHER PAGE IF NEEDED)

Concurrence of CDRH, Office of In Vitro Diagnostic Device Evaluation and Safety (OIVD)

Division Sign-Off
Office of In Vitro Diagnostic Device
Evaluation and Safety

510(k) K113830

Indication for Use

510(k) Number (if known): K113830

Device Name: NMR LipoProfile® test on Vantera® Clinical Analyzer

Indications for Use:

The *NMR LipoProfile®* test, when used with the Vantera® Clinical Analyzer, an automated NMR spectrometer, measures lipoprotein particles to quantify LDL particle number (LDL-P), HDL cholesterol (HDL-C), and triglycerides in human serum and plasma using nuclear magnetic resonance (NMR) spectroscopy. LDL-P and these NMR-derived concentrations of HDL-C and triglycerides are used in conjunction with other lipid measurements and clinical evaluation to aid in the management of lipoprotein disorders associated with cardiovascular disease.

Prescription Use __X__ (21 CFR Part 801 Subpart D) And/Or Over the Counter Use ____. (21 CFR Part 801 Subpart C)

(PLEASE DO NOT WRITE BELOW THIS LINE; CONTINUE ON ANOTHER PAGE IF NEEDED)

Concurrence of CDRH, Office of In Vitro Diagnostic Device Evaluation and Safety (OIVD)

Division Sign-Off
Office of In Vitro Diagnostic Device
Evaluation and Safety

510(k) K113830

Food and Drug Administration
Office of Device Evaluation &
Office of In Vitro Diagnostics

COVER SHEET MEMORANDUM

From: Reviewer Name Elizabeth O'Keeffe

Subject: 510(k) Number K113880|S1

To: The Record

Please list CTS decision code CS

☐ Refused to accept (Note: this is considered the first review cycle, See Screening Checklist http://eroom.fda.gov/eRoomReg/Files/CDRH3/CDRHPremarketNotification510kProgram/0_5631/Screening%20Checklist%207%202%2007.doc)

☐ Hold (Additional Information or Telephone Hold).

☒ Final Decision (SE, SE with Limitations, NSE (select code below), Withdrawn, etc.).

Not Substantially Equivalent (NSE) Codes

☐	NO	NSE for lack of predicate
☐	NI	NSE for new intended use
☐	NQ	NSE for new technology that raises new questions of safety and effectiveness
☐	NU	NSE for new intended use AND new technology raising new questions of safety and effectiveness
☐	NP	NSE for lack of performance data
☐	NS	NSE no response
☐	NL	NSE for lack of performance data AND no response
☐	NM	NSE pre-amendment device call for PMAs (515i)
☐	NC	NSE post-amendment device requires PMAs
☐	NH	NSE for new molecular entity requires PMA
☐	TR	NSE for transitional device

Please complete the following for a final clearance decision (i.e., SE, SE with Limitations, etc.):		YES	NO
Indications for Use Page	*Attach IFU*	✓	
510(k) Summary /510(k) Statement	*Attach Summary*	✓	
Truthful and Accurate Statement.	*Must be present for a Final Decision*	✓	
Is the device Class III?			✓
If yes, does firm include Class III Summary?	*Must be present for a Final Decision*		
Does firm reference standards? (If yes, please attach form from http://www.fda.gov/opacom/morechoices/fdaforms/FDA-3654.pdf)		✓	
Is this a combination product? (Please specify category _____, see http://eroom.fda.gov/eRoomReg/Files/CDRH3/CDRHPremarketNotification510kProgram/0_413b/COMBINATION%20PRODUCT%20ALGORITHM%20(REVISED%203-12-03).DOC			✓
Is this a reprocessed single use device? (Guidance for Industry and FDA Staff – MDUFMA - Validation Data in 510(k)s for Reprocessed Single-Use Medical Devices, http://www.fda.gov/cdrh/ode/guidance/1216.html)			✓
Is this device intended for pediatric use only?			✓
Is this a prescription device? (If both prescription & OTC, check both boxes.)		✓	
Did the application include a completed FORM FDA 3674, Certification with Requirements of ClinicalTrials.gov Data Bank?	9/A	✓	
Is clinical data necessary to support the review of this 510(k)?			✓
For United States-based clinical studies **only**: Did the application include a completed FORM FDA 3674, *Certification with Requirements of ClinicalTrials.gov Data Bank*? (If study was		✓	

	Yes	No
conducted in the United States, and FORM FDA 3674 was not included or incomplete, then applicant must be contacted to obtain completed form.)		
Does this device include an Animal Tissue Source?	✓	
All Pediatric Patients age<=21		✓
Neonate/Newborn (Birth to 28 days)		✓
Infant (29 days -< 2 years old)		✓
Child (2 years -< 12 years old)		✓
Adolescent (12 years -< 18 years old)		✓
Transitional Adolescent A (18 - <21 years old) Special considerations are being given to this group, different from adults age ≥ 21 (different device design or testing, different protocol procedures, etc.)		✓
Transitional Adolescent B (18 -<= 21; No special considerations compared to adults => 21 years old)		✓
Nanotechnology		✓
Is this device subject to the Tracking Regulation? (Medical Device Tracking Guidance, http://www.fda.gov/cdrh/comp/guidance/169.html) *Contact OC.*		✓

Regulation Number	Class*	Product Code
21 CFR 862.2570	II	NSU

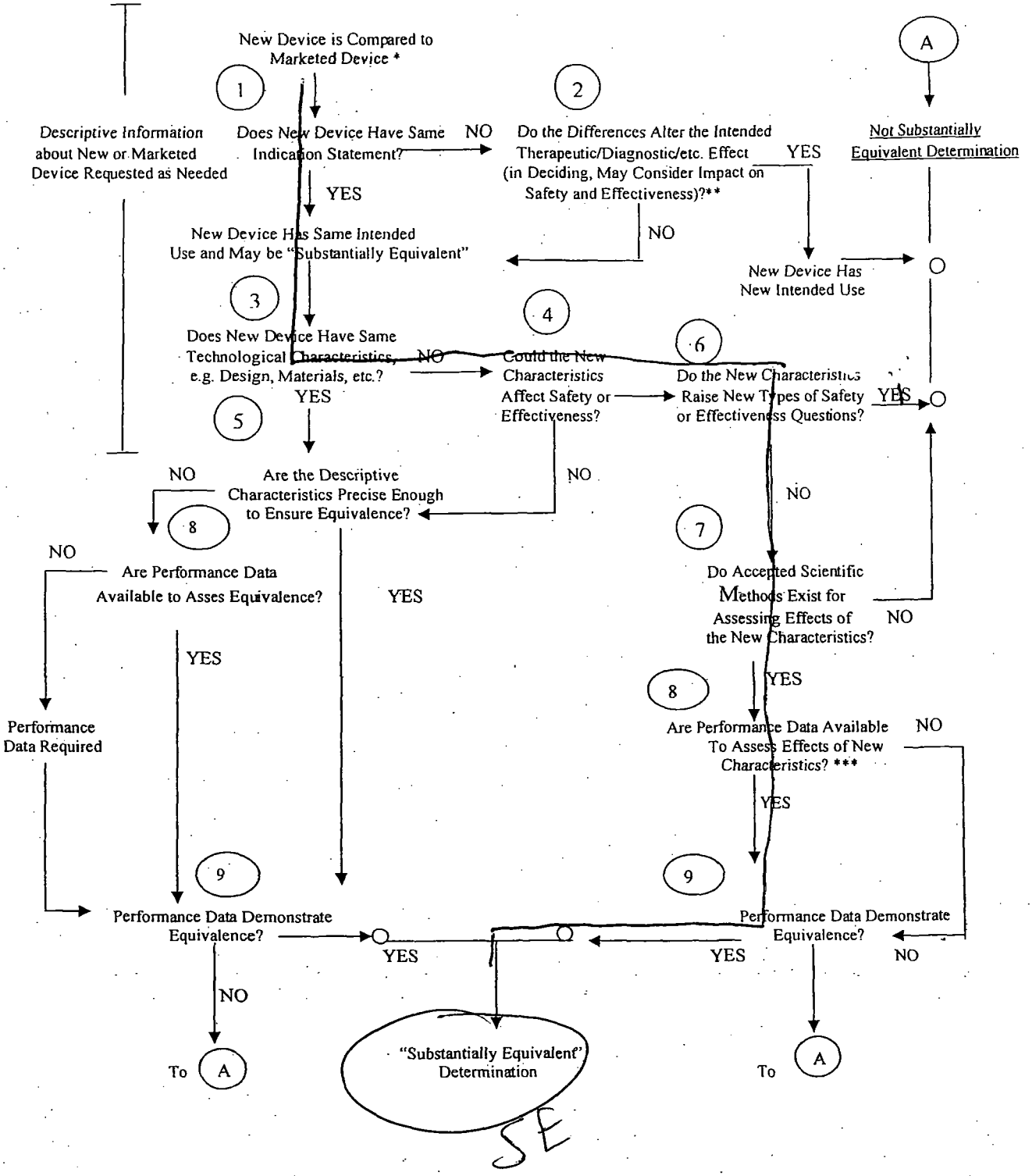
(*If unclassified, see 510(k) Staff)

Additional Product Codes: MRR, LBS, CDT

Review: [signature] (Branch Chief) DCTD (Branch Code) 8-30-2012 (Date)

Final Review: Carol C Benson (Division Director) Aug. 30, 2012 (Date)

510(k) "SUBSTANTIAL EQUIVALENCE" DECISION-MAKING PROCESS



* 510(k) Submissions compare new devices to marketed devices. FDA requests additional information if the relationship between marketed and "predicate" (pre-Amendments or reclassified post-Amendments) devices is unclear.

** This decision is normally based on descriptive information alone, but limited testing information is sometimes required.

*** Data maybe in the 510(k), other 510(k)s, the Center's classification files, or the literature.

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

A. 510(k) Number:

k113830

B. Purpose for Submission:

New device

C. Measurand:

LDL-P (low density lipoprotein particle number), HDL cholesterol (HDL-C), and triglycerides

D. Type of Test:

Nuclear Magnetic Resonance (NMR) spectroscopy assay

E. Applicant:

LipoScience Inc.

F. Proprietary and Established Names:

NMR LipoProfile® test on Vantera® Clinical Analyzer

G. Regulatory Information:

Product Code	Classification	Regulation Section	Panel
NSU	Class II	21 CFR 862.2570, Instrumentation for clinical multiplex test system	Clinical Chemistry (75)
MRR	Class I, meets limitations per 21 CFR 862.9(c)(4)	21 CFR 862.1475, Lipoprotein test system	Clinical Chemistry (75)
LBS		21 CFR 862.1175, Cholesterol test system	Clinical Chemistry (75)
CDT		21 CFR 862.1705, Triglyceride test system	Clinical Chemistry (75)

H. Intended Use:

1. Intended use(s):

   See Indications for use below.

2. Indication(s) for use:

   The Vantera® Clinical Analyzer is an automated laboratory test analyzer which measures the 400 MHz proton nuclear magnetic resonance (NMR) spectrum of clinical samples to produce signal amplitudes, converting these signal amplitudes to analyte concentration. The device includes a 400 MHz NMR spectrometer and software to analyze digitized spectral data. This instrumentation is intended to be used with NMR based assays to detect multiple analytes from clinical samples.

   The *NMR LipoProfile*® test, when used with the Vantera® Clinical Analyzer, an automated NMR spectrometer, measures lipoprotein particles to quantify LDL particle number (LDL-P), HDL cholesterol (HDL-C), and triglycerides in human serum and plasma using nuclear magnetic resonance (NMR) spectroscopy. LDL-P and these NMR-derived concentrations of HDL-C and triglycerides are used in conjunction with other lipid measurements and clinical evaluation to aid in the management of lipoprotein disorders associated with cardiovascular disease.

3. Special conditions for use statement(s):

   For *in vitro* diagnostic use only, for prescription use only.

4. Special instrument requirements:

   All performance was evaluated on the The Vantera® Clinical Analyzer

I. Device Description:

The test system includes the following components:

• **Diluent 1**(*NMR LipoProfile*® test) – 8 x 250mL bottles of aqueous solution containing Na2EDTA (5.0mM), CaCl2 (1.0mM), KCL (120mM), Na2HPO4 -7H20(50mM), pH 7.4, 6.0 M NaOH, 1.0 M HCl.

• **WASH** (NMR Fluidics System Solution) – single 2L bottle of Triton X-100-0.1%v/v, Liqui Nox 0.1% v/v in Type 2 water, pH 10.0, sodium bicarbonate (anhydrous), sodium carbonate (anhydrous), 6.0 M NaOH.

• **NMR Reference Standard (calibrator)** – 6 x 30mL bottles of 0.2% w/v aqueous solution of Trimethyl Acetate (TMA) disodium salt (15.0 mM) containing Na2EDTA (5.0 mM), CaCl2 (3.0 mM), KCl (120 nM), D2O 10% v/v, 6.0 M NaOH, 1.0 M HCl. Each box of NMR

Reference Standard is supplied with specimen tube barcodes.

• **QC Material** – 2 levels of human based control material (6 x 3mL each) which include values for LDL-P, TG, and HDL-C as assigned at LipoScience.

The control materials contain human source material. Each donor unit is tested by FDA – approved methods and found non-reactive for hepatitis B surface antigen (HBsAg), antibody to hepatitis C, and antibody to HIV-1/2.

All products using human source material should be handled as potentially infectious, because no test method can offer complete assurance that infectious agents are absent.

• **Vantera Clinical Analyzer** - 400 MHz proton nuclear magnetic resonance spectrometer interfaced with sample handling assembly, deconvolution software and provided with a system User's Manual.

J. Substantial Equivalence Information:

1. Predicate device name(s):

    1. NMR Profiler and *NMR Lipoprofile* test
    2. Luminex LX 100/200 Instrument

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

    1. k111516
    2. k073506

3. Comparison with predicate:

Instruments:

Items	Vantera® Clinical Analyzer for use with *NMR LipoProfile®* test (Candidate Device)	Luminex LX 100/200 Instrument (Perdicate Device) k073506
Similarities		
Instrument Intended Use	Same	A clinical multiplex instrument intended to measure and sort multiple signals generated in an *In Vitro* diagnostic assay from a clinical sample. This instrumentation is used with a specific assay to measure multiple similar analytes that establish a single indicator to aid in diagnosis. The device

		includes a signal reader unit, raw data storage mechanisms, data acquisition software and software to process detected signals.
Multi-Analyte	Same	Yes
System Fluidics	Same	Utilizes system fluidics to deliver sample to the site of sample analysis
System Calibration	Same	Calibration Required
Specimen Identification	Same	Barcode reader entry of sample ID
Data Acquisition Software	Same	Data acquisition software and software to process detected signals
Differences		
Test Principle	Nuclear magnetic resonance – 400 MHz proton NMR	Bead based multiplexing - Fluorescence
Sample handling	Serum/Plasma Samples are diluted onboard system	Samples are manually prepared then presented to system.

Device:

Items	Vantera® Clinical Analyzer for use with *NMR LipoProfile®* test (Candidate Device)	*LipoScience NMR LipoProfile®* test and NMR Profiler (Predicate Device) k111516
Similarities		
Device Intended Use	Same	For the measurement of lipoprotein particles to quantify LDL particle number (LDL-P), HDL cholesterol (HDL-C), and triglycerides in human serum and plasma using nuclear magnetic resonance (NMR) spectroscopy. LDL-P and these NMR-derived concentrations of HDL-C and triglycerides are used in conjunction with other lipid measurements and clinical evaluation to aid in the management of lipoprotein disorders associated with cardiovascular disease

Test Principle	Same	Nuclear magnetic resonance – 400 MHz proton NMR
Multi-Analyte	Same	Yes
System Fluidics	Same	Manual
Sample Type	Same	Human Serum and Plasma
System Calibration	Same	Calibration Required
Specimen Identification	Same	Barcode reader entry of sample ID
Data Acquisition Software	Same	Data acquisition software and software to process detected signals
Spectral Deconvolution	Same	Linear least-squares with singular value decomposition of the spectra from each specimen.
Measuring Range LDL-P	Same	300-3500 nmol/L
Measuring Range TG	Same	5-1100 mg/dL
Measuring Range HDL-C	Same	7-140 mg/dL
	Differences	
Sample handling	Serum/Plasma Samples are diluted onboard system	Samples are manually prepared then presented to system.
System Fluidics	Utilizes system fluidics to deliver sample to the site of sample analysis	Manual

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

- CLSI Guideline EP05-A2: Evaluation of Precision Performance of Qualitative Measurement Methods
- CLSI Guideline EP06-A: Evaluation of the Linearity of Qualitative Measurement Methods
- CLSI Guideline EP07-A2: Interference Testing in Clinical Chemistry
- CLSI Guideline EP09-A2: Method Comparison and Bias Estimation Using Patient Samples
- CLSI Guideline EP17-A: Protocols for Determination of Limits of Detection and Limits of Quantitation
- CLSI Guideline EP14-A2: Evaluation of Matrix Effects
- CLSI Guideline C28-A3: Defining Establishing, and Verifying Reference Intervals in the Clinical Laboratory
- IEC 610 I 0-1:200 I, 2nd Edition; Safety requirements for electrical equipment for measurement, control and laboratory use. Part I

L. Test Principle:

Vantera Clinical Analyzer

The Vantera Clinical Analyzer is a clinical laboratory analyzer that employs nuclear magnetic resonance spectroscopic detection to quantify multiple analytes in biological fluid specimens, specifically blood plasma and serum.

The Vantera Clinical Analyzer system design is divided into 3 major subassemblies: a sample handling assembly, an NMR subassembly, and an enclosure. The Vantera Clinical Analyzer control system is distributed across three separate computers:

- The Host (1U) controls user interface, data handling, results calculation, system startup and shutdown.

- The Process Control (4U) schedules and manages all activities required to process a sample, controls all hardware in the sample handling subsystem, and manages remote access to the system.

- The NMR Control Computer controls all magnet operations.

Two of these computers are contained within the Sample Handling Subassembly (1U and 4U) and one in the NMR Subassembly (NMR Console).

***NMR LipoProfile* test**

The *NMR LipoProfile* test involves measurement of the 400 MHz proton NMR spectrum of a plasma/serum sample, deconvolution of the composite signal at approximately 0.8 ppm to produce signal amplitudes of the lipoprotein subclasses that contribute to the composite plasma/serum signal, and conversion of these subclass signal amplitudes to lipoprotein subclass concentrations. The ~0.8 ppm plasma NMR signal arises from the methyl group protons of the lipids carried in the LDL, HDL and VLDL subclasses of varying diameters. The NMR signals from the various lipoprotein subclasses have unique and distinctive frequencies and line shapes, each of which is accounted for in the deconvolution analysis model. Each subclass signal amplitude is proportional to the number of subclass particles emitting the signal, which enables subclass particle concentrations to be calculated from the subclass signal amplitudes derived from the spectral deconvolution analysis. LDL subclass particle concentrations, in units of nanomoles of particles per liter (nmol/L), are summed to give the reported total LDL particle concentration (LDL-P). By employing conversion factors assuming that the various lipoprotein subclass particles have cholesterol and triglyceride contents characteristic of normolipidemic individuals, HDL cholesterol and triglyceride concentrations are also derived.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

   a. Precision/Reproducibility:

Within-run and within-laboratory precision were evaluated in accordance with the methods defined in the CLSI Guideline EP5-A, "Evaluation of Precision Performance of Clinical Chemistry Devices."

Three serum pools with different analyte concentrations were tested in multiple runs over multiple days. For the Within-Lab, multiple instruments, operators and reagent lots were incorporated into the testing and a variance component analysis was conducted to estimate the individual sources of the total system variability.

Within-run precision - A single run of 20 replicates for the low, medium and high pool was conducted on one NMR instrument. A single operator conducted all three runs.

(b)(4)

[redacted]

Within-laboratory precision – Two runs per day with two replicates per run for three pools were tested on three instruments for a total of 20 testing days.

(b)(4)

[redacted]

Reproducibility – A reproducibility study was conducted in accordance to EP5-A2 at 3 sites incorporating five levels of serum panels at or around the medical decision limits. The panels were tested for 5 days, 6 runs per day, 2 replicates per run. The overall precision estimates are described below.

(b)(4)

(b)(4)

b. *Linearity/assay reportable range:*

Three serum pools were prepared from patient specimens with low, medium and high values of LDL-P, HDL-C and Triglycerides (TG) as determined by *NMR LipoProfile* test. The pools were mixed in different proportions to produce eleven (for LDL-P) or Twelve (12) (TG and HDL-C) different samples with widely varying target concentrations. Mean values from analysis of four replicates of each pool were compared to the expected target values to determine the percent bias for each sample. The serum pools were analyzed according to EP6-A. Tables and regression plots of the linearity data for LDL-P, HDL-P and Triglycerides are given below:

LDL-P Linear Regression Analysis:
(b)(4)

HDL-C Linear Regression Analysis:
(b)(4)

TG Linear Regression Analysis:
(b)(4)

Claimed Reportable Range for each analyte:

LDL-P	300 – 3500 nmol/L
HDL-C	7 – 140 mg/dL
TG	5 – 1100 mg/dL

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

The sponsor states in the labeling that this device has not been certified or tested by the Cholesterol Reference Method Laboratory Network.

Traceability for calibrator – TMA (Trimethylacetic acid, Sodium salt, from Trimethyl acetate hydrate CAS-No 143174-36-1, and Ethylenediamine Tetraacetic acid CAS-No 139-33-3) is used as the NMR calibrator for the NMR clinical analyzers. TMA is used routinely as a calibrator once daily during instrument startup to establish daily normalization factors. It also serves as a quality assessment tool to ensure quality NMR spectra are produced by the NMR analyzer. New calibrator material is run in parallel with the existing calibrator in five separate runs. The TMA calibrator is characterized by the manufacturer using infrared spectrum (chemical structure), elemental analysis, and titration.

Traceability for control – Controls are included with the *NMR LipoProfile®* test. Bio-Rad Liquichek controls (k012513) are obtained by LipoScience and are assigned target values and expiration dates in house by LipoScience prior to providing the control sets to the users. The LDL-P specific value assignment occurs via in-house created master calibrators which are traceable to a purchased source material characterized by lipoprotein metabolism profiling using a combination of electrophoresis, ultracentrifugation, and automated enzymatic quantification of cholesterol and triglycerides (fractions HDL, LDL, VLDL, and Lp[a]). Each lot of control set is value assigned from the master calibrators through evaluation of 5 replicate measurements per run using 3 instruments analyzing 2 runs per day for 2 days.

Stability – The stability protocol of the TMA calibrator material and the control sets was reviewed and found to be adequate. Stability studies support a stability claim of TMA calibrator stability for 18 months either refrigerated or at room temperature. Stability for the quality controls is designated by the manufacturer and confirmed using stability studies in house. The stability protocols and acceptance criteria were reviewed and found to be adequate, with a specific stability claim for LDL-P of 6 months frozen at -20°C

Sample Stability – The sample stability protocol and acceptance criteria were reviewed and found to be adequate. The stability study supports a claim of the following:

Tube	**Processing**	**Storage**	**LDL-P Stability**	**TG Stability**	**HDL-C Stability**

LipoTube (serum)	Normal	Refrigerated	8 days	12 days	7 days
	Delayed Centrifugation	Refrigerated	3 days	12 days	4 days
EDTA (plasma)	Normal	Refrigerated	12 days	12 days	8 days

d. Detection limit:

Limit of the Blank – Five delipidated serum pools containing very low concentration were tested in replicates of 4 for 3 days. The Limit of Blank (LoB) was calculated non-parametrically for each analyte and determined to be the following:

LDL-P: 0.0 nmol/L
HDL-C: 2.7 mg/dL
TG: 1.1 mg/dL

Limit of Detection – Non-lipoprotein specimens were analyzed 60 consecutive times for 3 days. The Limit of Detection (LoD) was calculated parametrically for each analyte and supported the claimed measuring range of the assay.

LDL-P: 40.7 nmol/L
HDL-C: 3.5 mg/dL
TG: 2.5 mg/dL

Limit of Quantitation – Five serum pools containing very low concentrations were tested in replicates of 4 for 3 days. The Limit of Quantification (LoQ) was mathematically calculated for each analyte by plotting the %CV on the Y-axis against low concentration pools and determined to be the following:

LDL-P: 132 nmol/L
HDL-C: 4.0 mg/dL
TG: 4.0 mg/dL

The LoQ values listed above support the sponsors claimed measuring ranges of:

LDL-P	300 – 3500 nmol/L
HDL-C	7 – 140 mg/dL
TG	5 – 1100 mg/dL

e. Analytical specificity:

Endogenous substances normally found in blood and exogenous substances (common and prescription drugs) were evaluated for potential interference with the *NMR LipoProfile*® test by LipoScience. Each potential interferent was diluted in the appropriate solvent and analyzed on the NMR Profiler to determine if it demonstrated peak(s) in the 0.7 – 1.0 ppm region. Five endogenous agents and twenty three drugs were screened for potential interfering effects to NMR LipoProfile test using

concentrations in accordance to CLSI EP7-A2 guidelines.

If a potentially interfering substance was suspected to have significant interference defined as difference from control greater than 10%, a spiking study was completed where the substance was added to sample pools containing two different levels of LDL-P, HDL-C and triglycerides for a paired difference test.

Endogenous		***Exogenous (OTC drugs, etc.)***			
Potential Interferent	***Test Concentration***	***Potential Interferent***	***Test Concentration***	***Potential Interferent***	***Test Concentration***
Hemoglobin	0.5 g/dL	Acetaminophen	1324 µmol/L	Metformin Hydrochloride	3.62 mmol/L
Bilirubin, unconj.	342 µmol/L 20 mg/dL	Acetylsalicylic acid	3.62 mmol/L	Metoprolol tartrate	18.7 µmol/L
Creatinine	442 µmol/L 5 mg/dL	Atorvastatin	600 µg Eq/L	Naproxen Sodium	2170 µmol/L
Urea	42.9 mmol/L 260 mg/dL	Clopidogrel hydrogensulfate**	95.7 µmol/L	Nicotinic Acid Sodium salt	8.28 mmol/L
Uric acid	1.4 mmol/L 23.5 mg/dL	Enalaprilat Dihydrate	0.86 µmol/L	Nifedipine	1156 nmol/L
Protein (albumin)	6 g/dL, 60g/L	Fenofibrate	125 µmol/L	Pioglitazone hydrochloride	152.7µmol/L
Bilirubin, conj	342 µmol/L 28.9 mg/dL	Furosemide	181 µmol/L	Piroxicam	181 µmol/L
		Glipizide	4.48 µmol/L	Pravastatin	107.5 µmol/L
		Hydralazine hydrochloride	915.4 µmol/L	Salicylic Acid*	1.3 mmol/L
		Heparin	3000U/L	Simvastatin	114.7 µmol/L
		Ibuprofen Sodium salt	2425 µmol/L		

Isosorbide dinitrate	636 nmol/L
Menhaden oil (Fish Oil)	2.4 mg/mL

*Salicyclic acid at ≥ 1.3mmol/L was determined to interfere with LDL-P
**Clopidogrel hydrogensulfate at ≥ 95.7 µmol/L was determined to interfere with LDL-P

f. Assay cut-off:

Not applicable

2. Comparison studies:

a. Method comparison with predicate device:

LDL-P: The comparison was conducted in agreement with CLSI EP9-A2: *Method Comparison and Bias Estimation Using Patient Samples*. The study involved testing singlicates followed by statistical analysis of 1482 freshly-collected clinical de-identified specimens across the range of the LDL-P test on the Vantera Clinical Analyzer (candidate device) vs the NMR Profiler (predicate device). Bias was calculated for LDL-P from the linear regression line at the medical decision limits of 1000, 1300 and 1600 nmol/L as well. The range of the samples was 303 to 3479 nmol/L.

Linear regression/least squares analysis:
$y = 1.03x - 36.60$
$r = 0.978$

Observed LDL-P Bias per linear regression at Medical Decision Limits:

LDL-P (nmol/L)	**Absolute Bias**	**Percent Bias** (%)
1000	-10.0	-1.0
1300	-2.0	-0.2
1600	6.0	0.4

In addition to conducting a method comparison for the overall data set, the data were classified into the three following segments based on LDL-P values; (1) results below the medical decision limits of 1000 nmol/L, (2) results between 1000 and 1600

nmol/L and (3) results above 1600 nmol/L. For each segment the bias was determined. The determined % Bias for each segment was less than 5% for each level).

HDL-C: The comparison was conducted in agreement with CLSI EP9-A2: *Method Comparison and Bias Estimation Using Patient Samples*. The study involved testing singlicates followed by statistical analysis of 1518 freshly-collected clinical de-identified specimens across the range of the HDL-C test on the Vantera Clinical Analyzer (candidate device) vs the NMR Profiler (predicate device). Bias was calculated for HDL-C from the linear regression line at the medical decision limits of 40 and 60 mg/dL as well. The range of the samples was 7.0 to 132 mg/dL.

Linear regression/least squares analysis:
y = 1.04x – 1.20
r = 0.989

Observed HDL-C Bias per linear regression at Medical Decision Limits:

HDL-C (mg/dL)	**Absolute Bias**	**Percent Bias** (%)
40	0.3	0.8
60	1.1	1.8

In addition to conducting a method comparison for the overall data set, the data were classified into the three following segments based on HDL-C values; (1) results below the medical decision limits of 40 mg/dL, (2) results between 40 and 60 mg/dL and (3) results above 60 mg/dL. For each segment the bias was determined. The determined % Bias for each segment was less than 3% for each level.

TG: The comparison was conducted in agreement with CLSI EP9-A2: *Method Comparison and Bias Estimation Using Patient Samples*. The study involved testing singlicates followed by statistical analysis of 1520 freshly-collected clinical de-identified specimens across the range of the TG test on the Vantera Clinical Analyzer (candidate device) vs the NMR Profiler (predicate device). Bias was calculated for TG from the linear regression line at the medical decision limits of 150, 200 and 500 mg/dL as well. The range of the samples was 18.0 to 1095 mg/dL.

Linear regression/least squares analysis:
y = 1.00x + 0.92
r = 0.998

Observed TG Bias per linear regression at Medical Decision Limits:

TG (mg/dL)	**Absolute Bias**	**Percent Bias** (%)
150	1.2	0.8
200	1.3	0.7
500	1.8	0.4

In addition to conducting a method comparison for the overall data set, the data were classified into the three following segments based on TG values; (1) results below the medical decision limits of 150 mg/dL, (2) results between 150 and 200 mg/dL and (3) results above 200 mg/dL. For each segment the bias was determined. The determined % Bias for each segment was less than 3% for each level.

b. Matrix comparison:

Samples from 50 subjects (46 native and 4 contrived) were analyzed for each analyte by collecting the patient specimen into each of the claimed tube types. Comparative analysis of the LipoTube vs plain serum and EDTA plasma resulted in the following:

LipoTube vs Plain Serum

	LDL-P (nmol/L)	**TG** (mg/dL)	**HDL-C** (mg/dL)
Slope	0.9678	1.002	0.9739
Y-Int	26.4	-0.417	1.589
R sq	0.96	0.99	0.99

LipoTube vs EDTA Plasma

	LDL-P (nmol/L)	**TG** (mg/dL)	**HDL-C** (mg/dL)
Slope	0.9442	0.9212	0.9339
Y-Int	-13.9	2.414	2.079
R sq	0.97	1.00	0.99

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:

See expected values below

5. Expected values/Reference range:

The sponsor conducted a reference range study in order to determine the normal

distribution of LDL-P levels expected in a representative sampling of the general population. Healthy adult patient plasma samples were obtained (n=452) and analyzed (age ranging from 18 to 84 years). Samples or patients with specific history of diabetes or cardiac, renal or lipid disease were excluded, as well as any patients who were pregnant or being treated for cancer. Sample results were analyzed together, and also were partitioned into percentiles and separated based upon patient sex and age. The results of the reference range study are listed in the tables below:

Distribution of LDL-P Observed in a Reference Population

	All (n=452)	**Men (n=158)**	**Women (n=294)**	**All (n=452)**	**Men (n=158)**	**Women (n=294)**
Percentile	**LDL-P** (nmol/L)	**LDL-P** (nmol/L)	**LDL-P** (nmol/L)	**LDL-C** (mg/dL)	**LDL-C** (mg/dL)	**LDL-C** (mg/dL)
5	539	528	542	63	62	65
10	643	713	638	75	76	75
20	784	883	749	84	90	83
30	909	1004	863	94	100	91
40	1009	1087	970	102	107	98
50	1127	1241	1070	109	113	109
60	1248	1366	1202	118	128	115
70	1396	1505	1322	129	137	124
80	1572	1676	1482	140	147	136
90	1894	1941	1818	157	161	151
95	2047	2169	1986	169	171	169

Distribution of LDL-P Observed in a Reference Population of Healthy Subjects Ages 18 - 44

	All (n=329)	**Men (n=115)**	**Women (n=214)**	**All (n=329)**	**Men (n=115)**	**Women (n=214)**
Percentile	**LDL-P** (nmol/L)	**LDL-P** (nmol/L)	**LDL-P** (nmol/L)	**LDL-C** (mg/dL)	**LDL-C** (mg/dL)	**LDL-C** (mg/dL)
5	532	513	528	62	61	64
10	634	654	630	72	72	72
20	753	862	726	82	89	81
30	885	961	820	90	99	87
40	966	1041	930	98	106	94
50	1045	1149	1008	107	110	101
60	1191	1322	1115	113	126	109
70	1328	1466	1251	122	135	118
80	1492	1639	1406	136	145	127
90	1807	1945	1666	150	161	146
95	2028	2241	1976	165	171	156

Distribution of LDL-P Observed in a Reference Population of Healthy Subjects ≥Age 45

	All (n=123)	**Men (n=43)**	**Women (n=80)**	**All (n=123)**	**Men (n=43)**	**Women (n=80)**
Percentile	**LDL-P** (nmol/L)	**LDL-P** (nmol/L)	**LDL-P** (nmol/L)	**LDL-C** (mg/dL)	**LDL-C** (mg/dL)	**LDL-C** (mg/dL)
5	590	559	586	71	56	71
10	733	772	726	83	78	84
20	871	951	842	94	93	94
30	1025	1186	998	106	103	109
40	1188	1290	1158	113	110	115
50	1295	1364	1224	123	119	124
60	1402	1478	1368	134	133	134
70	1545	1643	1504	140	141	140
80	1752	1731	1796	150	153	146
90	1949	1934	1949	164	162	169
95	2075	2562	2016	186	181	188

Labeling for expected values states that each laboratory should verify the validity of the stated reference range values for the population the laboratory serves.

HDL concentration and triglycerides: The proposed device has similar reference values as the predicate. The reference values for patient classification have been recommended by the NCEP and taken from literature* for HDL cholesterol and triglycerides for the assessment and management of CVD risk. The labeling states that each laboratory should verify the validity of these reference values for the population it serves.

HDL Cholesterol, mg/dL Classification	
Low	*High*
< 40	≥ 60

Triglycerides, mg/dL Classification			
Normal	*Borderline High*	*High*	*Very High*
< 150	150 - 199	200 - 499	> 500

*Expert Panel on Detection, *Evaluation and Treatment of High Cholesterol in Adults (Adult Treatment Panel III)*, May (2001).
NIH Publication No. 01 3305, *ATP III Guidelines At-A-Glance*, Quick Desk Reference, May (2001).
NIH Publication No. 01 3670, Third Report of National Cholesterol Education Program (NCEP)

N. Instrument Name:

Vantera Clinical Analyzer

O. System Descriptions:

1. Modes of Operation:

   Not applicable

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:

   Internal barcode scanner identifies the specimens and automatically loads identification into the software.

4. Specimen Sampling and Handling:

   Samples are loaded onto the instrument manually and samples are scanned and diluted / prepared automatically by the system.

5. Calibration:

   Instrument calibration occurs daily (once every eight-hour shift) with the provided TMA calibrator (trimethyl acetic acid) to ensure the homogeneity of the magnetic field (line-shape specifications), to check the temperature of the NMR system, and to calculate the daily normalization factor. Calibration procedures are described in the labeling, and include a manual loading of the calibrant and automatic calibration by the instrument software.

6. Quality Control:

   Quality controls are treated as specimens with specific control barcode labels that are provided with the system. The operator's manual recommends running the quality controls once daily or in accordance with the laboratory practice.

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.

S. Other Supportive Device and Instrument Information:

The device labeling contains the following information that was not included in the public section of this decision summary as it was published expert recommendations and had not been validated on the candidate device or by a clinical study. The table is clinical recommendation values for LDL-P taken from an expert recommendation publication by the national Lipid Association (Davidson MH, et al. Clinical utility of inflammatory markers and advanced lipoprotein testing: Advice from an expert panel of lipid specialists. Journal of Clinical Lipidology. 2011; 5:338-367). These published recommendations were made based upon the analytical comparison of LDL-P with LDL-C in the MESA study data analysis by LipoScience:

Based on the recommendations from a National Lipids Association expert panel[8], suggested reference values are provided in Table 2. The recommendation by the NLA has not been validated by a clinical study. Each laboratory should verify the validity of these reference values for the population it serves

Table 2: Recommended LDL-P Reference Values

LDL-P, nmol/L			
Classification			
Low / Normal	*Intermediate*		*High*
	Moderate	*Borderline High*	
< 1000	1000-1299	1300-1599	≥ 1600

The decision to allow the table fell to the managers, product specialist and the lead reviewer. Based on concurrence by the division director in previous documentation allowing the table to be used in the patient reports sent to the ordering clinician, the decision was made to allow the table into the labeling with the included statement that the recommendations had not been validated with a clinical trial.

No postmarket signals were found for this device

T. Administrative Information:

1. Applicant Contact Information:

   a. Name of applicant:

LipoScience, Inc.

b. *Mailing address:*

2500 Summer Blvd.

Raleigh, NC 27616

c. *Phone #:*

919-256-1326

d. *Fax #:*

919-256-1149

e. *E-mail address (optional):*

suzette.warner@liposcience.com

f. *Contact:*

Suzette Warner

2. Review Documentation:

Call to sponsor requesting electronic copy of submission on 2/1/12

Email from sponsor with follow-ups on 2/6/12 discussing CLIA categorization

Email to sponsor with hold letter on 2/24/12

Teleconference on 3/1/12 with sponsor and FDA colleagues to discuss hold letter

Email to sponsor with example linearity table on 3/15/12

Email from sponsor with part 1 of study plans for review on 3/22/12

Email from sponsor with partial hold response on 4/6/12

Email from sponsor with reference range study design on 4/13/12

Call with sponsor to discuss study plans on 4/27/12

Email from sponsor on 5/4/12 concerning control material

Emails from sponsor with previous documentation of labeling table on 8/20/12

Call to sponsor requesting tables and updated PI and 510(k) summary on 8/24/12

Email from sponsor with requested information on 8/24/12

Call to sponsor requesting additional analysis on 8/29/12

Emails from sponsor with requested information on 8/29/12

Calls to sponsor requesting updated information on 8/30/12

Emails from sponsor with requested information on 8/30/12

3. Substantial Equivalence Discussion:

	Yes	No	
1. Same Indication Statement?	X		If **YES** = Go To 3
2. Do Differences Alter The Effect Or Raise New Issues of Safety Or Effectiveness?			If **YES** = Stop **NSE**
3. Same Technological Characteristics?		X	If **YES** = Go To 5
4. Could The New Characteristics Affect Safety Or Effectiveness?	X		If **YES** = Go To 6
5. Descriptive Characteristics Precise Enough?			If **NO** = Go To 8 If **YES** = Stop **SE**
6. New Types Of Safety Or Effectiveness Questions?		X	If **YES** = Stop **NSE**
7. Accepted Scientific Methods Exist?	X		If **NO** = Stop **NSE**
8. Performance Data Available?	X		If **NO** = Request Data
9. Data Demonstrate Equivalence?	X		Final Decision: **SE**

Note: See http://eroom.fda.gov/eRoomReq/Files/CDRH3/CDRHPremarketNotification510kProgram/0_4148/FLOWCHART%20DECISION%20TREE%20.DOC for Flowchart to assist in decision-making process. Please complete the following table and answer the corresponding questions. "Yes" responses to questions 2, 4, 6, and 9, and every "no" response requires an explanation.

a. Explain how the new indication differs from the predicate device's indication:

b. Explain why there is or is not a new effect or safety or effectiveness issue:

c. *Describe the new technological characteristics:*

Instrument:

The predicate instrument is a clinical multiplex test system that uses bead based multiplexing with fluorescent detection to analyze samples. Both the predicate and the candidate instruments are multiplex platforms, however the detection technology (bead based vs NMR), the sample handling (manual vs automated) and the measuring principle (fluorescence vs 400 MHz proton NMR Spectrum) are different.

Device:

The candidate device is different from the predicate device only in the sample handling – the candidate device includes an autosampler which can dilute and process the samples automatically, whereas all sample handling was manual for the predicate device.

d. *Explain how new characteristics could or could not affect safety or effectiveness:*

Instrument:

The predicate manual sampling instrument uses bead based multiplexing with fluorescent detection to analyze samples, all of which are potential differences that could affect the safety or effectiveness of the candidate instrument.

Device:

The only difference between the predicate and candidate devices is that the predicate uses manual sample workup and the candidate device is equipped with an autosampler. This may change the performance of the candidate device when compared to the predicate.

e. *Explain how descriptive characteristics are not precise enough:*

f. *Explain new types of safety or effectiveness question(s) raised or why the question(s) are not new:*

All performance data was reviewed and the new characteristic was found to not affect the analytical performance or the safety/efficacy of the device. There were no new types of safety or effectiveness questions raised by the performance of the device.

g. *Explain why existing scientific methods can not be used:*

h. *Explain what performance data is needed:*

i. Explain how the performance data demonstrates that the device is or is not substantially equivalent:

The submitted information in this premarket notification is complete and supports a substantial equivalence decision. See the decision summary template in section M.2.a. above for more information.

U. Reviewer Name and Signature:

Elizabeth O'Keeffe, Ph.D.
CDRH/OIVD/DCTD

Indication for Use

510(k) Number (if known): K113830

Device Name: Vantera® Clinical Analyzer

Indications for Use:

The Vantera® Clinical Analyzer is an automated laboratory test analyzer which measures the 400 MHz proton nuclear magnetic resonance (NMR) spectrum of clinical samples to produce signal amplitudes, converting these signal amplitudes to analyte concentration. The device includes a 400 MHz NMR spectrometer and software to analyze digitized spectral data. This instrumentation is intended to be used with NMR based assays to detect multiple analytes from clinical samples.

Prescription Use __X____ (21 CFR Part 801 Subpart D) And/Or Over the Counter Use ____. (21 CFR Part 801 Subpart C)

(PLEASE DO NOT WRITE BELOW THIS LINE; CONTINUE ON ANOTHER PAGE IF NEEDED)

Concurrence of CDRH, Office of In Vitro Diagnostic Device Evaluation and Safety (OIVD)

Division Sign-Off
Office of In Vitro Diagnostic Device
Evaluation and Safety

510(k) K113830

Indication for Use

510(k) Number (if known): K113830

Device Name: NMR LipoProfile® test on Vantera® Clinical Analyzer

Indications for Use:

The *NMR LipoProfile®* test, when used with the Vantera® Clinical Analyzer, an automated NMR spectrometer, measures lipoprotein particles to quantify LDL particle number (LDL-P), HDL cholesterol (HDL-C), and triglycerides in human serum and plasma using nuclear magnetic resonance (NMR) spectroscopy. LDL-P and these NMR-derived concentrations of HDL-C and triglycerides are used in conjunction with other lipid measurements and clinical evaluation to aid in the management of lipoprotein disorders associated with cardiovascular disease.

Prescription Use __X____ And/Or Over the Counter Use ____.
(21 CFR Part 801 Subpart D) (21 CFR Part 801 Subpart C)

(PLEASE DO NOT WRITE BELOW THIS LINE; CONTINUE ON ANOTHER PAGE IF NEEDED)

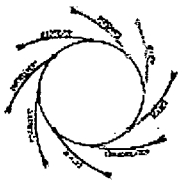
Concurrence of CDRH, Office of In Vitro Diagnostic Device Evaluation and Safety (OIVD)

Division Sign-Off
Office of In Vitro Diagnostic Device
Evaluation and Safety

510(k) K113830

TPLC Detailed View

from 1/01/2009 to 8/30/2012



Product Code	**CDT**
Manufacturer	**LIPOSCIENCE**
Class	**1**
Regulation Device Classification	**Triglyceride test system.**
Device Name	**LIPASE HYDROLYSIS/GLYCEROL KINASE ENZYME, TRIGLYCERIDES**
Date Last Listed	**Not Listed**

CDRH Gen Docs with Manufacturer (None)

Premarket Reviews Completed (1)

CTS	**K101023**	NMR LIPOPROFILE TEST BY LIPOSCIENCE AND NMR PROFILER	NE	Kellie Kelm
Image	*FDA.GOV*			

Under Review, Withdrawn or Closed without Product Code (1)

CTS	**K113830**	VANTERA CHINIAL ANALYZER	Review	Elizabeth O'Keeffe
Image	*FDA.GOV*	INSTRUMENTATION FOR CLINICAL MULIPLEX TEST SYSTEMS		

Standards and Guidance (None)

MDR Summary (None)

		Total
	0	
Total		

MDR Analyst (1)

Janne Cummings	janne.cummings@fda.hhs.gov

MDR Distribution by Brand - Death or Injury (None)

Patient Problems (None)

Patient Outcomes (None)

Device Problems (None)

Manufacturer Evaluation Results (None)

Manufacturer Evaluation Conclusions (None)

Recalls (None)

Inspections (None)

CDRH Gen Docs without Manufacturer (None)

Rad Health Reports (None)

Rad Health Correspondence (None)

Rad Health Adverse Events (None)

Rad Health EIRs (None)

TPLC Detailed View

from 1/01/2009 to 8/30/2012

Product Code	**LBS**
Manufacturer	**LIPOSCIENCE**
Class	**1**
Regulation Device Classification	**Lipoprotein test system.**
Device Name	**LDL & VLDL PRECIPITATION, CHOLESTEROL VIA ESTERASE-OXIDASE, HDL**
Date Last Listed	**Not Listed**

CDRH Gen Docs with Manufacturer (None)

Premarket Reviews Completed (1)

CTS	K101023	NMR LIPOPROFILE TEST BY LIPOSCIENCE AND NMR PROFILER	NE	Kellie Kelm
Image	*FDA.GOV*			

Under Review, Withdrawn or Closed without Product Code (1)

CTS	K113830	VANTERA CHINIAL ANALYZER	Review	Elizabeth O'Keeffe
Image	*FDA.GOV*	INSTRUMENTATION FOR CLINICAL MULIPLEX TEST SYSTEMS		

Standards and Guidance (1)

Reference Number	Title	Contact	Relevant Guidance
C37-A	Preparation and Validation of Commutable Frozen Human Serum Pools as Secondary Reference Materials for Cholesterol Measurement Procedures; Approved Guideline	Carol C. Benson	Guidance for 510(K)s on Cholesterol Tests for Clinical Laboratory, Physician's Office Laboratory, and Home Use Guidance for Industry - Abbreviated 510 (K) Submissions for In Vitro Diagnostic Calibrators Points to Consider for Collection of Data in Support of In Vitro Device Submissions for 510(K) Clearance.

MDR Summary (None)

	[redacted]	Total
[redacted]	0	
Total		

MDR Analyst (1)

Yung Chan	yung.chan@fda.hhs.gov

MDR Distribution by Brand - Death or Injury (None)

Patient Problems (None)

Patient Outcomes (None)

Device Problems (None)

Manufacturer Evaluation Results (None)

Manufacturer Evaluation Conclusions (None)

Recalls (None)

Inspections (None)

CDRH Gen Docs without Manufacturer (None)

Rad Health Reports (None)

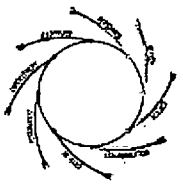
Rad Health Correspondence (None)

Rad Health Adverse Events (None)

Rad Health EIRs (None)

TPLC Detailed View

from 1/01/2009 to 8/30/2012



Product Code	**MRR**
Manufacturer	**LIPOSCIENCE**
Class	**1**
Regulation Device Classification	**Lipoprotein test system.**
Device Name	**SYSTEM, TEST, LOW DENSITY, LIPOPROTEIN**
Date Last Listed	**Not Listed**

CDRH Gen Docs with Manufacturer (None)

Premarket Reviews Completed (1)

CTS	K101023	NMR LIPOPROFILE TEST BY LIPOSCIENCE AND NMR PROFILER	NE	Kellie Kelm
Image	*FDA.GOV*			

Under Review, Withdrawn or Closed without Product Code (1)

CTS	K113830	VANTERA CHINIAL ANALYZER	Review	Elizabeth O'Keeffe
Image	*FDA.GOV*	INSTRUMENTATION FOR CLINICAL MULIPLEX TEST SYSTEMS		

Standards and Guidance (1)

Reference Number	Title	Contact	Relevant Guidance
C37-A	Preparation and Validation of Commutable Frozen Human Serum Pools as Secondary Reference Materials for Cholesterol Measurement Procedures; Approved Guideline	Carol C. Benson	Guidance for 510(K)s on Cholesterol Tests for Clinical Laboratory, Physician's Office Laboratory, and Home Use Guidance for Industry - Abbreviated 510 (K) Submissions for In Vitro Diagnostic Calibrators Points to Consider for Collection of Data in Support of In Vitro Device Submissions for 510(K) Clearance.

MDR Summary (None)

		Total
[redacted]	0	
Total		

MDR Analyst (1)

Yung Chan	yung.chan@fda.hhs.gov

MDR Distribution by Brand - Death or Injury (None)

Patient Problems (None)

Patient Outcomes (None)

Device Problems (None)

Manufacturer Evaluation Results (None)

Manufacturer Evaluation Conclusions (None)

Recalls (None)

Inspections (None)

CDRH Gen Docs without Manufacturer (None)

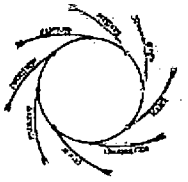
Rad Health Reports (None)

Rad Health Correspondence (None)

Rad Health Adverse Events (None)

Rad Health EIRs (None)

TPLC Detailed View from 1/01/2009 to 8/30/2012



Product Code	**NSU**
Manufacturer	**LIPOSCIENCE**
Class	**2**
Regulation Device Classification	**Instrumentation for clinical multiplex test systems**
Device Name	**INSTRUMENTATION FOR CLINICAL MULTIPLEX TEST SYSTEMS**
Date Last Listed	**Not Listed**

CDRH Gen Docs with Manufacturer (None)

Premarket Reviews Completed (None)

Under Review, Withdrawn or Closed without Product Code (1)

CTS	K113830	VANTERA CHINIAL ANALYZER	Review	Elizabeth O'Keeffe
Image	*FDA.GOV*	INSTRUMENTATION FOR CLINICAL MULIPLEX TEST SYSTEMS		

Standards and Guidance (None)

MDR Summary (None)

		Total
	0	
Total		

MDR Analyst (1)

MDR Distribution by Brand - Death or Injury (None)

Patient Problems (None)

Patient Outcomes (None)

Device Problems (None)

Manufacturer Evaluation Results (None)

Manufacturer Evaluation Conclusions (None)

Recalls (None)

Inspections (None)

CDRH Gen Docs without Manufacturer (1)

Link	Document / Type / Title / Manufacturer	Decision	Reviewer	Description

TPLC Detailed View from 1/01/2009 to 8/30/2012

Link	Document / Type / Title / Manufacturer	Decision	Reviewer	Description
CTS	GEN1200218/S001 / De Novo K113336 ALL	Approved Evaluation of Auto Class III Desig.	Beena Puri	The CDC DENV-1-4 Real-Time RT-PCR Assay provides for detection and typing of dengue virus (DENV) nucleic acid in suspected symptomatic cases of dengue

Rad Health Reports (None)

Rad Health Correspondence (None)

Rad Health Adverse Events (None)

Rad Health EIRs (None)

TPLC disclaimers

We are continuing to improve and enhance the TPLC Universe and the TPLC sheets. When more data is available we will update this message.

Please realize that in this initial release:

- *Recall data is only available since October, 2009.*
- In the Premarket Under Review section and the Recall section, the premarket submission or recall is only included if the product code is specified in CTS.
- The MDR count is a count of reports and contains duplicate reports.
- MDR track action or additional information letters is not available yet.
- EIR data related to inspections is not yet displayed.
- EIR data is accessed from CTS at this time, rather than FACTS.
- The TPLC name which consolidates variations on manufacturer names is not yet implemented.
- Publications are not yet linked in.
- Adverse events for radiation emitting products are submitted under 21 CFR 1002.20.
- Adverse events due to radiation problems for medical devices are submitted under 21 CFR 803.

We are working hard to address these issues and many can be addressed before the next release.

O'Keeffe, Elizabeth

From: Suzette Warner <suzette.warner@liposcience.com>
:nt: Thursday, August 30, 2012 2:00 PM
To: O'Keeffe, Elizabeth
Subject: Revised 510(k) Summary
Attachments: Sec 6 510(k) Summary 8-30-2012_(2).docx

Elizabeth
The revised 510(k) summary is attached. As discussed, I removed the references to the controls and calibrators in Section C.

Suzette M. Warner
Regulatory Affairs, Manager
O: 919-256-1326
Cell: 919-357-7801
LIPOSCIENCE
2500 Sumner Boulevard
Raleigh, NC 27616
Main: 877-547-6837

"It is not necessary to do extraordinary things to get extraordinary results."
Warren Buffett

Final Version

510(k) Summary

LIPOSCIENCE

A. 510(k) Number: _____

B. Submitter Contact Information:

Submitter:
LipoScience, Inc.
2500 Sumner Boulevard
Raleigh, NC 27616
Ph: (919) 256-1326
Fax: (919) 256-1149

Contact Person:
Suzette Warner
Manager, Regulatory Affairs
LipoScience, Inc.
Ph: (919) 256-1326
Fax: (919) 256-1149
Suzette.Warner@liposcience.com

C. Device Name:

Trade Name: Vantera® Clinical Analyzer
Common Name: *NMR LipoProfile®* test on Vantera® Clinical Analyzer
Classification Names:

Instrumentation for clinical multiplex test system, 21 CFR 862.2570, Product Code NSU
Lipoprotein test system, 21 CFR 862.1475, Product Code MRR and LBS
Cholesterol test system 21 CFR 862.1175, Product Code LBS
Triglyceride test system, 21 CFR 862.1705, Product Code CDT

Panel: Clinical Chemistry (75)

D. Legally Marketed Device to which Equivalence is Claimed (Predicate Device):

NMR Profiler and *NMR Lipoprofile* test	k111516
Luminex LX 100/200 Instrument	k073506

E. Device Description:

For the Instrument

The Vantera Clinical Analyzer is a clinical laboratory analyzer that employs nuclear magnetic resonance spectroscopic detection to quantify multiple analytes in biological fluid specimens, specifically blood plasma and serum.

The Vantera Clinical Analyzer system design is divided into 3 major subassemblies: a sample handling assembly, an NMR subassembly, and an enclosure. The Vantera Clinical Analyzer control system is distributed across three separate computers:

- The Host (1U) controls user interface, data handling, results calculation, system startup and shutdown.
- The Process Control (4U) schedules and manages all activities required to process a sample, controls all hardware in the sample handling subsystem, and manages remote access to the system.
- The NMR Control Computer controls all magnet operations.

  Two of these computers are contained within the Sample Handling Subassembly (1U and 4U) and one in the NMR Subassembly (NMR Console).

For the Assay

The *NMR LipoProfile* test involves measurement of the 400 MHz proton NMR spectrum of a plasma/serum sample, deconvolution of the composite signal at approximately 0.8 ppm to produce signal amplitudes of the lipoprotein subclasses that contribute to the composite plasma/serum signal, and conversion of these subclass signal amplitudes to lipoprotein subclass concentrations. The ~0.8 ppm plasma NMR signal arises from the methyl group protons of the lipids carried in the LDL, HDL and VLDL subclasses of varying diameters. The NMR signals from the various lipoprotein subclasses have unique and distinctive frequencies and lineshapes, each of which is accounted for in the deconvolution analysis model. Each subclass signal amplitude is proportional to the number of subclass particles emitting the signal, which enables subclass particle concentrations to be calculated from the subclass signal amplitudes derived from the spectral deconvolution analysis. LDL subclass particle concentrations, in units of nanomoles of particles per liter (nmol/L), are summed to give the reported total LDL particle concentration (LDL-P). By employing conversion factors assuming that the various lipoprotein subclass particles have cholesterol and triglyceride contents characteristic of normolipidemic individuals, HDL cholesterol and triglyceride concentrations are also derived.

F. Indications for Use

For the Instrument

The Vantera Clinical Analyzer is an automated laboratory test analyzer which measures the 400 MHz proton nuclear magnetic resonance (NMR) spectrum of clinical samples to produce signal amplitudes, converting these signal amplitudes to analyte concentration. The device includes a 400 MHz NMR spectrometer and software to analyze digitized

spectral data. This instrumentation is intended to be used with NMR based assays to detect multiple analytes from clinical samples by technologists trained in laboratory techniques, procedures and on the use of the analyzer.

For the Assay

The *NMR LipoProfile*test, when used with the Vantera Clinical Analyzer, an automated NMR spectrometer, measures lipoprotein particles to quantify LDL particle number (LDL-P), HDL cholesterol (HDL-C), and triglycerides in human serum and plasma using nuclear magnetic resonance (NMR) spectroscopy. LDL-P and these NMR-derived concentrations of HDL-C and triglycerides are used in conjunction with other lipid measurements and clinical evaluation to aid in the management of lipoprotein disorders associated with cardiovascular disease.

G. Technological Characteristics and Substantial Equivalence:

The Vantera Clinical Analyzer is as safe and effective as the predicate device, k073506. The Vantera has similar intended use and indication for use as well as the same multi-analyte capability and the same system calibration requirement as the predicate device. The minor technological differences between the Vantera and the predicate device raise no new issues of safety or effectiveness.

Instrument Comparison Table

	Luminex LX 100/200 Instrument **(Predicate)**	***Vantera Clinical Analyzer*** **(Proposed Device)**
510(k) Number	k073506	Pending
Intended Use / Indications for Use	The Luminex LX 100/200 Instrument is a clinical multiplex test system intended to measure and sort multiple signals generated in an *In Vitro* diagnostic assay from a clinical sample. This instrumentation is used with a specific assay to measure multiple similar analytes that establish a single indicator to aid in diagnosis. The device includes a signal reader unit, raw data storage mechanisms, data acquisition software and software to process detected signals.	similar
Technology	Bead based multiplexing	Nuclear magnetic resonance
Multi-Analyte	Yes	same
Detection Method	Fluorescent	400 MHz proton NMR Spectrum
System Fluidics	Utilizes system fluidics to deliver sample to the site of sample analysis	same
Specimen Sampling and Handling	Samples are manually prepared then presented to system.	Serum/Plasma Samples are diluted onboard system
System Calibration	System calibration required	same

	Luminex LX 100/200 Instrument **(Predicate)**	***Vantera Clinical Analyzer*** **(Proposed Device)**
Quality Control Checks	System level quality control checks available e.g. Classification (CON1) and reporter (CON2)	similar E.g. Signal to noise ratio – internal system check that occur during system calibration
Specimen Identification	Barcode reader entry of sample ID	same
Data Acquisition Software	Posses data acquisition software and software to process detected signals	same

Similarity to the Predicate Device (Assay)

Performance data further demonstrate that the Vantera Clinical Analyzer when used with the *NMR LipoProfile* test is as safe and effective as its predicate device, k111516. As with the predicate test, the NMR LipoProfile test on Vantera is intended for the separation and quantification of LDL-P, HDL-C and triglycerides in serum and plasma, measurements of which are used in conjunction with other lipid measurements and clinical evaluation to aid in the management of lipoprotein disorders associated with cardiovascular disease.

Assay General Attributes

	***LipoScience NMR LipoProfile®* test and NMR Profiler (Predicate)**	**Vantera® Clinical Analyzer for use with *NMR LipoProfile®* test (Proposed Device)**
510(k) Number	k111516	Pending
Intended Use / Indications for Use	The NMR LipoProfile® test, used with the NMR Profiler, an automated nuclear magnetic resonance (NMR) spectrometer, measures lipoprotein particles to quantify LDL particle number (LDL-P), HDL cholesterol (HDL-C), and triglycerides in serum and plasma using NMR spectroscopy. LDL-P and these NMR-derived concentrations of triglycerides and HDL-C are used in conjunction with other lipid measurements and clinical evaluation to aid in the management of lipoprotein disorders associated with cardiovascular disease. This test is performed and provided as a service by LipoScience Laboratory.	similar
Patient Population	General	same
Instrument Platform	NMR Profiler	Vantera Clinical Analyzer
Specimen	Human serum and plasma	same
Analyzer	400 MHz NMR Spectrometer	same

	***LipoScience NMR LipoProfile®* test and NMR Profiler (Predicate)**	**Vantera® Clinical Analyzer for use with *NMR LipoProfile®* test (Proposed Device)**
Reagents and Materials	• NMR Diluent 1 - aqueous solution containing Na_2EDTA (5.0mM), $CaCl_2$ (1.0mM), KCL(120mM), Na_2HPO_4-$7H_20$(50mM), (50mM), pH 7.4, 6.0 M NaOH, 1.0 M HCl. • NMR WASH - Triton X-100- 0.1%v/v, Liqui Nox 0.1% v/v in Type 2 water, pH 10.0, sodium bicarbonate (anhydrous), sodium carbonate (anhydrous), 6.0 M NaOH • NMR Calibrator - aqueous solution of Trimethyl Acetate (TMA) disodium salt (15.0 mM) containing Na_2EDTA (5.0 mM), CaC_2 (3.0 mM), KCl (120 nM), D_2O 10% v/v • NMR LipoProfile Quality Control materials 1 and 2 contains two levels of pooled human serum-based control material, labeled Control 1 and Control 2, with pre-determined target ranges, containing sodium azide as a preservative.	Similar

	***LipoScience* *NMR LipoProfile®* test and NMR Profiler (Predicate)**	**Vantera® Clinical Analyzer for use with *NMR LipoProfile®* test (Proposed Device)**
Spectral Deconvolution Computational Process	Linear least-squares with singular value decomposition of the spectra from each specimen.	Same
Reference Range	Distribution of LDL-P Observed in Reference population – MESA	Distribution of LDL-P observed in a general apparently healthy population of men and women

We performed analytical validations to demonstrate that the *NMR LipoProfile®* test on the Vantera Clinical Analyzer is equivalent to the *NMR LipoProfile®* test on the NMR Profiler. The comparative analytical performance is found in tables below.

Analytical Performance for LDL-P

LDL-P (nmol/L)	**Vantera clinical analyzer for use with the *NMR LipoProfile* test**			**Predicate Device k111516**		
LoB	0			0		
LoD	40.7			41		
LoQ	132			157		
Measuring Range	300-3500 nmol/L			300-3500 nmol/L		
Linearity Regression	y=1.02x+7.82			y=0.99x-22.37		
Linearity R^2	0.9949			0.9979		
Within-Run Precision	**Level 1**	**Level 2**	**Level 3**	**Level 1**	**Level 2**	**Level 3**
Mean	842.6	1309.5	1837.7	908	1493	1967
SD	48.5	39.1	50.3	45.4	64.8	72.8
CV%	5.8%	3.0%	2.7%	5.0%	4.3%	3.7%
Within-Lab Precision	**Level 1**	**Level 2**	**Level 3**	**Level 1**	**Level 2**	**Level 3**
Mean	988.6	1266.7	1943.5	920.4	1508.3	1991.8
SD	48.84	32.57	63.42	70.5	67.7	84.6
CV%	5.3%	4.0%	3.9%	7.6%	4.5%	4.3%
Method Comparison	Linear regression: y=1.03x-36.60, R=0.978			Linearity Regression: y=0.98x+45.2, R=0.973		
Medical Decision Limits	No change.			1000, 1300 and 1600 nmol/L		
Interference Study	7 Endogenous and 23 Exogenous were tested. Salicyclic acid at ≥ 1.3mmol/L was determined to interfere with LDL-P and Clopidogrel hydrogensulfate at ≥ 95.7 µmol/L was determined to interfere with LDL-P			5 Endogenous and 22 Exogenous were tested, no interference was found.		
Specimen Stability	Lipotube: Refrigerated Stability: 6 days			Lipotube: Refrigerated Stability: 5 days		

Triglycerides Analytical Performance Summary

TG (mg/dL)	Vantera clinical analyzer for use with the *NMR LipoProfile* test			Predicate Device k111516		
LoB	1.1			1.4		
LoD	2.4			2.6		
LoQ	4			2.6		
Measuring Range	5			1100		
Linearity Regression	y=1.008x-0.3979			y=0.95x-12.21		
Linearity R^2	0.9999			0.999		
Within-Run Precision	**Level 1**	**Level 2**	**Level 3**	**Level 1**	**Level 2**	**Level 3**
Mean	70.1	169.2	356.1	81.0	140.6	649.5
SD	1.6	3.5	4.2	2.1	2.5	8.7
CV%	2.3%	2.1%	1.2%	2.6%	1.8%	1.3%
Within-Lab Precision	**Level 1**	**Level 2**	**Level 3**	**Level 1**	**Level 2**	**Level 3**
Mean	68.8	166.3	352.2	78.4	145.4	624.6
SD	1.59	3.92	9.36	2.8	3.7	15.4
CV%	2.3%	2.4%	2.7%	3.6%	2.6%	2.5%
Method Comparison	Linear regression: y=1.00x+0.92, R=0.998			Linear regression: y=1.00x+1.25, R=1.00		
Medical Decision Limits	No change.			Normal (<150) Borderline-High (150-199) High (200-499) Very High (≥500)		
Interference Study	7 Endogenous and 23 Exogenous were tested, no interference was found.			5 Endogenous and 22 Exogenous were tested, no interference was found except Ibuprofen may interfere with TG measurement at and above 210µg/mL.		
Specimen Stability	Lipotube: Refrigerated Stability: 6 days			Lipotube: Refrigerated Stability: 10 days		

HDL-C Analytical Performance Summary

HDL-C (mg/dL)	Vantera clinical analyzer for use with the *NMR LipoProfile* test			Predicate Device k111516		
LoB	2.7			4.3		
LoD	3.5			5.2		
LoQ	4			5.2		
Measuring Range	7-140			7-140		
Linearity Regression	y=1.049x-0.3459			y=1.004x-0.5956		
Linearity R^2	0.9961			0.9998		
Within-Run Precision	**Level 1**	**Level 2**	**Level 3**	**Level 1**	**Level 2**	**Level 3**
Mean	29.1	51.1	86.9	23.7	54.9	95.1
SD	1.17	1.43	2.29	0.5	1.0	0.9
CV%	4.0%	2.8%	2.6%	2.0%	1.9%	0.9%
Within-Lab Precision	**Level 1**	**Level 2**	**Level 3**	**Level 1**	**Level 2**	**Level 3**
Mean	28.9	50.7	85.2	23.7	56.7	96.1
SD	0.80	1.02	1.51	0.8	1.1	1.7
CV%	2.8%	2.0%	1.8%	3.3%	2.0%	1.8%
Method Comparison	Linear regression: y=1.04x-1.20, R=0.989			Linear regression: y=1.00x+0.03, R=0.999		
Medical Decision Limits	No change.			Low(<40), High(≥60)		
Interference Study	7 Endogenous and 23 Exogenous were tested, no interference was found.			5 Endogenous and 22 Exogenous were tested, no interference was found.		
Specimen Stability	Lipotube: Refrigerated Stability: 6 days			Lipotube: Refrigerated Stability: 10 days		

H. Performance Data – Non-Clinical:

Analytical Sensitivity

The analytical sensitivity of the *NMR LipoProfile* test measurements of LDL-P, HDL-C, and triglycerides was determined as the lowest concentration measurable with acceptable precision and accuracy. Limits of quantification (LoQ), Limit of Blank (LoB) and Limit of Detection (LoD) for LDL-P, HDL-C and Triglycerides following EP17-A are listed

LDL-P
Five serum pools containing very low concentration were tested in replicates of 4 for 3 days. The Limit of Quantification (LoQ) was mathematically calculated for LDL-P by plotting the %CV on the Y-axis against low concentration pools and determined to be: LoQ = 132 nmol/L.
Non-lipoprotein specimens were analyzed 60 consecutive times for 3 days. The Limit of Blank (LoB) was calculated non-parametrically for LDL-P and determined to be: LoB = 0.0 nmol/L.
Five serum pools containing very low concentration were tested in replicates of 4 for 3 days. The Limit of Detection (LoD) was calculated parametrically for LDL-P and determined to be: LoD = 40.7 nmol/L.

HDL-C
Five serum pools containing very low concentration were tested in replicates of 4 for 3 days. The Limit of Quantification (LoQ) was mathematically calculated for HDL-C by plotting the %CV on the Y-axis against low concentration pools and determined to be: LoQ = 4 mg/dL.
Non-lipoprotein specimens were analyzed 60 consecutive times for 3 days. The Limit of Blank (LoB) was calculated non-parametrically for HDL-C and determined to be: LoB = 2.7 mg/dL.
Five serum pools containing very low concentration were tested in replicates of 4 for 3 days. The Limit of Detection (LoD) was calculated parametrically for HDL-C and determined to be: LoD = 3.5 mg/dL.

Triglycerides
Five serum pools containing very low concentration were tested in replicates of 4 for 3 days. The Limit of Quantification (LoQ) was mathematically calculated for Triglycerides by plotting the %CV on the Y-axis against low concentration pools and determined to be: LoQ = 4 mg/dL.
Non-lipoprotein specimens were analyzed 60 consecutive times for 3 days. The Limit of Blank (LoB) was calculated non-parametrically for Triglycerides and determined to be: LoB = 1.1 mg/dL.
Five serum pools containing very low concentration were tested in replicates of 4 for 3 days. The Limit of Detection (LoD) was calculated parametrically for Triglycerides and determined to be: LoD = 2.4 mg/dL.

Assay Precision

Within-run precision and within-laboratory precision were determined by testing 20 replicates of three patient serum pools in the same run and in 20 different runs over 20 days. The pools were analyzed according to EP-5A. The results of this testing are summarized below:

Within-run Precision (n=20)

	Pool #1			Pool #2			Pool #3		
	Mean	**SD**	**%CV**	**Mean**	**SD**	**%CV**	**Mean**	**SD**	**%CV**
LDL-P, nmol/L	842.6	48.5	5.8	1309.5	39.1	3.0	1837.7	50.3	2.7
HDL-C, mg/dL	29.1	1.17	4.0	51.1	1.43	2.8	86.9	2.29	2.6
Triglycerides, mg/dL	70.1	1.6	2.3	169.2	3.5	2.1	356.1	4.2	1.2

Within-Laboratory Precision (n=80)

	Pool #1			Pool #2			Pool #3		
	Mean	**SD**	**%CV**	**Mean**	**SD**	**%CV**	**Mean**	**SD**	**%CV**
LDL-P, nmol/L	988.6	52.20	5.3	1266.7	50.08	4.0	1943.5	75.11	3.9
HDL-C, mg/dL	28.9	0.80	2.8	50.7	1.02	2.0	85.2	1.51	1.8
Triglycerides, mg/dL	68.8	1.59	2.3	166.3	3.92	2.4	352.2	9.36	2.7

Reproducibility

A reproducibility study was conducted in accordance to EP5-A2 at 3 sites incorporating five levels of serum panels at or around the medical decision limits. The panels were tested for 5 days, 6 runs per day, 2 replicates per run. The overall precision estimates are described below.

	LDL-P (nmol/L)				
Pool #	**1**	**11**	**7**	**3**	**9**
NMR 8001	**Panel 1**	**Panel 2**	**Panel 3**	**Panel 4**	**Panel 5**
Mean (nmol/L)	513.4	1129.4	1361.6	1957.7	3286.5
n	60	60	60	59	60
SD (nmol/L)	32.86	65.60	87.36	103.55	197.94
CV (%)	6.4	5.8	6.4	5.3	6.0
min (nmol/L)	431	988	1163	1641	2938
max (nmol/L)	573	1318	1510	2179	3636
median (nmol/L)	517	1127	1380.5	1962	3288.5
NMR 8002	**Panel 1**	**Panel 2**	**Panel 3**	**Panel 4**	**Panel 5**
Mean (nmol/L)	566.7	1260.6	1364.5	2050.7	3204.7
n	59	60	59	59	60
SD (nmol/L)	39.22	38.00	76.99	65.41	85.41
CV (%)	6.9	3.0	5.6	3.2	2.7
min (nmol/L)	457	1168	1155	1843	3036
max (nmol/L)	660	1346	1555	2176	3419
median (nmol/L)	574	1258.5	1366	2050	3197
NMR 8003	**Panel 1**	**Panel 2**	**Panel 3**	**Panel 4**	**Panel 5**
Mean (nmol/L)	479.8	1156.3	1304.4	1980.6	3153.3
n	58	60	60	60	60
SD (nmol/L)	45.00	70.60	113.21	91.78	165.47
CV (%)	9.4	6.1	8.7	4.6	5.2
min (nmol/L)	388	871	891	1671	2561
max (nmol/L)	558	1255	1491	2136	3386
median (nmol/L)	485.5	1167	1337	1999	3192
All	**Panel 1**	**Panel 2**	**Panel 3**	**Panel 4**	**Panel 5**
Mean (nmol/L)	520.2	1182.1	1343.4	1996.2	3214.8
n	177	180	179	178	180
SD (nmol/L)	52.94	82.19	97.37	96.39	165.44
95% CI (nmol/L)	47.94- 59.11	74.48-91.68	88.22- 108.66	87.31- 107.59	149.93- 184.55
CV (%)	10.2	7.0	7.2	4.8	5.1
min (nmol/L)	388	871	891	1641	2561
max (nmol/L)	660	1346	1555	2179	3636
median (nmol/L)	491	1165	1330	2006	3179

	HDL-C (mg/dL)				
Pool #	**1**	**8**	**4**	**10**	**11**
NMR 8001	**Panel 1**	**Panel 2**	**Panel 3**	**Panel 4**	**Panel 5**
Mean (mg/dL)	21.5	33.4	53.7	80.1	92.1
n	60	60	60	60	60
SD (mg/dL)	0.75	1.39	1.81	3.70	2.61
CV (%)	3.5	4.2	3.4	4.6	2.8
min (mg/dL)	20	30	49	74	87
max (mg/dL)	23	36	57	88	97
median (mg/dL)	21.5	34	54	78.5	92
NMR 8002	**Panel 1**	**Panel 2**	**Panel 3**	**Panel 4**	**Panel 5**
Mean (mg/dL)	19.4	29.2	52.3	72.9	87.5
n	59	60	60	60	60
SD (mg/dL)	0.68	1.13	1.34	1.49	1.28
CV (%)	3.5	3.9	2.6	2.0	1.5
min (mg/dL)	17	27	48	70	85
max (mg/dL)	21	31	56	76	90
median (mg/dL)	19	29	52	73	88
NMR 8003	**Panel 1**	**Panel 2**	**Panel 3**	**Panel 4**	**Panel 5**
Mean (mg/dL)	19.4	28.3	49.9	74.4	84.9
n	58	60	60	60	60
SD (mg/dL)	0.90	1.41	2.36	4.26	3.39
CV (%)	4.6	5.0	4.7	5.7	4.0
min (mg/dL)	17	24	41	66	72
max (mg/dL)	21	31	53	83	89
median (mg/dL)	19	28	50	73	86
All	**Panel 1**	**Panel 2**	**Panel 3**	**Panel 4**	**Panel 5**
Mean (mg/dL)	20.1	30.3	52.0	75.8	88.2
n	177	180	180	180	180
SD (mg/dL)	1.26	2.60	2.45	4.56	3.91
95% CI (mg/dL)	1.14- 1.41	2.35- 2.90	2.22- 2.73	4.14- 5.09	3.55- 4.36
CV (%)	6.3	8.6	4.7	6.0	4.4
min (mg/dL)	17	24	41	66	72
max (mg/dL)	23	36	57	88	97
median (mg/dL)	19	28	50	73	86

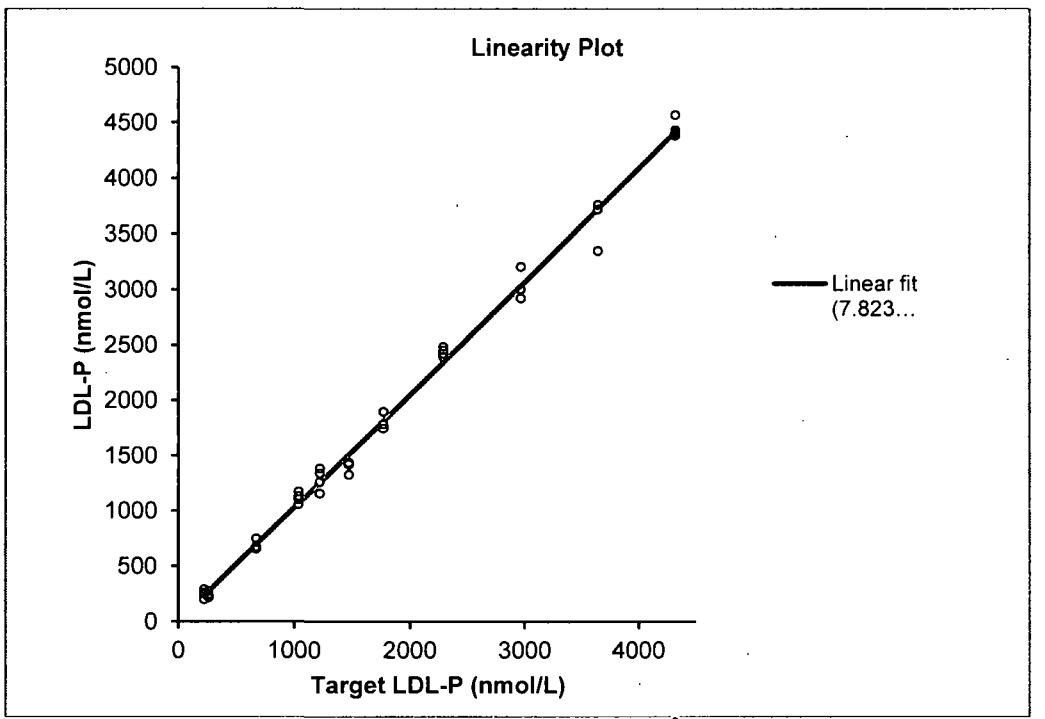
	TG (mg/dL)				
Pool #	**2**	**4**	**3**	**6**	**9**
NMR 8001	**Panel 1**	**Panel 2**	**Panel 3**	**Panel 4**	**Panel 5**
Mean (mg/dL)	66.1	70.3	133.5	153.5	343.3
n	60	60	59	60	60
SD (mg/dL)	1.84	2.15	4.35	5.92	7.09
CV (%)	2.8	3.1	3.3	3.9	2.1
min (mg/dL)	61	64	120	129	321
max (mg/dL)	69	73	141	163	356
median (mg/dL)	66	71	134	155	345
NMR 8002	**Panel 1**	**Panel 2**	**Panel 3**	**Panel 4**	**Panel 5**
Mean (mg/dL)	70.3	74.6	141.4	169.7	361.1
n	59	60	59	60	60
SD (mg/dL)	1.30	1.59	3.03	3.10	5.01
CV (%)	1.8	2.1	2.1	1.8	1.4
min (mg/dL)	68	72	131	160	341
max (mg/dL)	74	82	149	176	372
median (mg/dL)	70	74	142	170	361
NMR 8003	**Panel 1**	**Panel 2**	**Panel 3**	**Panel 4**	**Panel 5**
Mean (mg/dL)	66.5	70.4	134.3	160.9	339.8
n	60	60	60	60	60
SD (mg/dL)	2.70	3.44	4.77	7.10	18.50
CV (%)	4.1	4.9	3.5	4.4	5.4
min (mg/dL)	57	58	119	123	267
max (mg/dL)	71	74	145	169	357
median (mg/dL)	67	72	135	162	346
All	**Panel 1**	**Panel 2**	**Panel 3**	**Panel 4**	**Panel 5**
Mean (mg/dL)	67.6	71.8	136.4	161.4	348.0
n	179	180	178	180	180
SD (mg/dL)	2.76	3.21	5.41	8.66	14.99
95% CI (mg/dL)	2.50-3.08	2.91- 3.59	4.90- 6.03	7.75- 9.66	13.59- 16.72
CV (%)	4.1	4.5	4.0	5.4	4.3
min (mg/dL)	57	58	119	123	267
max (mg/dL)	74	82	149	176	372
median (mg/dL)	67	71	135	162	344

Linearity

Three serum pools were prepared from patient specimens with low, medium and high values of LDL-P, HDL-C and Triglycerides as determined by *NMR LipoProfile* test. Each were mixed and diluted in different proportions to produce eleven (for LDL-P) or Twelve (12) (TG and HDL-C) different samples with widely varying target concentrations. Mean values from analysis of four replicates of each pool were compared to the expected target values to determine the percent bias for each sample. The serum pools were analyzed according to EP6-A. Tables and regression plots of the linearity data for LDL-P, HDL-P and Triglycerides are given below:

LDL-P Measuring Range: 300-3500 nmol/L

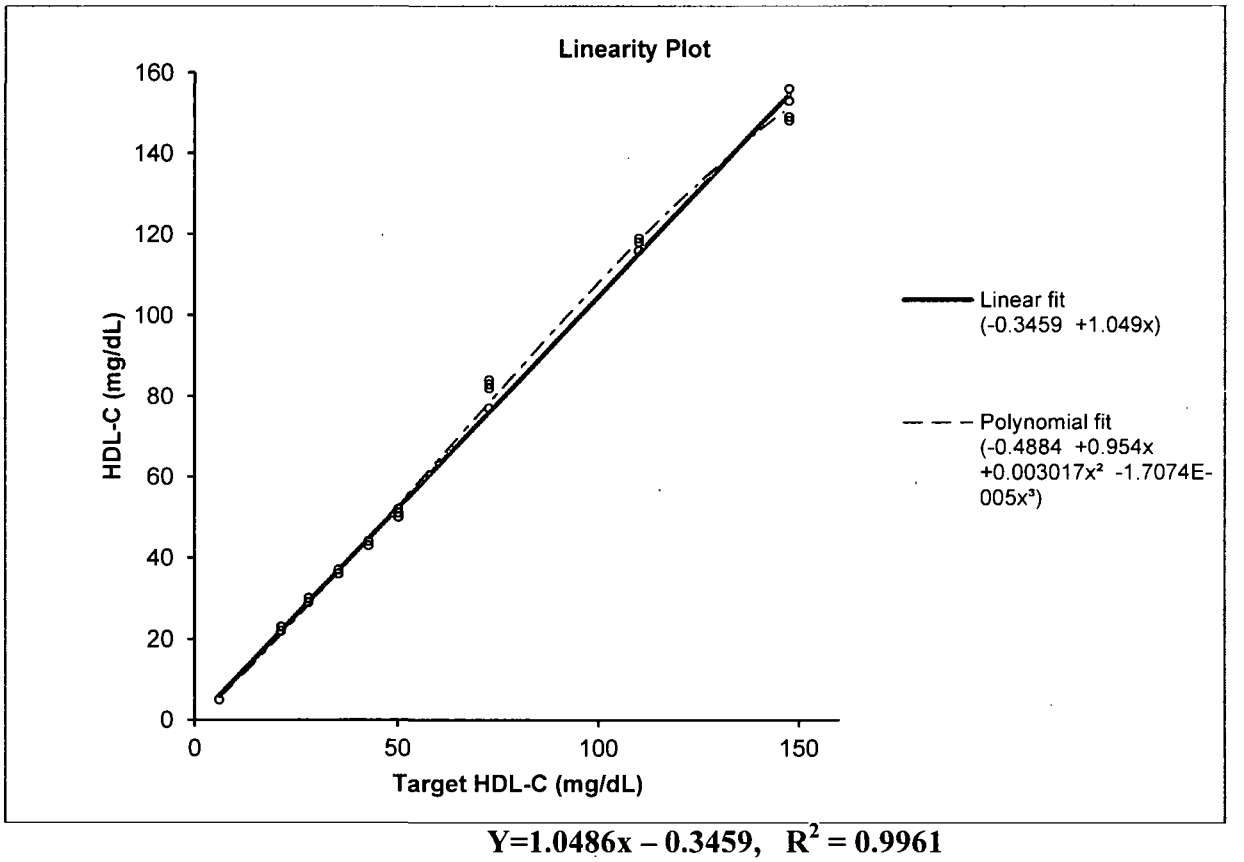
Level	1	2	3	4	5	6	7	8	9	10	11
Target value	225.4	263.375	673.75	1039.25	1222	1473.28	1770.25	2291.41	2968.22	3645.03	4321.84
Observed Mean	248.8	243.8	682.0	1115.0	1285.8	1402.3	1829.8	2437.5	3032.3	3644.3	4442.8
% Bias	10.3	-7.5	1.2	7.3	5.2	-4.8	3.4	6.4	2.2	0.0	2.8



$Y=1.0193x + 7.8226$, $R^2 = 0.9949$

HDL-C Measuring Range: 7-140 mg/dL

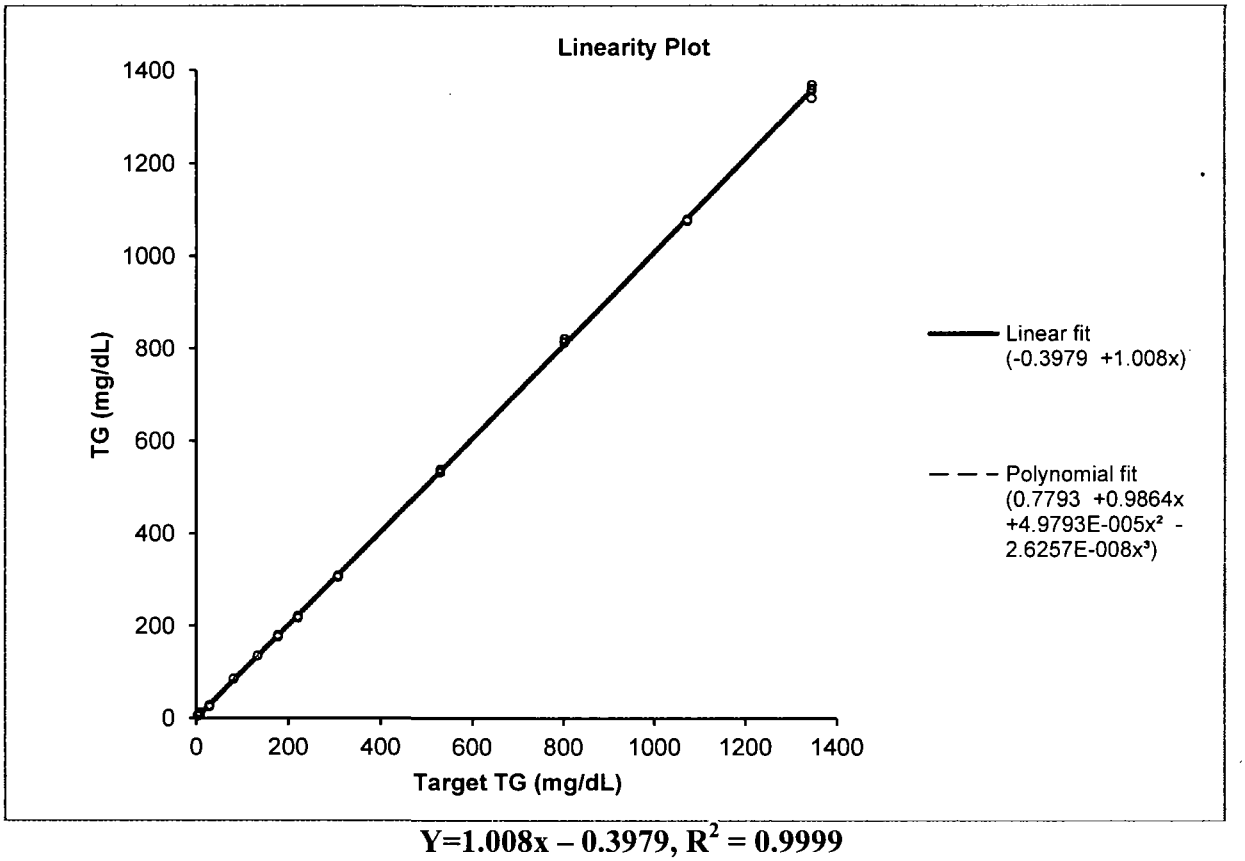
Level	1	2	3	4	5	6	7	8	9
Target value	6.13	21.44	28.19	35.56	42.94	50.31	72.75	110.25	147.75
Observed Mean	5.00	22.50	29.25	36.25	43.25	50.75	81.50	117.25	151.50
% Bias	-	5.0	3.8	1.9	0.7	0.9	12.0	6.3	2.5



$Y=1.0486x - 0.3459$, $R^2 = 0.9961$

Triglycerides Measuring Range: 5-1100 mg/dL

Level	1	2	3	4	5	6	7	8	9	10	11	12	13
Target value	3.8	5.1	9.2	29.0	82.5	134.6	178.1	221.5	308.4	531.0	802.6	1074.2	1345.7
Observed average	5.5	6.8	11.0	26.3	84.5	135.0	177.8	219.3	306.0	536.0	816.8	1079.0	1356.3
% Bias	43.1	31.7	19.2	-9.5	2.4	0.3	-0.2	-1.0	-0.8	0.9	1.8	0.5	0.8



$Y=1.008x - 0.3979$, $R^2 = 0.9999$

Reportable Range

The following are the reportable ranges for LDL-P, HDL-C and Triglycerides:

LDL-P	300 – 3500 nmol/L
HDL-C	7 – 140 mg/dL
Triglycerides	5 – 1100 mg/dL

Traceability, Stability, Assigned values (controls, calibrators)

The NMR Reference Standard

The NMR Reference Standard, TMA (Trimethylacetic acid, Sodium salt), is used as the NMR calibrator for the Vantera Clinical Analyzer. TMA is used routinely as a calibrator once daily during instrument startup to establish daily normalization factors. It also serves as a quality assessment tool to ensure quality NMR spectra are produced by the NMR analyzer.

The stability of the TMA calibrator material and storage conditions was evaluated for a period of 18 months across multiple NMR Analyzers. It was stored at room temperature and refrigerated at 4°C, in glass bottles and plastic bottles. TMA samples were evaluated for TMA signal methyl integrals every other month. The quality of the TMA spectra was not affected by the storage conditions during the study. The NMR Reference Standard is stable for 18 months in either glass or plastic bottle regardless of room temperature or refrigerated storage.

Liquichek™ Lipids Control

Liquichek™ Lipids Control material for LDL-P is frozen human serum in two pools, Level 1 and Level 2, prepared and packaged by Bio-Rad Laboratories. To assign values, new lots of Liquicheck™ Lipids Control material are run on 3 qualified Vantera Clinical Analyzers in house for 3 days. Means, Standard Deviations and % CVs are computed and new values are assigned.
The Liquicheck™ Lipids Control material is stable up to 6 months. Change in recovery over this period was estimated to be less than 0-6% for LDL-P.

Interfering Substances

Endogenous substances normally found in blood and exogenous substances (common and prescription drugs) were evaluated for potential interference with the *NMR LipoProfile®* test by LipoScience. Seven endogenous agents and twenty three drugs were screened for potential interfering effects to *NMR LipoProfile* test using concentrations in accordance to CLSI EP7-A2 guidelines.

Endogenous		***Exogenous (OTC drugs, etc.)***			
Potential Interferent	***Test Concentration***	***Potential Interferent***	***Test Concentration***	***Potential Interferent***	***Test Concentration***
Hemoglobin	0.5 g/dL	Acetaminophen	1324 µmol/L	Metformin Hydrochloride	3.62 mmol/L
Bilirubin, unconj.	342 µmol/L 20 mg/dL	Acetylsalicylic acid	3.62 mmol/L	Metoprolol tartrate	18.7 µmol/L
Creatinine	442 µmol/L 5 mg/dL	Atorvastatin	600 µg Eq/L	Naproxen Sodium	2170 µmol/L
Urea	42.9 mmol/L 260 mg/dL	Clopidogrel hydrogensulfate**	95.7 µmol/L	Nicotinic Acid Sodium salt	8.28 mmol/L
Uric acid	1.4 mmol/L 23.5 mg/dL	Enalaprilat Dihydrate	0.86 µmol/L	Nifedipine	1156 nmol/L
Protein (albumin)	6 g/dL60g/L	Fenofibrate	125 µmol/L	Pioglitazone hydrochloride	152.7µmol/L
Bilirubin, conj	342 µmol/L 28.9 mg/dL	Furosemide	181 µmol/L	Piroxicam	181 µmol/L
		Glipizide	4.48 µmol/L	Pravastatin	107.5 µmol/L
		Hydralazine hydrochloride	915.4 µmol/L	Salicylic Acid*	1.3 mmol/L
		Heparin	3000U/L	Simvastatin	114.7 µmol/L
		Ibuprofen Sodium salt	2425 µmol/L		
		Isosorbide dinitrate	636 nmol/L		
		Menhaden oil (Fish Oil)	2.4 mg/mL		

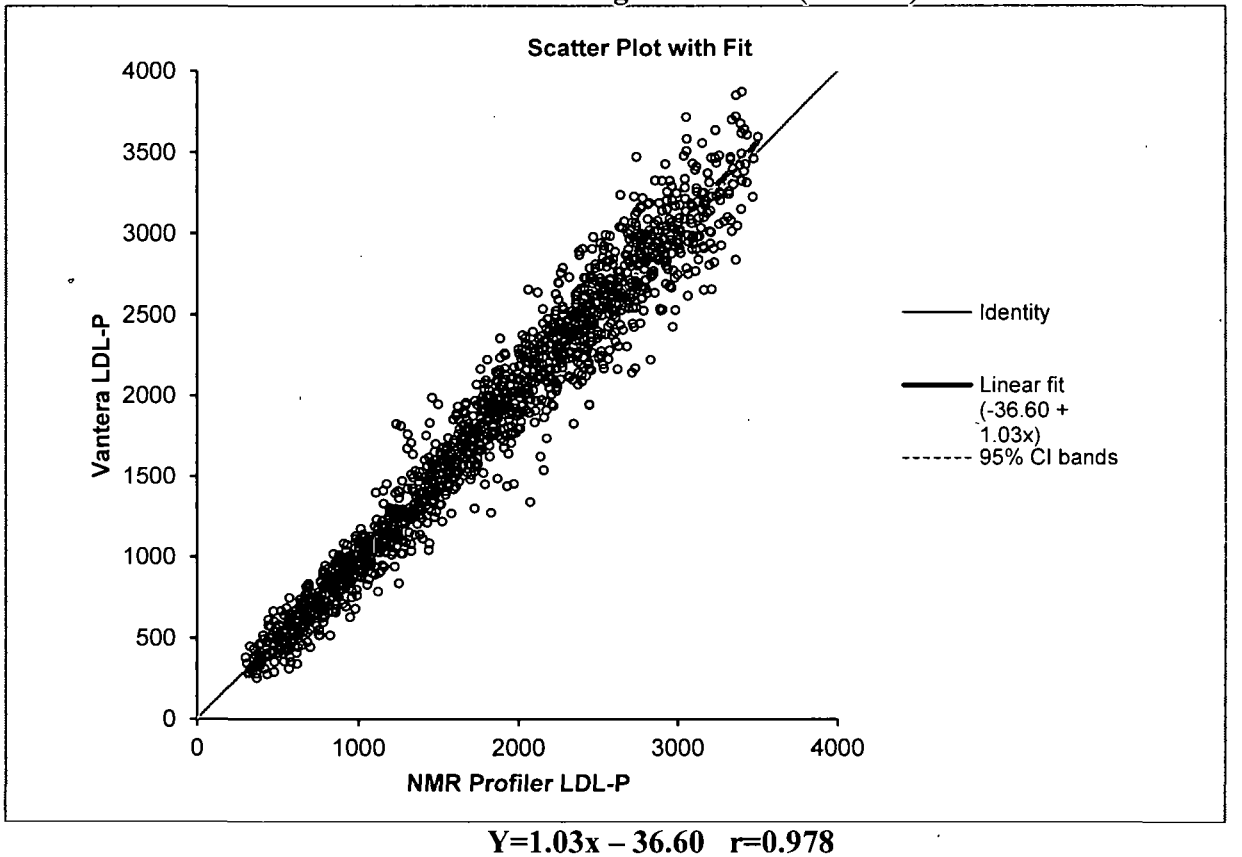
*Salicyclic acid at ≥ 1.3mmol/L was determined to interfere with LDL-P
**Clopidogrel hydrogensulfate at ≥ 95.7 µmol/L was determined to interfere with LDL-P

H. Method Comparison – Non-Clinical:

Method Comparison – LDL-P

Method comparison was evaluated by using serum samples across the reportable range of the *NMR LipoProfile* test for LDL-P on the Vantera Clinical Analyzer. LDL-P concentrations ranged from 303.0 to 3505.0nmol/L.

Vantera vs. NMR Profiler LDL-P Linear Regression Plot (n=1483)

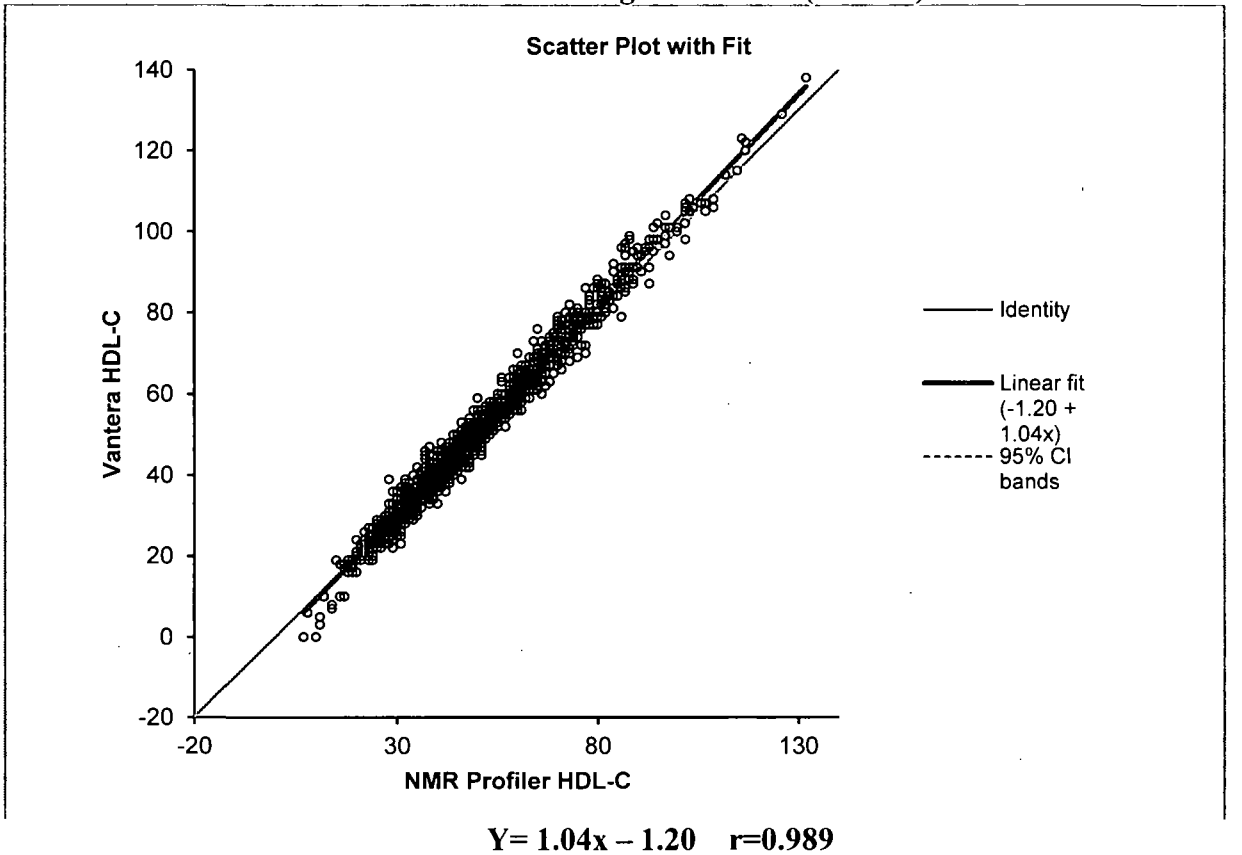


Y=1.03x – 36.60 r=0.978

Method Comparison – HDL-C

Method comparison was evaluated by using serum samples across the reportable range of the *NMR LipoProfile* test for HDL-C on the Vantera Clinical Analyzer. HDL-C concentrations ranged from 7.0 to 132 mg/dL.

Vantera vs. NMR Profiler HDL-C Linear Regression Plot (n=1518)

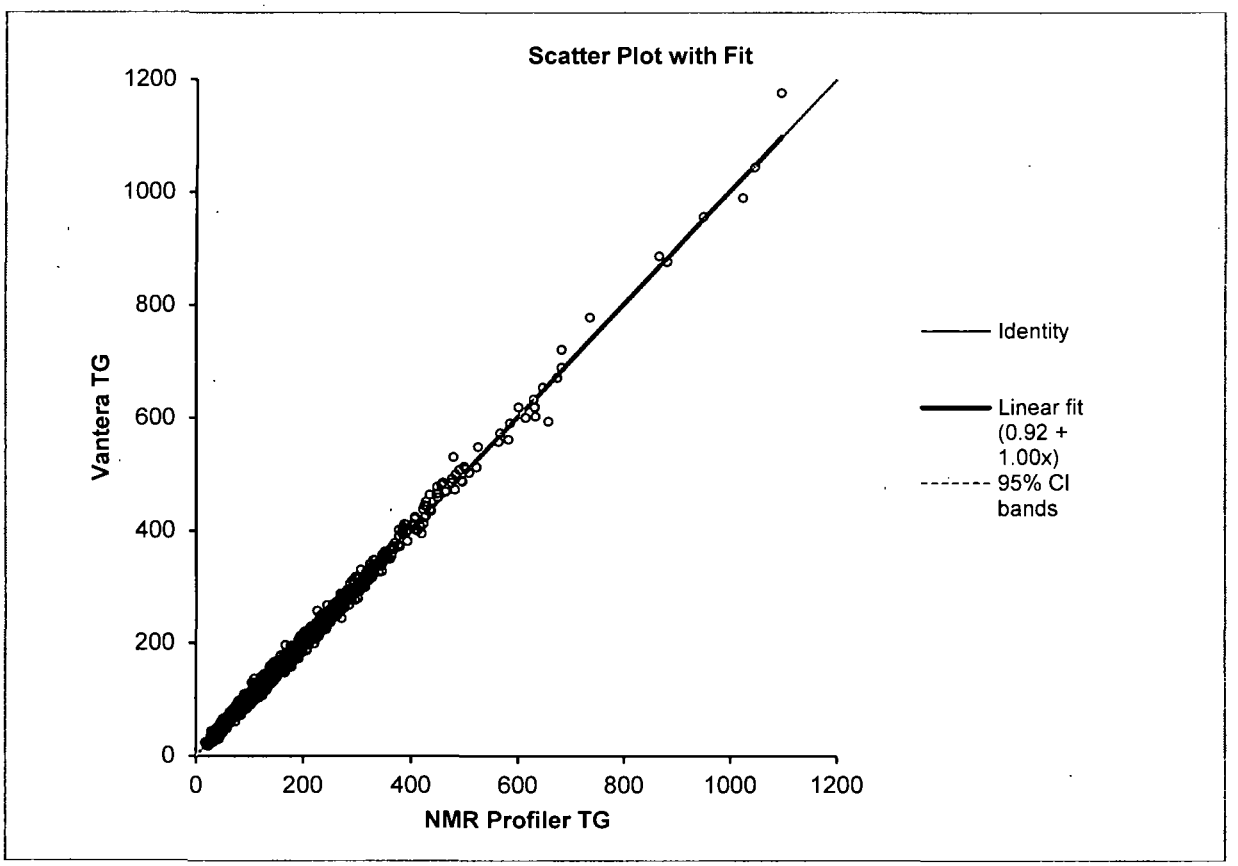


Y= 1.04x – 1.20 r=0.989

Method comparison Triglycerides

Method comparison was evaluated by using serum samples across the reportable range of the *NMR LipoProfile* test for Triglycerides on the Vantera Clinical Analyzer. Triglyceride concentrations ranged from 18.0 to 1095.0 mg/dL.

Vantera vs. NMR Profiler TG Linear Regression Plot (n=1520)



Y=1.00x + 0.92 r=0.998

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

Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices.

Class II Special Controls Guidance Document: Instrumentation for Clinical Multiplex Test Systems

EP5-A2: Evaluation of Precision Performance of Quantitative Measurement Methods; Approves Guideline – Second Edition

EP6-A: Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline

EP7-A2: Interference Testing in Clinical Chemistry; Approved Guideline – Second Edition

EP9-A2: Method Comparison and Bias Estimation Using Patient Samples; Approved Guideline – Second Edition

EP17-A: Protocols for Determination of Limits of Detection and Limits of Quantification; Approved Guideline

EP14-A2: Evaluation of Matrix Effects: Approved Guideline – Second Edition

C28-A3: Defining, Establishing, and Verifying Reference Intervals in the Clinical

C53-A: Characterization and Qualification of Commutable Reference Materials for Laboratory Medicine; Approved Guideline

IEC 61010-1:2001-2nd Edition: Safety requirements for electrical equipment for measurement, control and laboratory use Part: General requirements

This device has not been tested by the Cholesterol Reference Method Laboratory Network.

M. 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

1. Clinical cut-off:

Not Applicable

2. Expected values/Reference range:

In order to determine the distribution of LDL-P levels expected in a representative sampling of the general population, serum samples (n=452) were analyzed from apparently healthy men (n=158) and women (n=294) (ranging from 18 to 84 years). The following table provides the concentrations of LDL-P by percentile in this reference population:

Distribution of LDL-P Observed in a Reference Population

	All (n=452)	Men (n=158)	Women (n=294)	All (n=452)	Men (n=158)	Women (n=294)
Percentile	LDL-P (nmol/L)	LDL-P (nmol/L)	LDL-P (nmol/L)	LDL-C (mg/dL)	LDL-C (mg/dL)	LDL-C (mg/dL)
5	539	528	542	63	62	65
10	643	713	638	75	76	75
20	784	883	749	84	90	83
30	909	1004	863	94	100	91
40	1009	1087	970	102	107	98
50	1127	1241	1070	109	113	109
60	1248	1366	1202	118	128	115
70	1396	1505	1322	129	137	124
80	1572	1676	1482	140	147	136
90	1894	1941	1818	157	161	151
95	2047	2169	1986	169	171	169

Based on the recommendations from a National Lipids Association expert panel, suggested reference values are provided in Table 2. The recommendation by the NLA has not been validated by a clinical study. Each laboratory should verify the validity of these reference values for the population it serves.

Recommended LDL-P Reference Values

LDL-P, nmol/L			
Classification			
	Intermediate		
Low / Normal	*Moderate*	*Borderline High*	*High*
< 1000	1000-1299	1300-1599	≥ 1600

HDL Cholesterol and Triglycerides
The following reference values for patient classification have been recommended by the NCEP and Adult Treatment Panel III Guidelines for HDL cholesterol and triglycerides for the assessment and management of CVD risk. Each laboratory should verify the validity of these reference values for the population it serves.

HDL Cholesterol, mg/dL	
Classification	
Low	*High*
< 40	≥ 60

Triglycerides, mg/dL			
Classification			
Normal	*Borderline High*	*High*	*Very High*
< 150	150-199	200-499	≥ 500

O. System Description:

1. Modes of Operation:

   The Vantera Clinical Analyzer is a 400 MHz proton nuclear magnetic resonance spectrometer.

2. Software:

   The FDA has reviewed the applicant's Hazard Analysis and software development process for this line of product type:

   Yes _____ No_____

3. Specimen Identification:

   Bar code of source tube

4. Specimen Sampling and Handling:

   The processing of specimens on the Vantera Clinical Analyzer starts with their placement on the system. The user places serum or plasma specimen tubes in racks, and then places the racks on the system. After reading the bar code on a specimen tube, the system schedules the test or tests to be performed. The specimen is then aliquoted by the Metering Arm and is transferred to a dilution cup. Samples are prepared by diluting 2-fold (1:1) with specimen Diluent 1 performed by the Metering Arm assembly.

5. Calibration:

   The instrument is calibrated with an aqueous solution of Trimethyl Acetate (TMA) as a disodium salt (15.0 mM) containing Na_2EDTA (5.0 mM), $CaCl_2$ (3.0 mM), KCl (120mM), D_2O 10% v/v.

6. Quality Control:

   It is recommended that two levels of quality control materials are tested in the same manner as patient samples, before or during patient sample processing for each analyte being tested. To verify system performance, analyze control materials:

- After calibration
- According to federal, state or local regulations or at least once every day when patient testing is being performed.

Refer to the Liquichek™ Lipids Controls LDL-P value assignment card for LDL-P Target Ranges. It is recommended that each laboratory establish its own mean and acceptance range for each new lot of controls. Patient results should not be reported if the Quality Control values are not within the expected range.

Real-time quality control data indicate that stability for BioRad Liquichek Lipids controls is at least 6 months. A stability study is currently ongoing to extend the dating for the Bio-Rad Liquichek Lipids Controls.

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.

O'Keeffe, Elizabeth

From: Suzette Warner <suzette.warner@liposcience.com>
nt: Thursday, August 30, 2012 10:45 AM
To: O'Keeffe, Elizabeth
Subject: Final Documents
Attachments: Vantera Clinical Analyzer - NMR LipoProfile test PI Final 8-30-2012.docx; Sec 6 510(k) Summary 8-30-2012.docx

Elizabeth
Here are the Package Insert and the 510(k) Summary.

Thank you for your support and let us know if you need anything else.

Suzette M. Warner
Regulatory Affairs, Manager
O: 919-256-1326
Cell: 919-357-7801
LIPOSCIENCE
2500 Sumner Boulevard
Raleigh, NC 27616
Main: 877-547-6837

"It is not necessary to do extraordinary things to get extraordinary results."
Warren Buffett

Final Version

NMR LIPOPROFILE® test

NMR *LipoProfile*® test on Vantera® Clinical Analyzer by LipoScience

For *In Vitro* Diagnostic Use Only

INTENDED USE

The *NMR LipoProfile*® test by LipoScience, used with Vantera® Clinical Analyzer, an automated NMR spectrometer, measures lipoprotein particles to quantify LDL particle number (LDL-P), HDL cholesterol (HDL-C), and triglycerides (TG) in serum and plasma using nuclear magnetic resonance (NMR) spectroscopy. LDL-P and these NMR-derived concentrations of triglycerides and HDL-C are used in conjunction with other lipid measurements and clinical evaluation to aid in the management of lipoprotein disorders associated with cardiovascular disease.

SUMMARY AND EXPLANATION

Lipoprotein (HDL, LDL, and VLDL) particles play key roles in atherogenesis and their concentrations in plasma or serum are important cardiovascular disease (CVD) risk factors. For clinical use, lipoprotein levels are traditionally estimated by measuring one or more of their lipid constituents. The cholesterol within LDL and HDL particles (LDL-C and HDL-C) is used to approximate serum or plasma LDL and HDL levels, while total plasma triglycerides approximate VLDL levels. The *NMR LipoProfile*® test by LipoScience employs a novel automated process to measure NMR signals from LDL, HDL, and VLDL particles simultaneously [1]. The detected lipoprotein signals are proportional in amplitude to the numbers of lipoprotein particles emitting the signals, enabling a calculation of their concentrations. LDL is reported in terms of particle numbers (LDL-P) providing another measure of a patient's LDL level.

Lipoproteins that interact with the arterial wall set in motion the cascade of events leading to atherosclerosis [2]. LDL is the major atherogenic lipoprotein and is identified in ATP III guidelines as the primary target of treatment for reducing coronary heart disease risk [3]. According to a report from the American Diabetes Association (ADA) and American College of Cardiology (ACC), measurement of LDL-C may not accurately reflect the true burden of atherogenic LDL particles, especially in those patients with the typical lipoprotein abnormalities of cardiometabolic risk [4]. The ADA/ACC report also states that measurements of apolipoprotein B or LDL-P may more closely quantitate the atherogenic lipoprotein load. [4] Thus, they may aid in the management of patients with elevated risk of CVD. LDL-P measured by the *NMR LipoProfile*® test by LipoScience has been shown to be a determinant of CVD risk in two prospective case-control studies [5, 6].

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O'Keeffe, Elizabeth

From: Suzette Warner <suzette.warner@liposcience.com>
Sent: Thursday, August 30, 2012 8:24 AM
To: O'Keeffe, Elizabeth
Subject: RE: Revisions for Package Insert for k1113830
Attachments: Matrix comparison updated tables 8-30-12.docx

Elizabeth
Here are the tables for the matrix comparison. The analysis includes the second observation. I should get the PI and the 510(k) Summary to you shortly.

SW

From: O'Keeffe, Elizabeth [mailto:Elizabeth.OKeeffe@fda.hhs.gov]
Sent: Wednesday, August 29, 2012 3:33 PM
To: Suzette Warner
Subject: RE: Revisions for Package Insert for k1113830

Also... the matrix data table (table 11) doesn't have the r squared values... do you have these?

From: Suzette Warner [mailto:suzette.warner@liposcience.com]
Sent: Wednesday, August 29, 2012 3:29 PM
To: O'Keeffe, Elizabeth
Subject: RE: Revisions for Package Insert for k1113830

Will do.

From: O'Keeffe, Elizabeth [mailto:Elizabeth.OKeeffe@fda.hhs.gov]
Sent: Wednesday, August 29, 2012 3:29 PM
To: Suzette Warner
Subject: RE: Revisions for Package Insert for k1113830

Great! Could you also check and make sure that nothing in the 510(k) summary needs updating? If it does then I will need that updated as well. Thanks!

~Elizabeth

From: Suzette Warner [mailto:suzette.warner@liposcience.com]
Sent: Wednesday, August 29, 2012 3:26 PM
To: O'Keeffe, Elizabeth
Subject: RE: Revisions for Package Insert for k1113830

Elizabeth
Here are the revisions we discussed today. The attached are

1. Package Insert (pdf and word document).
2. Recalculated Matrix Comparison study results.

Regards
Suzette

From: O'Keeffe, Elizabeth [mailto:Elizabeth.OKeeffe@fda.hhs.gov]
Sent: Wednesday, August 29, 2012 2:54 PM
To: Suzette Warner
Subject: Revisions for Package Insert for k1113830

ATP III guideline references:

*Expert Panel on Detection, *Evaluation and Treatment of High Cholesterol in Adults (Adult Treatment Panel III)*, May (2001).
NIH Publication No. 01 3305, *ATP III Guidelines At-A-Glance*, Quick Desk Reference, May (2001). NIH Publication No. 01 3670, Third Report of National Cholesterol Education Program (NCEP)

Also, change the wording for the NLA recommendations table from:

In the study, a LDL-P level of ~1000 nmol/L and the percentile equivalent was found to correspond to an LDL-C value of~ 100 mg/dL at the same percentile level. Based on the recommendations from a National Lipids Association expert panel, suggested reference values are provided in Table 2. The recommendation by the NLA has not been validated by an independent clinical study. Each laboratory should verify the validity of these reference values for the population it serves

To the fllowing (remove the first sentence and take out the word "independent"):

Based on the recommendations from a National Lipids Association expert panel, suggested reference values are provided in Table 2. The recommendation by the NLA has not been validated by a clinical study. Each laboratory should verify the validity of these reference values for the population it serves.

Thanks

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Table 1: (b)(4)

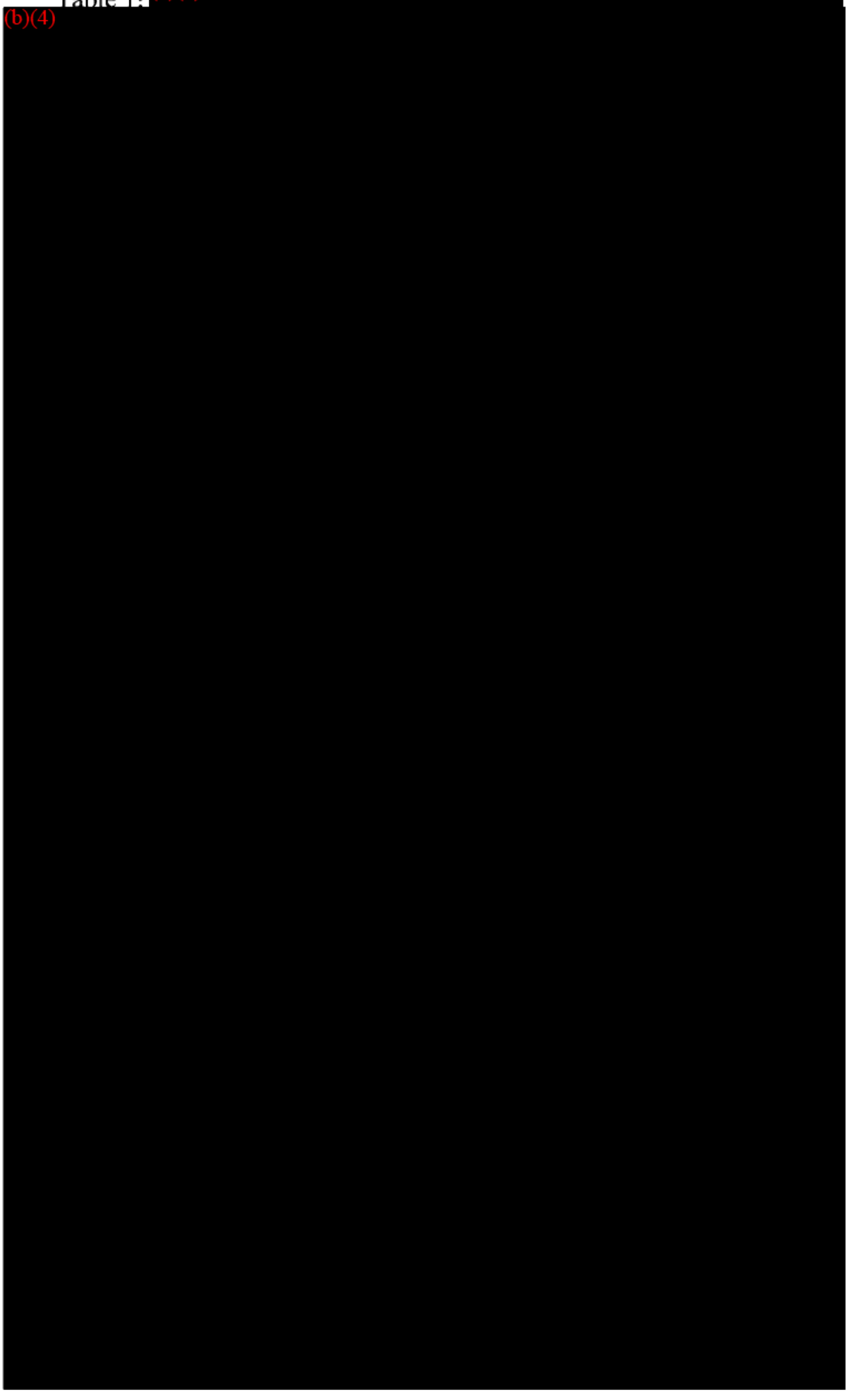

Table 2: (b)(4)

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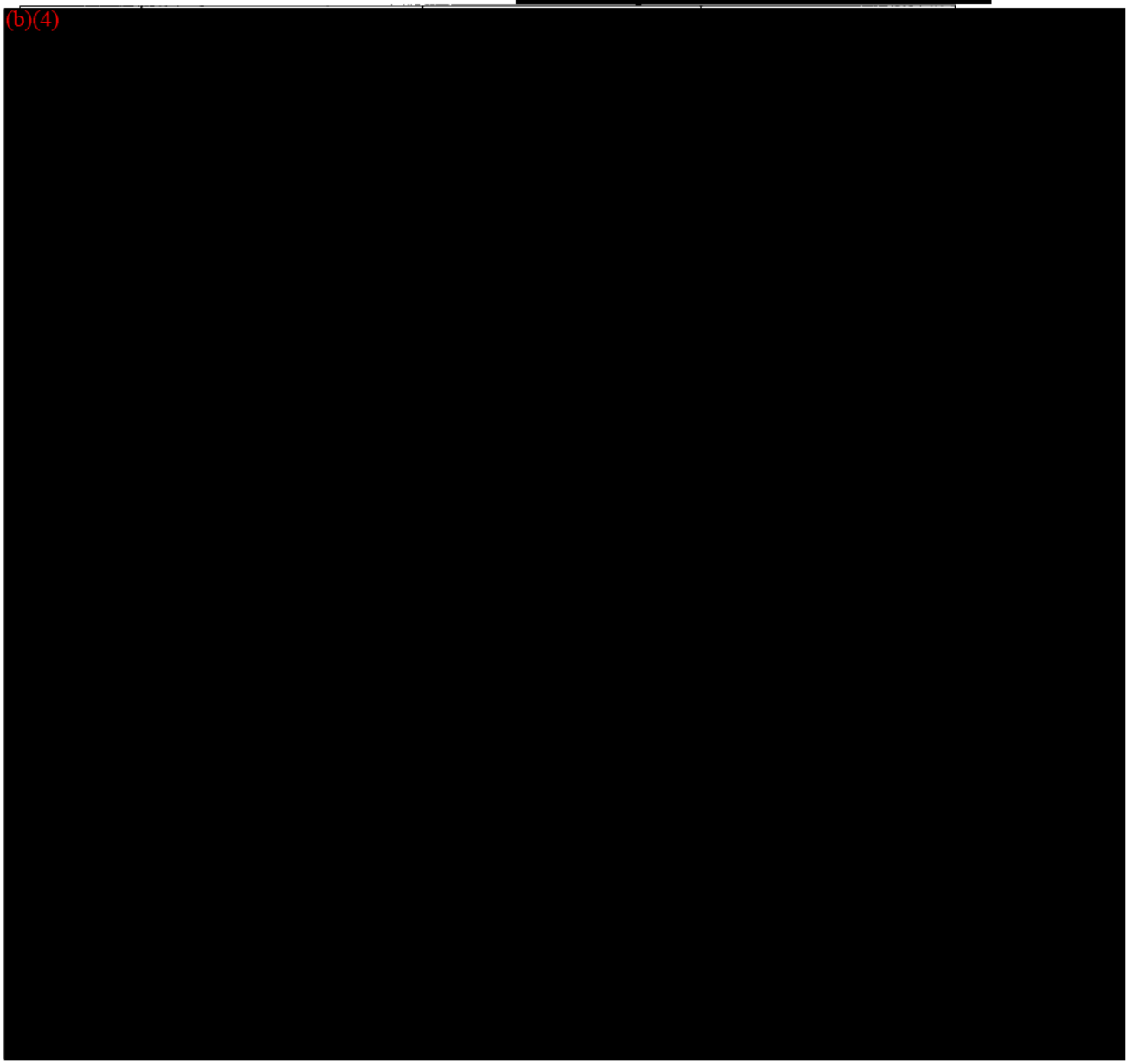

O'Keeffe, Elizabeth

From: Suzette Warner <suzette.warner@liposcience.com>
nt: Friday, August 24, 2012 3:46 PM
To: O'Keeffe, Elizabeth
Subject: RE: Revised Package Insert for k1113830
Attachments: Vantera Clinical Analyzer - NMR LipoProfile test PI Final 8-24-2012.docx; Sec 6 510(k) Summary 8-24-2012.docx; Requested Tables for k113830.docx

Elizabeth
I am probably a bit redundant with what I am providing you but I wanted you to have everything at your fingertips. The attached are

1. Word Document "request tables" of the tables you requested: Sample Stability, Reference Range tables 4 and 5; and the matrix comparison table with "r squared" values.
2. Package Insert: revised to add the LDL-P goals table, added the sentence stating that the NLA "has not been validated by an independent clinical study". The statement addressing clinical lab's role in verifying the validity of the reference values was already present. Also, the within lab, within run, and reproducibility tables are available here and is not found in item 1. Also, the interference substance table is available in this document.
3. 510(k) Summary: this was revised to add the comparison tables for the predicates (instrument and assay).

Have a great weekend and thank you for time and attentiveness to the review process.

Regards
Suzette

From: O'Keeffe, Elizabeth [mailto:Elizabeth.OKeeffe@fda.hhs.gov]
Sent: Friday, August 24, 2012 12:41 PM
To: Suzette Warner
Subject: RE: Revised Package Insert for k1113830

Please include the following statement with the Recommended LDL-P reference values table:

... recommended by the NLA... "has not been validated by an independent clinical study"...

Thanks!

~Elizabeth

From: Suzette Warner [mailto:suzette.warner@liposcience.com]
Sent: Monday, August 20, 2012 4:29 PM
To: O'Keeffe, Elizabeth
Subject: Revised Package Insert for k1113830

Dr. O'Keeffe
The revised package insert is attached. The revision includes the removal of the MESA study under Expected Values and adding the table which shows the relationship of LDL-P and LDL-C in the reference range study. The table which stated the LDL-P goal was also removed.

I believe this satisfies your recommendations, if not please let me know of additional changes that might be necessary.

Regards,
Suzette

Suzette M. Warner
ɜulatory Affairs, Manager
919-256-1326
Cell: 919-357-7801
LIPO**SCIENCE**
2500 Sumner Boulevard
Raleigh, NC 27616
Main: 877-547-6837

"It is not necessary to do extraordinary things to get extraordinary results."
Warren Buffett

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mail and any attachments, notify the sender immediately, and notify the LipoScience Privacy Officer at HIPAA@lip

August 24, 2012

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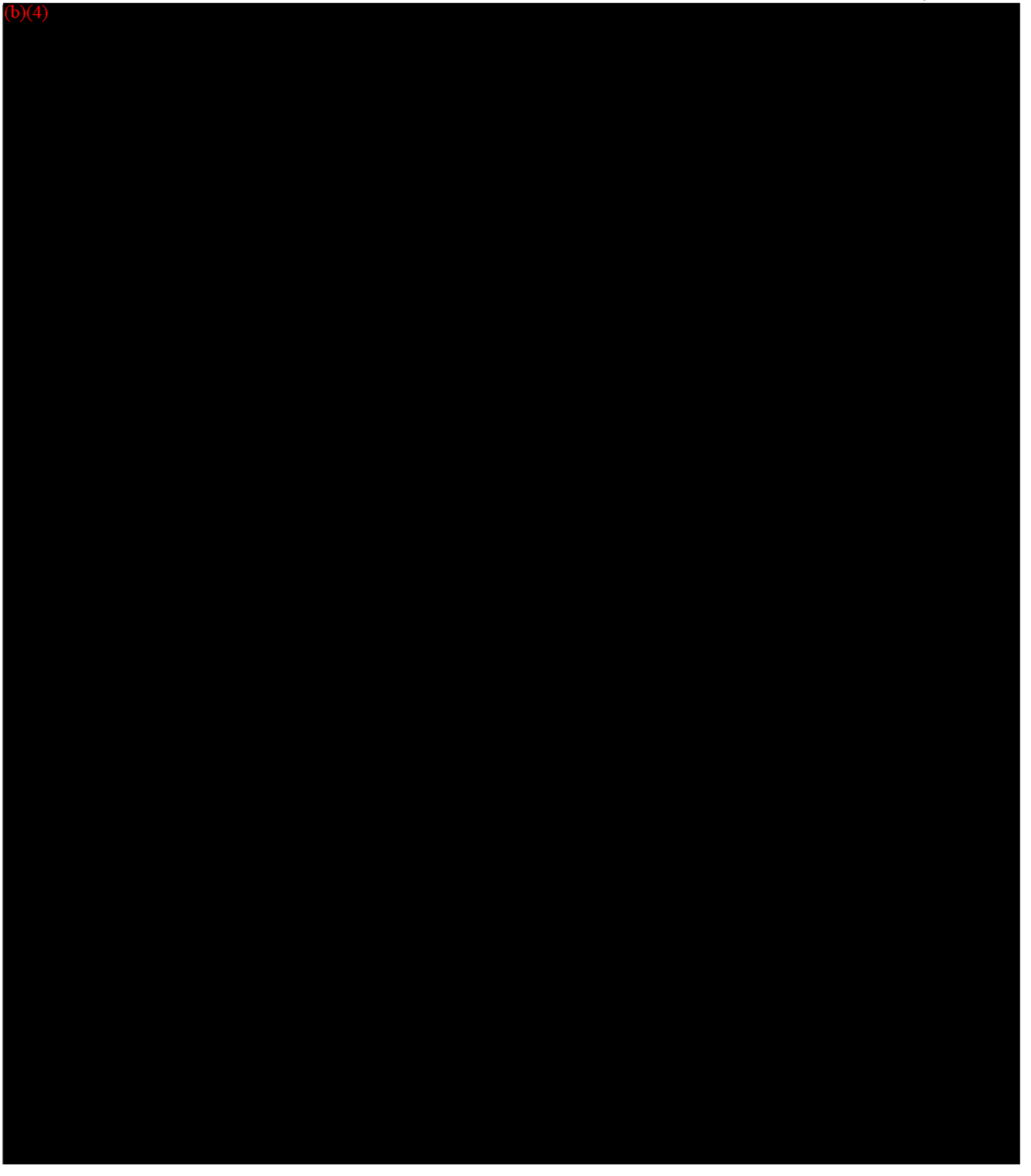

August 24, 2012

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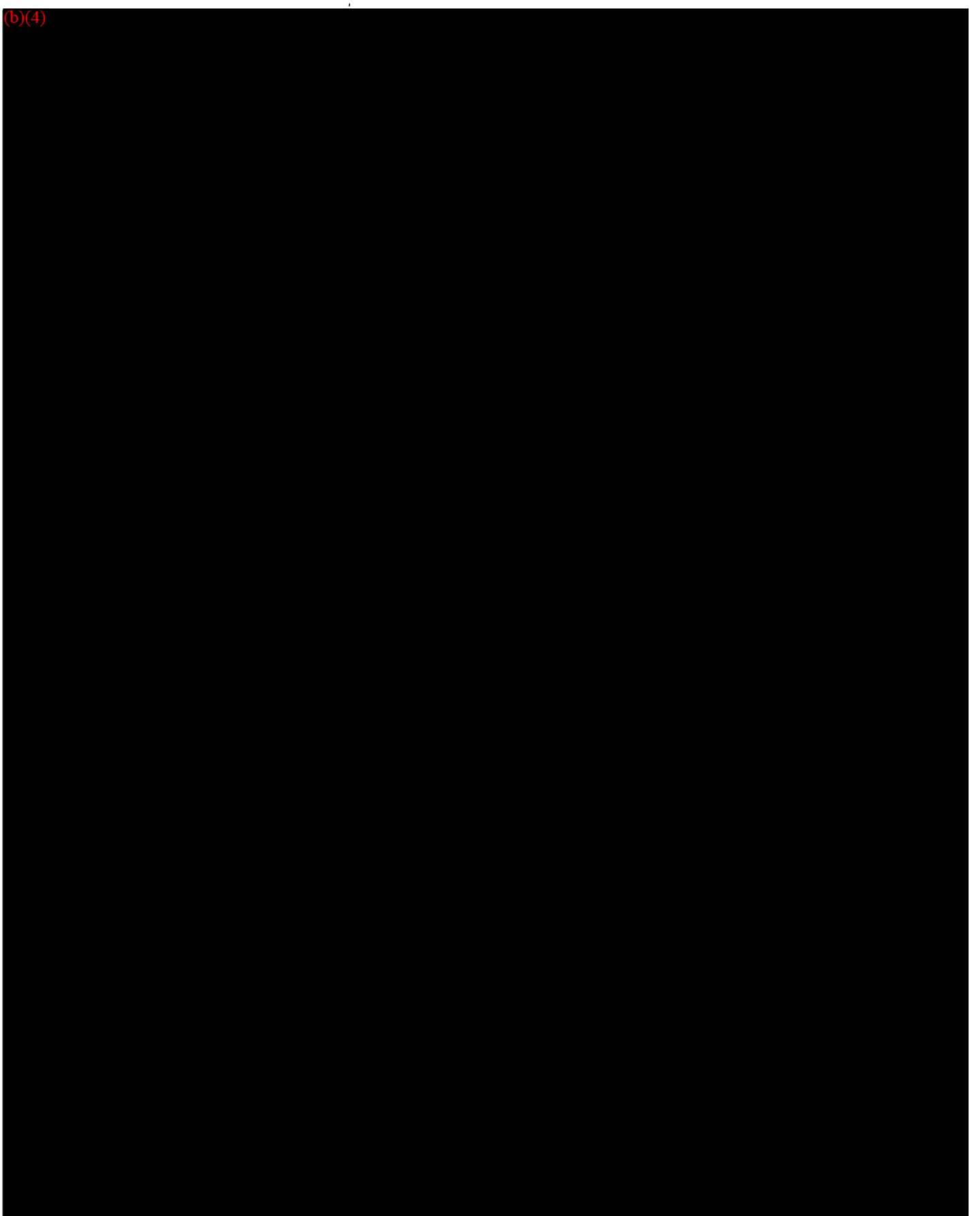

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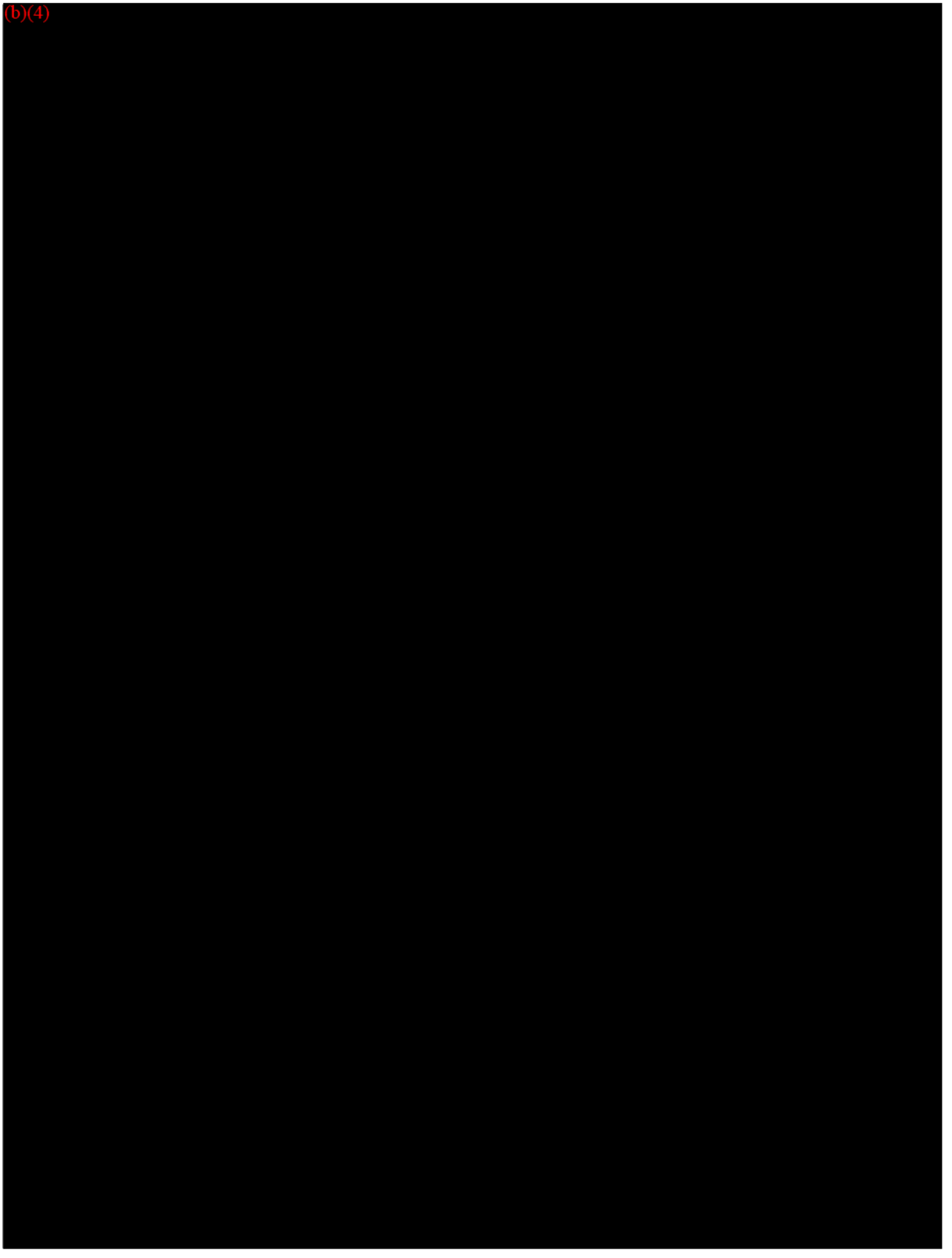

August 24, 2012

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O'Keeffe, Elizabeth

From: Suzette Warner <suzette.warner@liposcience.com>
Sent: Friday, April 27, 2012 9:21 AM
To: O'Keeffe, Elizabeth
Subject: RE: Vantera Study Plans

Eleven is fine. It gives us some time to gather our thoughts.

From: O'Keeffe, Elizabeth [mailto:Elizabeth.OKeeffe@fda.hhs.gov]
Sent: Friday, April 27, 2012 9:20 AM
To: Suzette Warner
Subject: RE: Vantera Study Plans

I did... thanks. I may be able to do it in a few minutes if you prefer.

Elizabeth O'Keeffe, Ph.D.
Scientific Reviewer

Food and Drug Administration
10903 New Hampshire Avenue
WO66, 3627
Silver Spring, MD 20993-0002

301-796-1567
Elizabeth.okeeffe@fda.hhs.gov

From: Suzette Warner [mailto:suzette.warner@liposcience.com]
Sent: Friday, April 27, 2012 9:09 AM
To: O'Keeffe, Elizabeth
Subject: RE: Vantera Study Plans

Eleven it is. Let me know if you received the call in numbers.

From: O'Keeffe, Elizabeth [mailto:Elizabeth.OKeeffe@fda.hhs.gov]
Sent: Friday, April 27, 2012 8:59 AM
To: Suzette Warner
Subject: RE: Vantera Study Plans

I will give you a call at 11:00. :)

Elizabeth O'Keeffe, Ph.D.
Scientific Reviewer

Food and Drug Administration
10903 New Hampshire Avenue
WO66, 3627
Silver Spring, MD 20993-0002

301-796-1567
elizabeth.okeeffe@fda.hhs.gov

From: Suzette Warner [mailto:suzette.warner@liposcience.com]
Sent: Friday, April 27, 2012 8:55 AM
To: O'Keeffe, Elizabeth
Subject: RE: Vantera Study Plans

Elizabeth
This morning we are available from 11:00- 12:00 noon and free all afternoon.

Suzette

From: O'Keeffe, Elizabeth [mailto:Elizabeth.OKeeffe@fda.hhs.gov]
Sent: Friday, April 27, 2012 8:52 AM
To: Suzette Warner
Subject: RE: Vantera Study Plans

I have time today to chat if you are available. As of yet my calendar is free but I am waiting to hear from 3 other sponsors about meeting times, so let me know asap when would be a good time for you. I will be in my office until about 3:00 pm est.

~Elizabeth

Elizabeth O'Keeffe, Ph.D.
Scientific Reviewer

Food and Drug Administration
10903 New Hampshire Avenue
WO66, 3627
Silver Spring, MD 20993-0002

301-796-1567
elizabeth.okeeffe@fda.hhs.gov

From: Suzette Warner [mailto:suzette.warner@liposcience.com]
Sent: Wednesday, April 18, 2012 5:52 PM
To: O'Keeffe, Elizabeth
Cc: Tom Clement
Subject: RE: Vantera Study Plans

Elizabeth
Would you have some time on Thursday morning between 9:00 am to 10:00 am or Thursday afternoon between 1:00 pm to 2:00 pm?

I would like to discuss some concerns we have regarding the reference range study for which we are desperate to have your input. Specifically our concerns are as follows:

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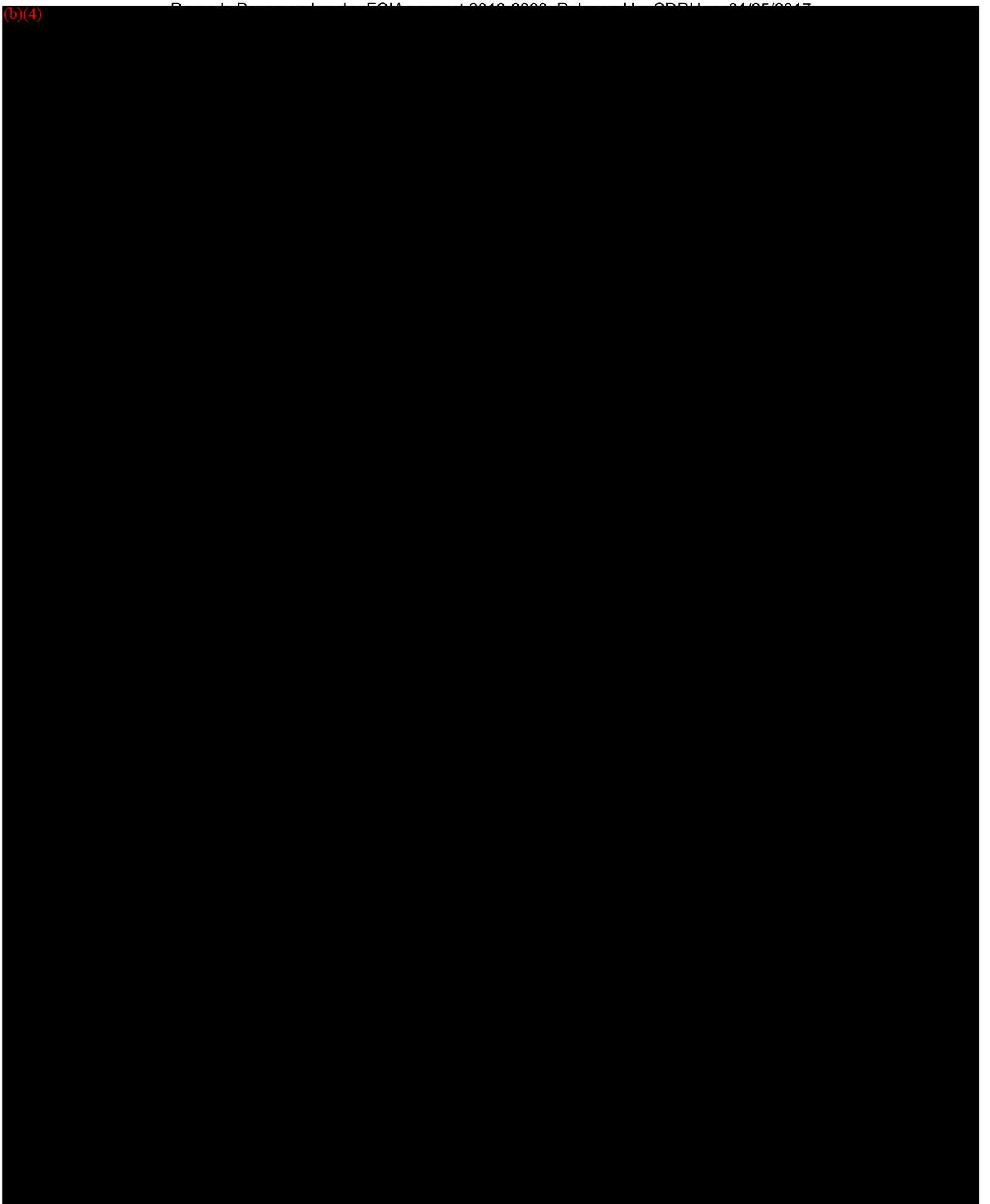

From: Suzette Warner
Sent: Thursday, March 22, 2012 12:09 PM
To: 'O'Keeffe, Elizabeth'
Subject: Vantera Study Plans

Elizabeth
The attached are the study plans that support our response to the deficiency letter for informal review. In our discussion on March 19, 2012, I initially proposed that I would provide you with protocols instead I decided to provide you with summaries of the studies we will be conducting. If you need more information, just let me know.

Also, in a few days I would like to start sending you responses to the deficiency letter, that are independent of the studies we need to conduct, for your review. I anticipate if the responses are satisfactory, I will then send the packet to the document mail center to be added to the file. Let me know if this approach is satisfactory.

Suzette M. Warner
Regulatory Affairs, Manager
O: 919-256-1326
Cell: 919-357-7801
LIPOSCIENCE
2500 Sumner Boulevard
Raleigh, NC 27616
Main: 877-547-6837

"It is not necessary to do extraordinary things to get extraordinary results."
Warren Buffett

O'Keeffe, Elizabeth

From: Suzette Warner <suzette.warner@liposcience.com>
Sent: Friday, April 13, 2012 9:53 AM
To: O'Keeffe, Elizabeth
Subject: RE: Vantera Study Plans
Attachments: Vantera_reference range study outline.doc

Good Day Elizabeth,
Thanks for taking the call this morning. Here is the revision for the reference range study I mentioned. Your feedback is greatly appreciated.

Regards
Suzette

From: Suzette Warner
Sent: Thursday, March 22, 2012 12:09 PM
To: 'O'Keeffe, Elizabeth'
Subject: Vantera Study Plans

Elizabeth
The attached are the study plans that support our response to the deficiency letter for informal review. In our discussion on March 19, 2012, I initially proposed that I would provide you with protocols instead I decided to provide you with summaries of the studies we will be conducting. If you need more information, just let me know.

so, in a few days I would like to start sending you responses to the deficiency letter, that are independent of the studies we need to conduct, for your review. I anticipate if the responses are satisfactory, I will then send the packet to the document mail center to be added to the file. Let me know if this approach is satisfactory.

Suzette M. Warner
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LIPOSCIENCE
2500 Sumner Boulevard
Raleigh, NC 27616
Main: 877-547-6837

"It is not necessary to do extraordinary things to get extraordinary results."
Warren Buffett

The following is the outline of a proposed reference range study to support the Vantera 510k submission with FDA.

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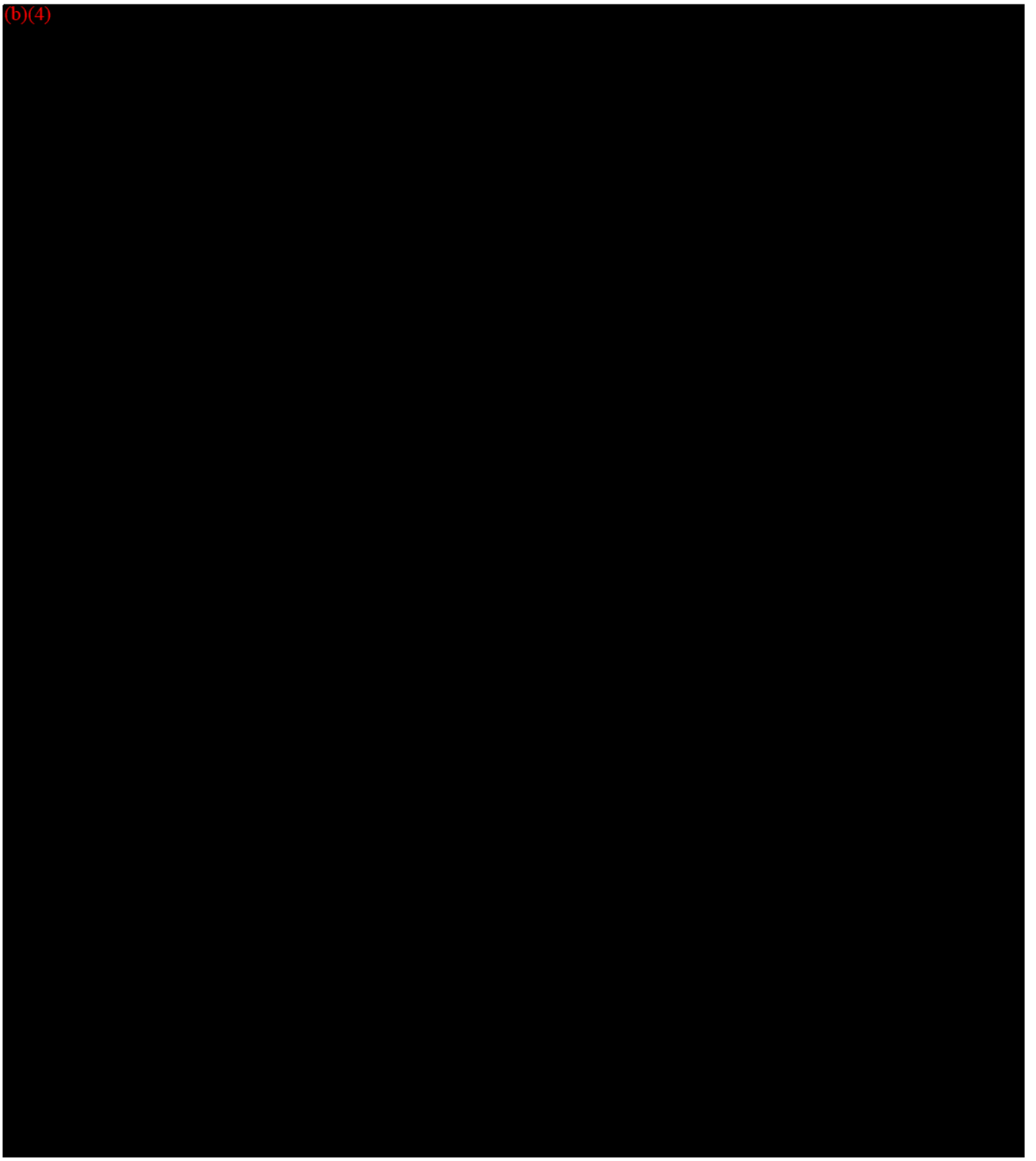

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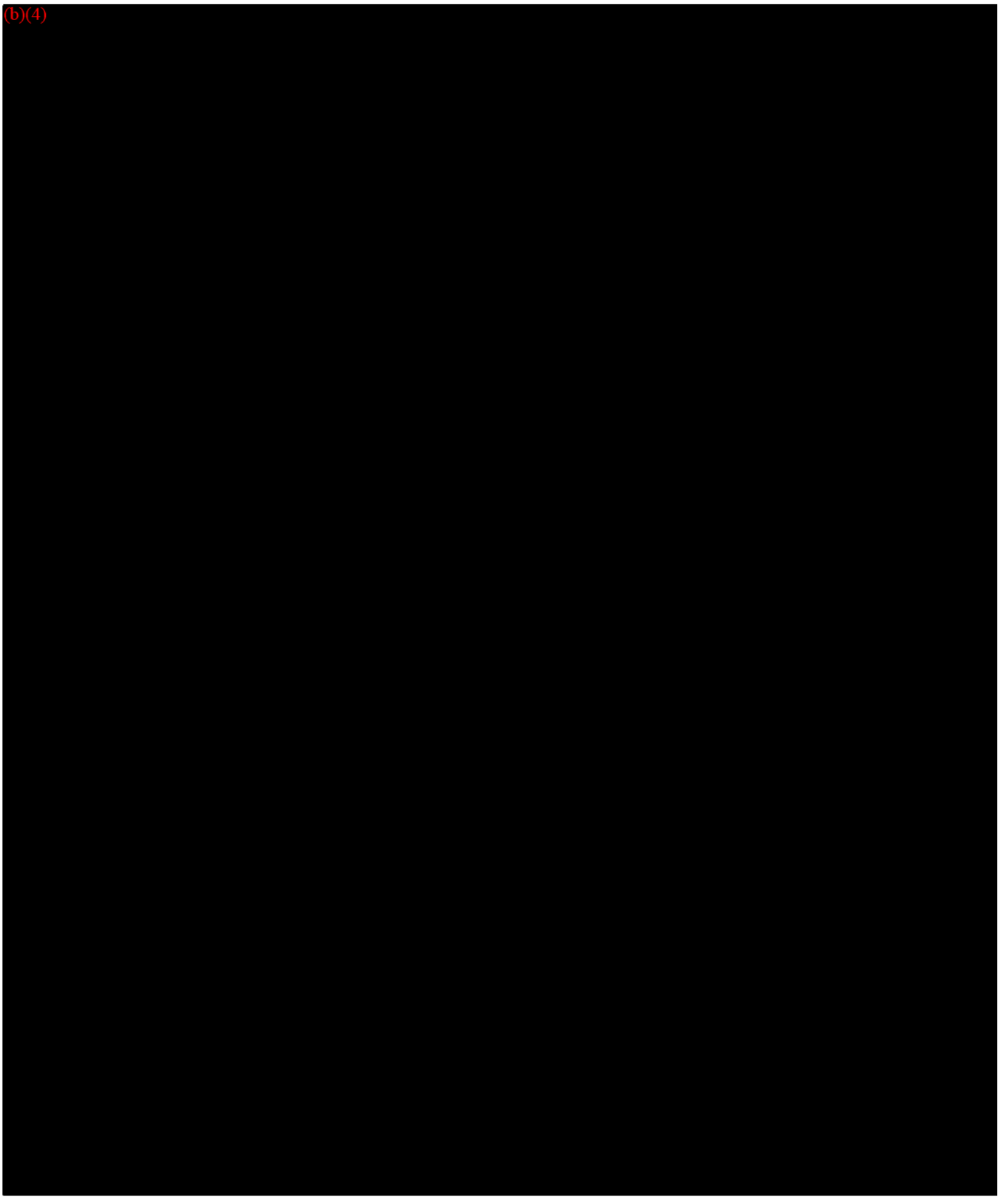

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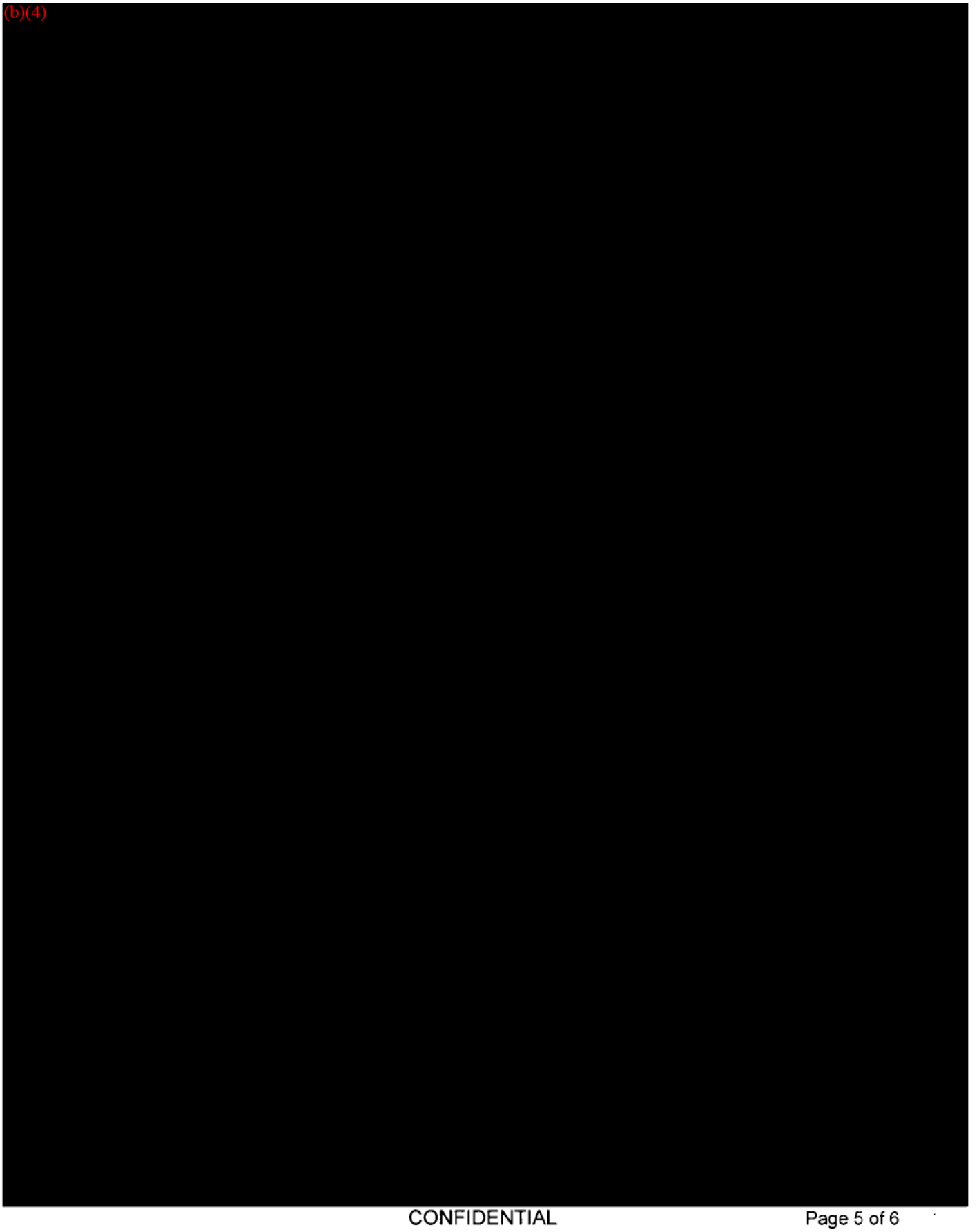

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O'Keeffe, Elizabeth

From: Suzette Warner <suzette.warner@liposcience.com>
Sent: Friday, April 06, 2012 2:32 PM
To: O'Keeffe, Elizabeth
Subject: k113830 Partial Response Packet to Deficiency Letter
Attachments: k113850 Partial Response Packet.pdf

Elizabeth
Here is the partial response packet we discussed on March 19, 2012. It includes responses to question 1, 4, 5, and 11 of the deficiency letter. The remaining responses will be submitted once the studies recommended by the deficiency letter is completed. . I anticipate if the responses are satisfactory, you will let me know and I will then send the packet to the document mail center to be added to the file. Please let me know if this approach is satisfactory.

Next week I would like to share with you our written plan, for how we will be addressing the Master Calibrator lot qualification and value assignment, for review, so keep an eye out for that.

Regards
Suzette

Suzette M. Warner
Regulatory Affairs, Manager
O: 919-256-1326
Cell: 919-357-7801
'POSCIENCE
.00 Sumner Boulevard
Raleigh, NC 27616
Main: 877-547-6837

"It is not necessary to do extraordinary things to get extraordinary results."
Warren Buffett

LIPOSCIENCE

April 6, 2012

U.S. Food and Drug Administration
Center for Devices and Radiological Health
Document Mail Center – WO66-0609
10903 New Hampshire Avenue
Silver Spring, MD 20993

Attn: Elizabeth O'Keeffe, PhD

RE: 510(k) Submission K113830 - Information provided in response to FDA regarding the *NMR LipoProfile®* test on Vantera Clinical Analyzer.

Dear Dr. O'Keeffe:

This correspondence is provided in response to your e-mail dated February 24, 2012 requesting additional information regarding the *NMR LipoProfile®* test on Vantera Clinical Analyzer 510k submission. The responses presented are to questions 1, 4, 5 and 11 of the deficiency letter. As discussed on March 19, 2012, this packet is a partial packet for review. The remaining packet will be submitted once the studies recommended by the deficiency letter are complete. Also included, is the rationale for why we believe the Vantera system is of a moderate complexity.

We have structured our response such that the FDA comment is cited followed by our response. We hope that the information provided will facilitate your continued review of this submission.

Should you have any questions or require additional information, please contact me at (919) 256-1326 or via email at suzette.warner@liposcience.com.

Sincerely,

Suzette M. Warner

Suzette M. Warner
Regulatory Affairs Manager

Enc:

Greiner Bio-One Letter
Magnet Release Testing Documentation
LipoScience rational – CLIA Categorization Criteria

Dr. Elizabeth O'Keefe
FDA/CDRH/OVID
April 4, 2012

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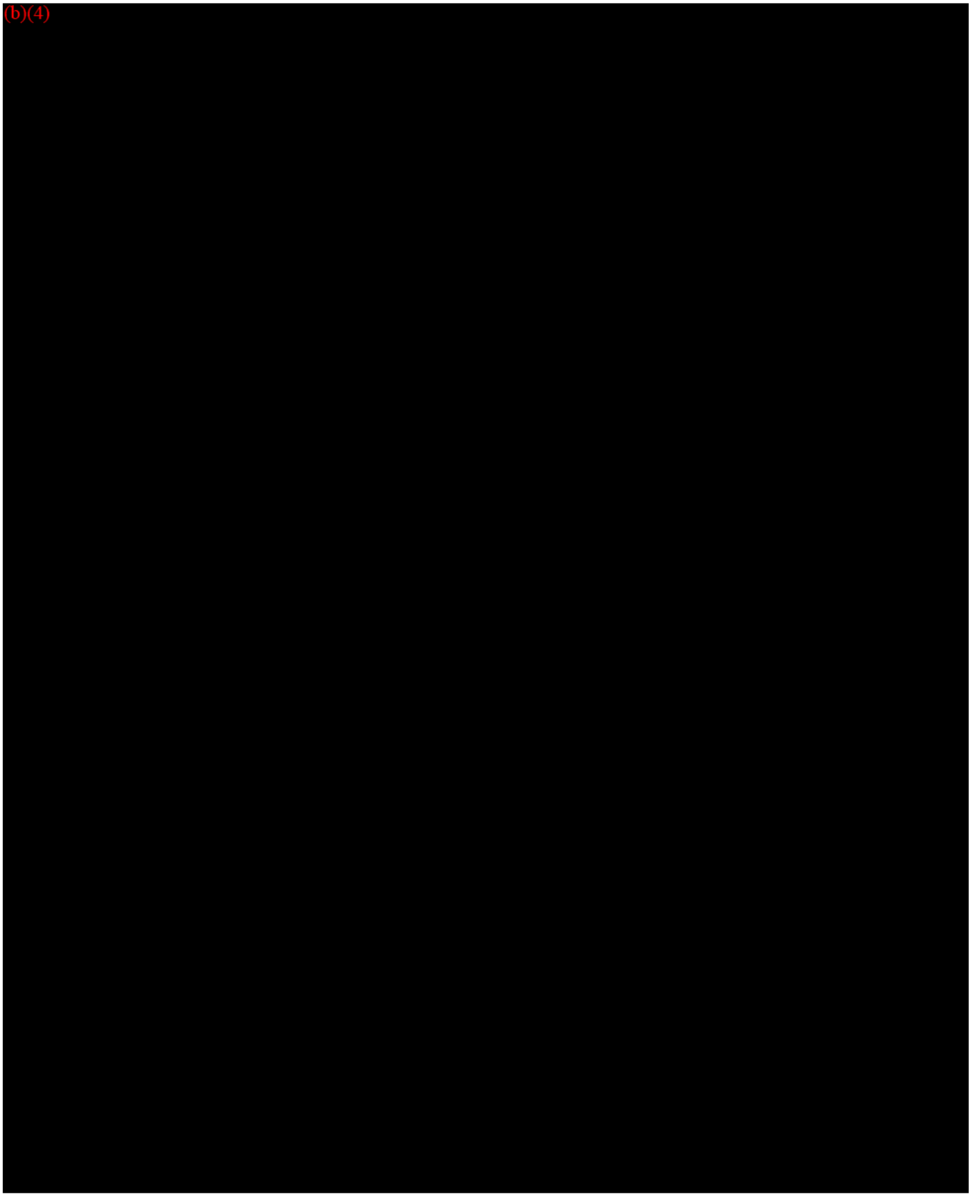

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O'Keeffe, Elizabeth

From: Suzette Warner <suzette.warner@liposcience.com>
Sent: Wednesday, March 28, 2012 10:22 AM
To: O'Keeffe, Elizabeth
Subject: RE: k113830 - LDL-P Quality Controls

Elizabeth
Thursday at 11:00 am will work well for us. For convenience, here is the call in number.

Call in #: 877-226-9607
Conference ID: 1404298379#

Regards
Suzette

From: O'Keeffe, Elizabeth [mailto:Elizabeth.OKeeffe@fda.hhs.gov]
Sent: Wednesday, March 28, 2012 8:16 AM
To: Suzette Warner
Subject: RE: k113830 - LDL-P Quality Controls

Suzette,

I have not had a chance yet to discuss your protocols with either the product specialist or my supervisor, so any discussion we have will be preliminary and I may not be able to answer all of your questions. However, whatever questions are brought up in the discussion can then be discussed with my manager before giving you any solid feedback. I have meetings every Wed at 10:00 and 11:00, and I am off work every day at 3:00. I will have time to chat tomorrow (Thurs) Anytime between 7:00 - 9:00 and 10:00 - 3:00. Let me know if any of these times work for you.

~Elizabeth

Elizabeth O'Keeffe, Ph.D.
Scientific Reviewer

Food and Drug Administration
10903 New Hampshire Avenue
WO66, 3627
Silver Spring, MD 20993-0002

301-796-1567
elizabeth.okeeffe@fda.hhs.gov

From: Suzette Warner [mailto:suzette.warner@liposcience.com]
Sent: Tuesday, March 27, 2012 5:29 PM
To: O'Keeffe, Elizabeth
Cc: Tom Clement
Subject: k113830 - LDL-P Quality Controls

Elizabeth

Tom and I would like to talk with you about our proposal for addressing items 6, 7, 8 of the deficiency letter. Would you have some time on Wednesday morning between 10:00 am – 12:00 am or Wednesday afternoon between 4:00 pm to 5:00pm?

Regards
Suzette

Suzette M. Warner
Regulatory Affairs, Manager
O: 919-256-1326
Cell: 919-357-7801
LIPOSCIENCE
2500 Sumner Boulevard
Raleigh, NC 27616
Main: 877-547-6837

"It is not necessary to do extraordinary things to get extraordinary results."
Warren Buffett

O'Keeffe, Elizabeth

From: Suzette Warner <suzette.warner@liposcience.com>
Sent: Thursday, March 22, 2012 12:09 PM
To: O'Keeffe, Elizabeth
Subject: Vantera Study Plans
Attachments: Vantera Study Plans.pdf

Elizabeth
The attached are the study plans that support our response to the deficiency letter for informal review. In our discussion on March 19, 2012, I initially proposed that I would provide you with protocols instead I decided to provide you with summaries of the studies we will be conducting. If you need more information, just let me know.

Also, in a few days I would like to start sending you responses to the deficiency letter, that are independent of the studies we need to conduct, for your review. I anticipate if the responses are satisfactory, I will then send the packet to the document mail center to be added to the file. Let me know if this approach is satisfactory.

Suzette M. Warner
Regulatory Affairs, Manager
O: 919-256-1326
Cell: 919-357-7801
LIPOSCIENCE
2500 Sumner Boulevard
Raleigh, NC 27616
Main: 877-547-6837

"It is not necessary to do extraordinary things to get extraordinary results."
Warren Buffett

LIPOSCIENCE

March 22, 2012

U.S. Food and Drug Administration
Center for Devices and Radiological Health
Document Mail Center – WO66-0609
10903 New Hampshire Avenue
Silver Spring, MD 20993

Attn: Elizabeth O'Keeffe, PhD

RE: 510(k) Submission K113830 – Study plans provided in response to FDA regarding the *NMR LipoProfile*® test on Vantera Clinical Analyzer deficiency letter dated February 24, 2012.

Dear Dr. O'Keeffe:

This correspondence is provided in response to the teleconference discussion on March 1, 2012. It is the intent of LipoScience to provide FDA with the study details we are proposing to support our responses to FDA concerns cited in the February 24, 2012 Deficiency Letter and to receive feedback on study design.

The specific study plans for which we would appreciate FDA review and comment include:

(b)(4)

[redacted]

Should you have any questions or require additional information, please contact me at (919) 256-1326 or via email at suzette.warner@liposcience.com.

Sincerely,
Suzette M. Warner
Suzette M. Warner
Regulatory Affairs Manager

Enc: Reference Range Study Questionnaire

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O'Keeffe, Elizabeth

From: Suzette Warner <suzette.warner@liposcience.com>
Sent: Thursday, March 15, 2012 4:39 PM
To: O'Keeffe, Elizabeth
Subject: RE: k113830 hold letter

Dr. O'Keeffe
Monday morning at 10:30 am will be reasonable for me. I will call you at your number.

Thank you and have a wonderful weekend.

Regards
Suzette

From: O'Keeffe, Elizabeth [mailto:Elizabeth.OKeeffe@fda.hhs.gov]
Sent: Thursday, March 15, 2012 4:33 PM
To: Suzette Warner
Subject: RE: k113830 hold letter

Suzette,

I will be out of the office tomorrow, but I can chat with you on Monday if that works for you. I have an 8:30-10:00 and a 1:00-2:00, but any other time would be just fine. Let me know when you would like to talk, and I will be here.

~Elizabeth

Elizabeth O'Keeffe, Ph.D.
Scientific Reviewer

Food and Drug Administration
10903 New Hampshire Avenue
WO66, 3627
Silver Spring, MD 20993-0002

301-796-1567
elizabeth.okeeffe@fda.hhs.gov

From: Suzette Warner [mailto:suzette.warner@liposcience.com]
Sent: Thursday, March 15, 2012 3:44 PM
To: O'Keeffe, Elizabeth
Subject: RE: k113830 hold letter

Dr. O'Keeffe
Thank you for providing the table.

Would you have about half hour on Friday morning for a quick phone call? I would like to go over with you our plan for addressing the issues raised in the deficiency letter.

Regards
Suzette

From: O'Keeffe, Elizabeth [mailto:Elizabeth.OKeeffe@fda.hhs.gov]
Sent: Thursday, March 15, 2012 12:57 PM
To: Suzette Warner
Subject: RE: k113830 hold letter

Suzette,

Here is an example table of linearity data (I concocted this with no units... just numbers to give you an idea of how it would look). Additionally, you would provide your acceptance criteria (generally not to exceed 10% bias) and the linear regression graph and analysis (equation with coefficient). Please let me know if you have any additional questions.

Sample Number	Expected Value	Observed Value	Absolute Bias	% Bias	% Recovery	Acceptable Bias?
1	6	5.44	-0.56	9.33	90.67	Yes
2	12	11.64	-0.36	3.00	97.00	Yes
3	24	22.45	-1.55	6.46	93.54	Yes
4	48	43.96	-4.04	8.42	91.58	Yes
5	60	59.7	-0.3	0.50	99.50	Yes
6	96	92.89	-3.11	3.24	96.76	Yes
7	124	120.63	-3.37	2.72	97.28	Yes
8	148	139.87	-8.13	5.49	94.51	Yes
9	172	164.35	-7.65	4.45	95.55	Yes
10	200	198.99	-1.01	0.50	99.50	Yes

~Elizabeth

Elizabeth O'Keeffe, Ph.D.
Scientific Reviewer

Food and Drug Administration
10903 New Hampshire Avenue
WO66, 3627
Silver Spring, MD 20993-0002

301-796-1567
elizabeth.okeeffe@fda.hhs.gov

From: Suzette Warner [mailto:suzette.warner@liposcience.com]
Sent: Wednesday, March 07, 2012 9:30 AM
To: O'Keeffe, Elizabeth
Subject: RE: k113830 hold letter

O'Keeffe, Elizabeth

From: Suzette Warner <suzette.warner@liposcience.com>
Sent: Wednesday, February 29, 2012 9:26 AM
To: O'Keeffe, Elizabeth
Subject: RE: k113830 hold letter

Dr. O'Keefe
Thursday at 1:00 pm works for us. Below is the conference call number for you to call in.

Call in #: 877-226-9607
Conference ID: 1404298379#

Regards
Suzette

From: O'Keeffe, Elizabeth [mailto:Elizabeth.OKeeffe@fda.hhs.gov]
Sent: Wednesday, February 29, 2012 8:32 AM
To: Suzette Warner
Subject: RE: k113830 hold letter

Suzette,

Would tomorrow at 1:00 est work?... it seems to be the only available time this week if you want to include the CLIA categorization conversation. Please let me know f this works and I will send you a teleconference call-in number. Thanks!

~Elizabeth

Elizabeth O'Keeffe, Ph.D.
Scientific Reviewer

Food and Drug Administration
10903 New Hampshire Avenue
WO66, 3627
Silver Spring, MD 20993-0002

301-796-1567
elizabeth.okeeffe@fda.hhs.gov

From: Suzette Warner [mailto:suzette.warner@liposcience.com]
Sent: Tuesday, February 28, 2012 12:29 PM
To: O'Keeffe, Elizabeth
Subject: RE: k113830 hold letter

Dr. O'Keefe
I would like the opportunity to have a teleconference with you to obtain clarification on some of the questions listed in the deficiency letter.

Will this week work for you? Let me know what times are feasible for you and I will work on my end to get the right players for the call. The call will probably include myself, the VP of RA (Tom Clement) and a representative from R&D.

:gards
Suzette

From: O'Keeffe, Elizabeth [mailto:Elizabeth.OKeeffe@fda.hhs.gov]
Sent: Friday, February 24, 2012 2:59 PM
To: Suzette Warner
Subject: k113830 hold letter

Hi Suzette,

Here is the hold letter that I spoke with you briefly about. Please let me know if you have any questions regarding any of the listed deficiencies, and when you would like to set up a teleconference to discuss both the deficiencies in the hold letter and the CLIA categorization that we discussed. You automatically have 30 days to respond to the hold letter, and if you would like more time you can request an extension of up to 180 days from the document mail center. Again don't hesitate to contact me with any questions, and I look forward to working with you on your submission. Have a great weekend!

~Elizabeth

Elizabeth O'Keeffe, Ph.D.
Scientific Reviewer

)od and Drug Administration
10903 New Hampshire Avenue
WO66, 3627
Silver Spring, MD 20993-0002

301-796-1567
elizabeth.okeeffe@fda.hhs.gov

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DEPARTMENT OF HEALTH & HUMAN SERVICES **Public Health Service**

U.S. Food and Drug Administration
Center for Devices and Radiological Health
Document Control Center WO66-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

July 30, 2012

LIPOSCIENCE
2500 SUMMER BLVD.
RALEIGH, NORTH CAROLINA 27616
ATTN: SUZETTE WARNER

510k Number: K113830

Product: VANTERA CHINIAL ANALYZER

The additional information you have submitted has been received.

We will notify you when the processing of this submission has been completed or if any additional information is required. Pleaseremember that all correspondence concerning your submission MUST be sent to the Document Mail Center at the above letterhead address. Correspondence sent to any address other than the one above will not be considered as part of your official premarket notification submission. Also, please note the new Blue Book Memorandum regarding Fax and E-mail Policy entitled, "Fax and E-Mail Communication with Industry about Premarket Files Under Review. Please refer to this guidance for information on current fax and e-mail practices at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089402.htm. On August 12, 2005 CDRH issued the Guidance for Industry and FDA Staff: Format for Traditional and Abbreviated 510(k)s. This guidance can be found at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm084365.htm. Please refer to this guidance for assistance on how to format an original submission for a Traditional or Abbreviated 510(k).

The Safe Medical Devices Act of 1990, signed on November 28, states that you may not place this device into commercial distribution until you receive a letter from FDA allowing you to do so. As in the past, we intend to complete our review as quickly as possible. Generally we do so in 90 days. However, the complexity of a submission or a requirement for additional information may occasionally cause the review to extend beyond 90 days. Thus, if you have not received a written decision or been contacted within 90 days of our receipt date you may want to check with FDA to determine the status of your submission.

Please ensure that whether you submit a 510(k) Summary as per 21 CFR 807.92, or a 510(k) Statement as per 21 CFR 807.93, it meets the content and format regulatory requirements.

If you have procedural questions, please contact the Division of Small Manufacturers International and Consumer Assistance (DSMICA) at (301)796-7100 or at their toll-free number (800)638-2041, or contact the 510k staff at (301)796-5640.

Sincerely,

510(k) Staff

Grayson, Giovanna *

From: Microsoft Outlook
To: 'suzette.warner@liposcience.com'
Sent: Monday, July 30, 2012 1:56 PM
Subject: Relayed: ack letter

Delivery to these recipients or distribution lists is complete, but delivery notification was not sent by the destination:

'suzette.warner@liposcience.com'

Subject: ack letter

Sent by Microsoft Exchange Server 2007

K113830/31
CH/SCTS

LIPOSCIENCE

July 27, 2012

U.S. Food and Drug Administration
Center for Devices and Radiological Health
Document Mail Center – WO66-0609
10903 New Hampshire Avenue
Silver Spring, MD 20993

FDA CDRH DMC
JUL 30 2012
Received

Attn: Elizabeth O'Keeffe, PhD

RE: 510(k) Submission K113830 - Information provided in response to FDA regarding the *NMR LipoProfile®* test on Vantera Clinical Analyzer.

Dear Dr. O'Keeffe:

This correspondence is provided in response to your e-mail dated February 24, 2012 requesting additional information regarding the *NMR LipoProfile®* test on Vantera Clinical Analyzer 510k submission. On April 6, 2012 a partial response was submitted by email addressing FDA questions (b)(4) [redacted]. To provide a complete packet for review, questions (b)(4) [redacted] are resubmitted in this correspondence. Also submitted in this correspondence is a revised 510(k) summary and Declarations of Conformity and Summary Reports which includes information on the quality control material for the LDL-P assay. They can be found in Attachment 13 and Attachment 14 respectively.

We have structured our response such that the FDA comment is cited followed by our response. We hope that the information provided will facilitate your continued review of this submission.

Should you have any questions or require additional information, please contact me at (919) 256-1326 or via email at suzette.warner@liposcience.com.

Sincerely,

Suzette M. Warner

Suzette M. Warner
Regulatory Affairs Manager

2500 Sumner Blvd | Raleigh, NC 27616 | 919-212-1999 | LipoScience.com

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FDA Correspondence:

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LipoScience Response:

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FDA Correspondence:

5. **Precision:**

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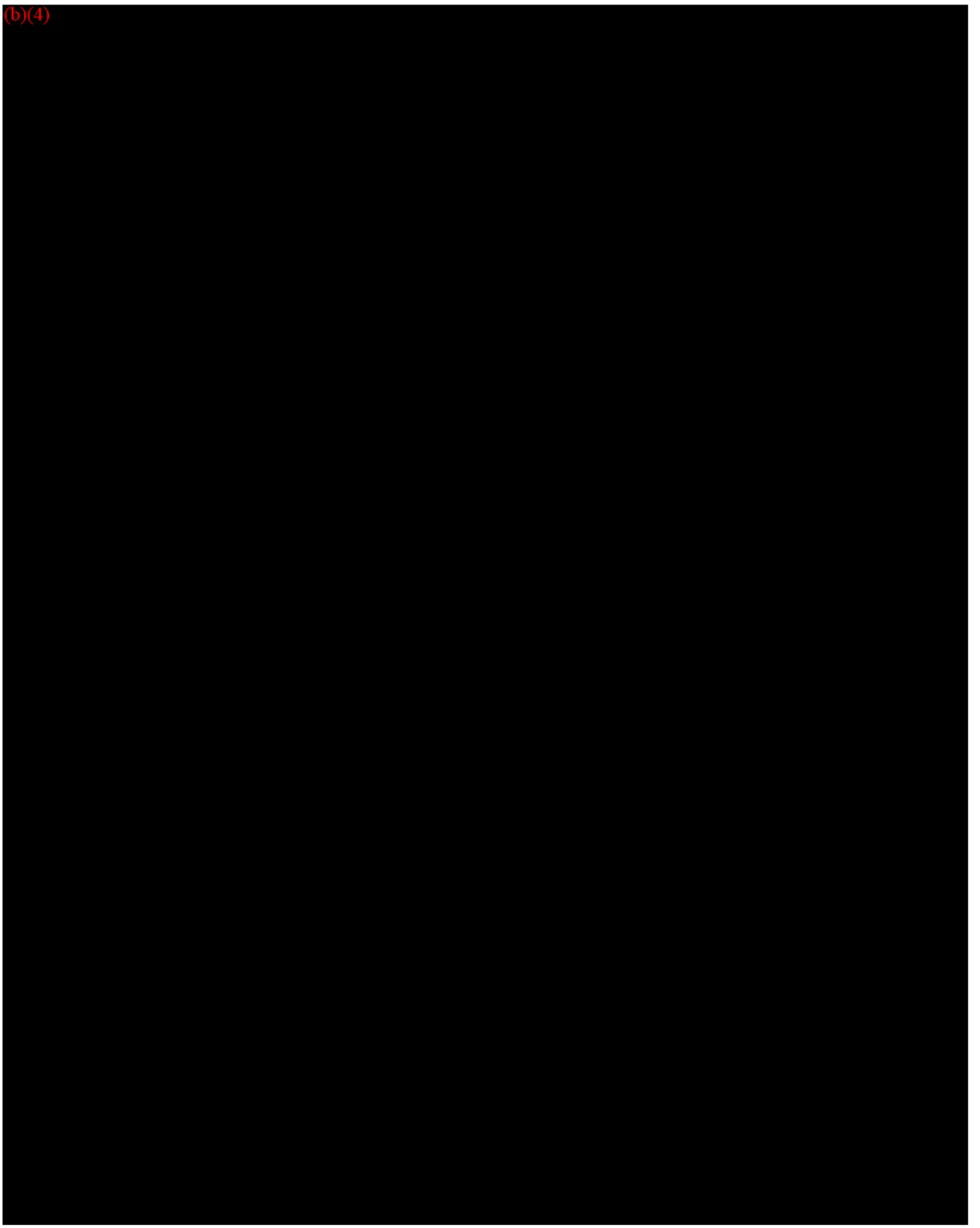

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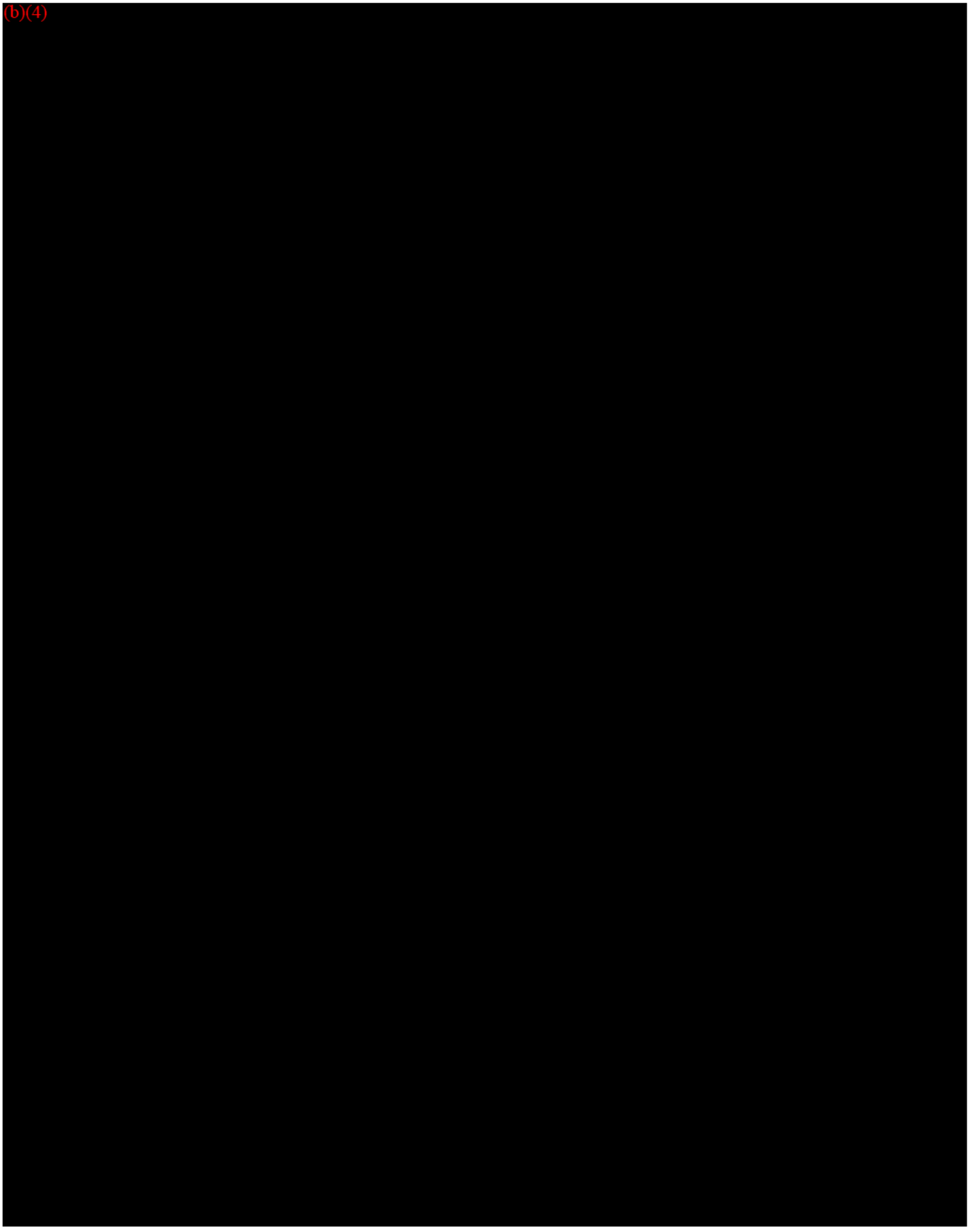

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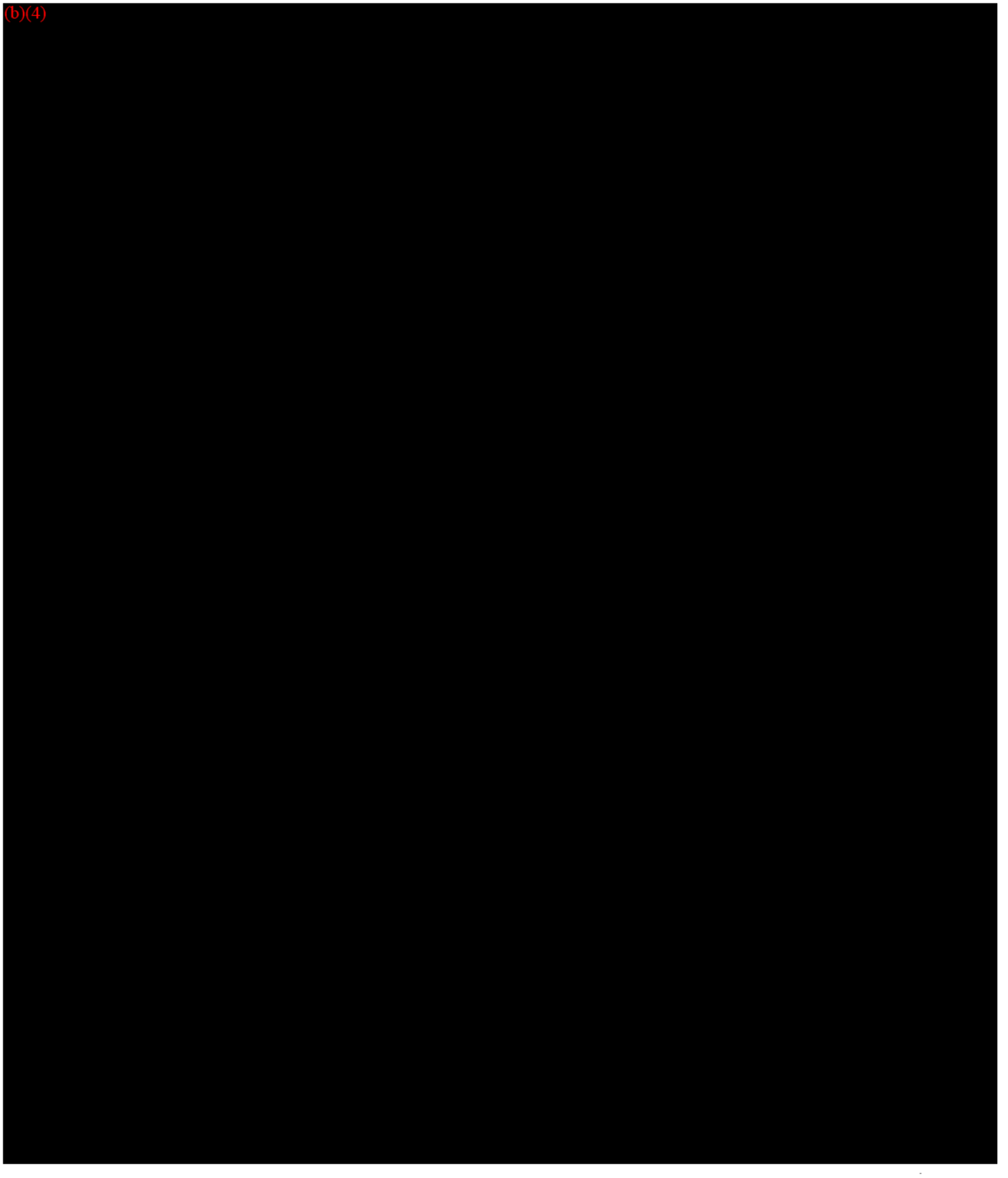

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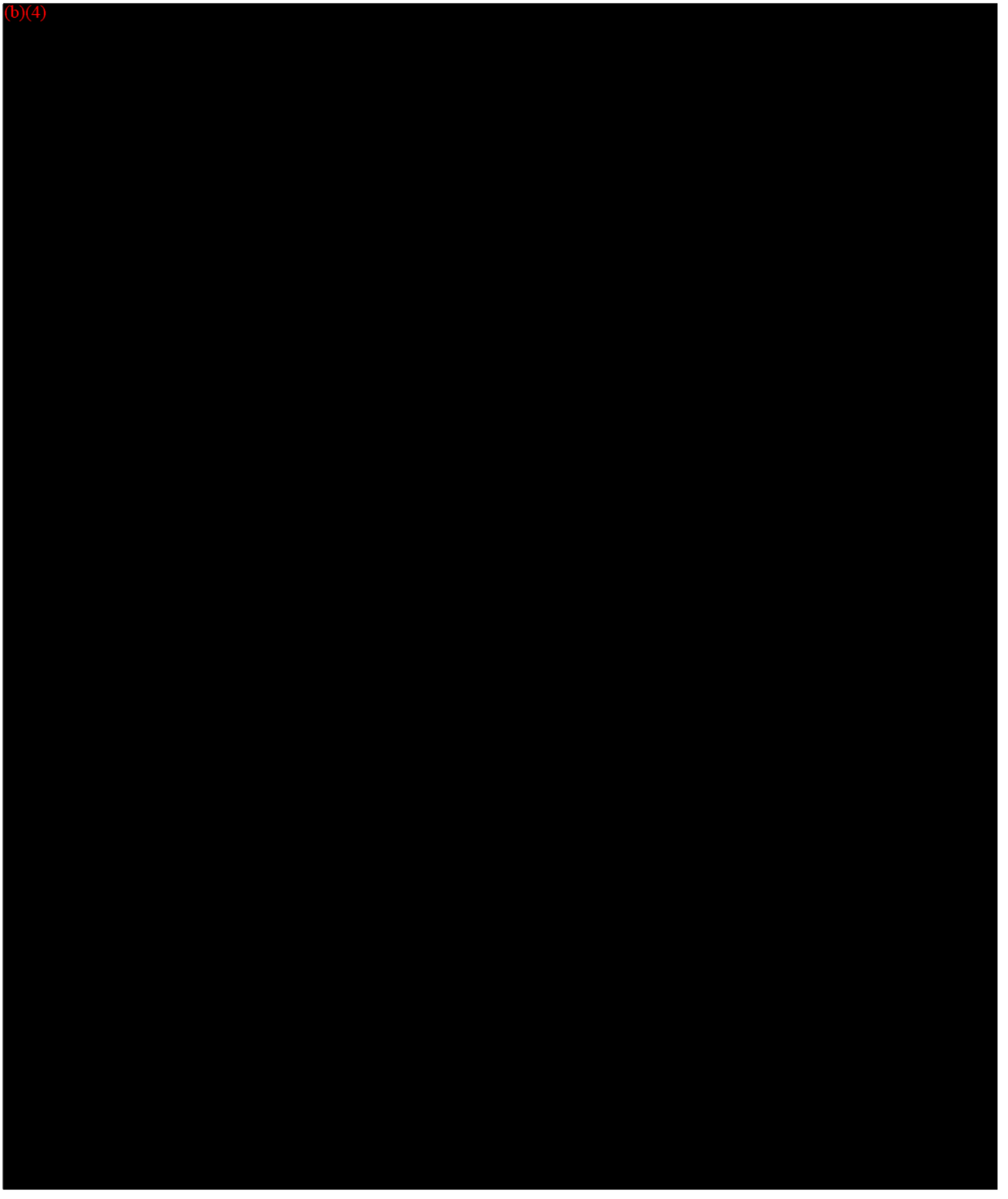

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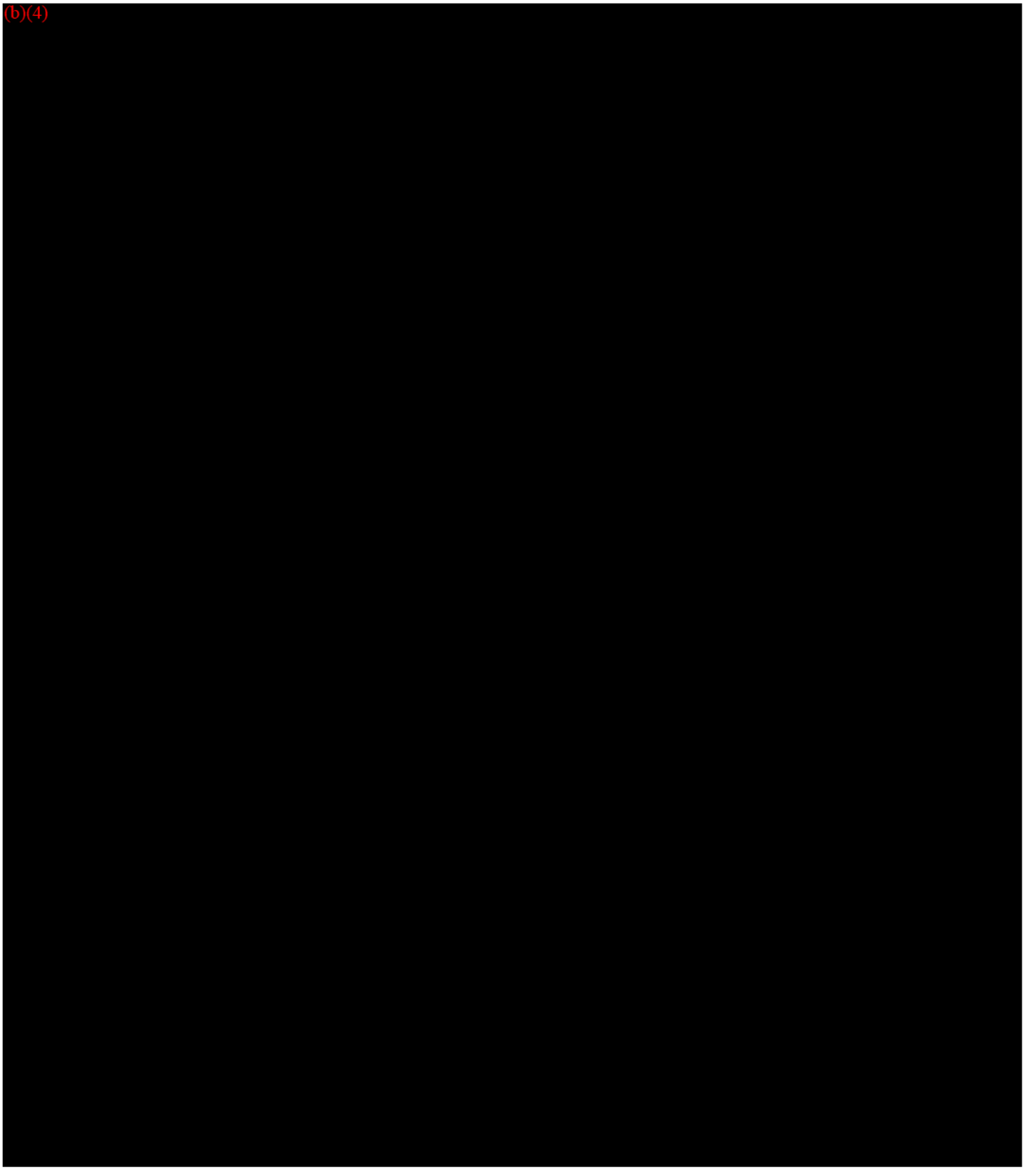

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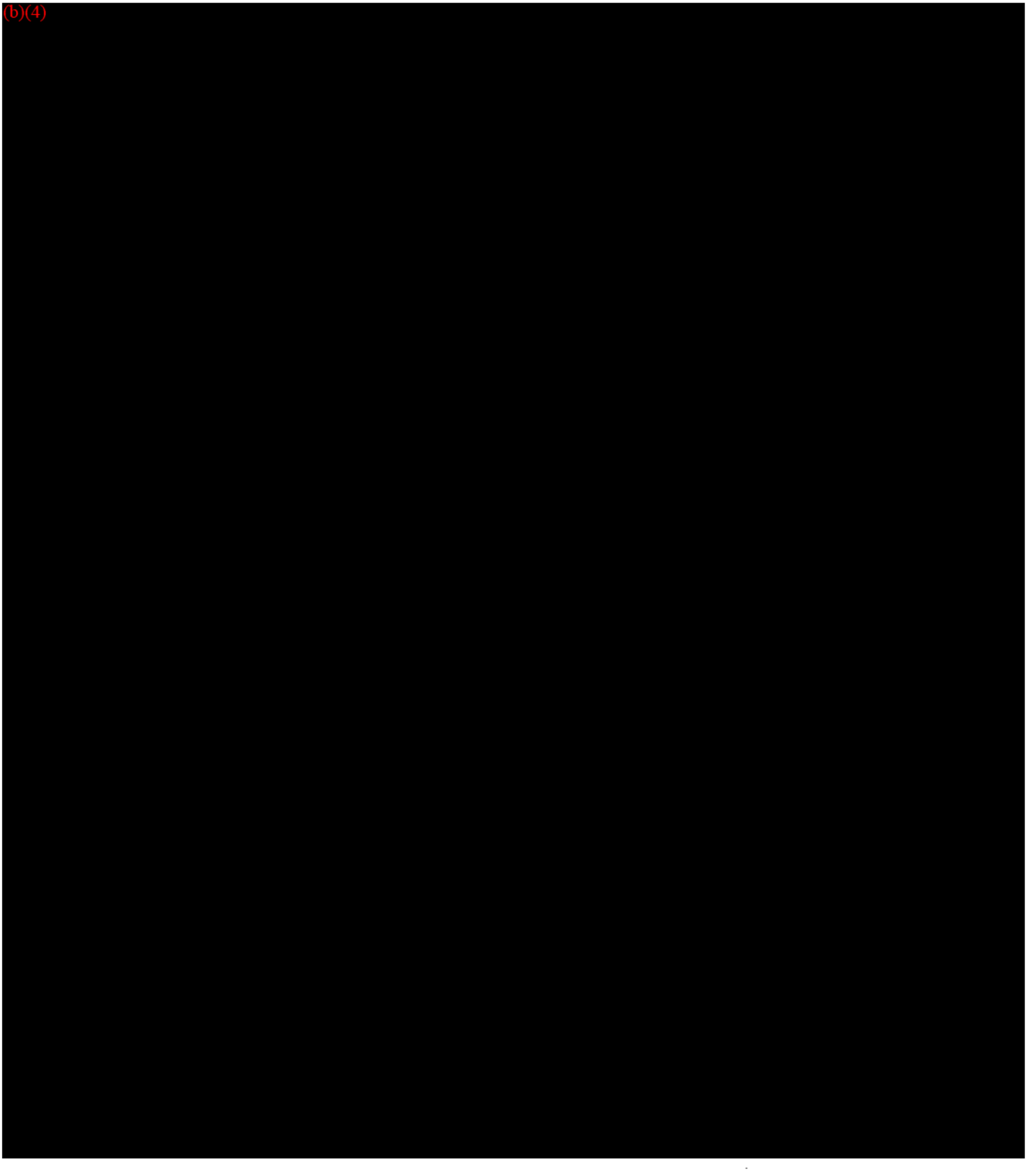

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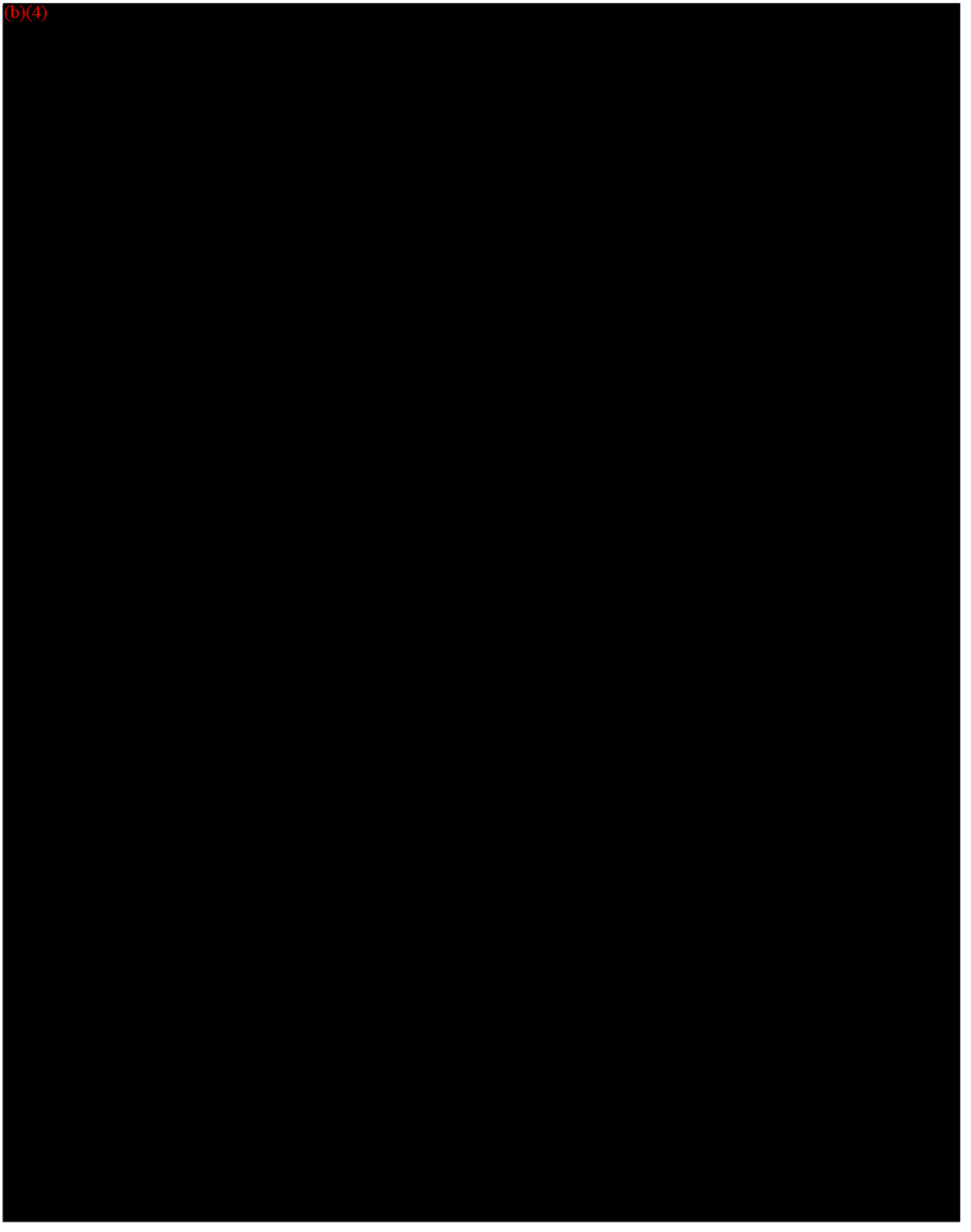

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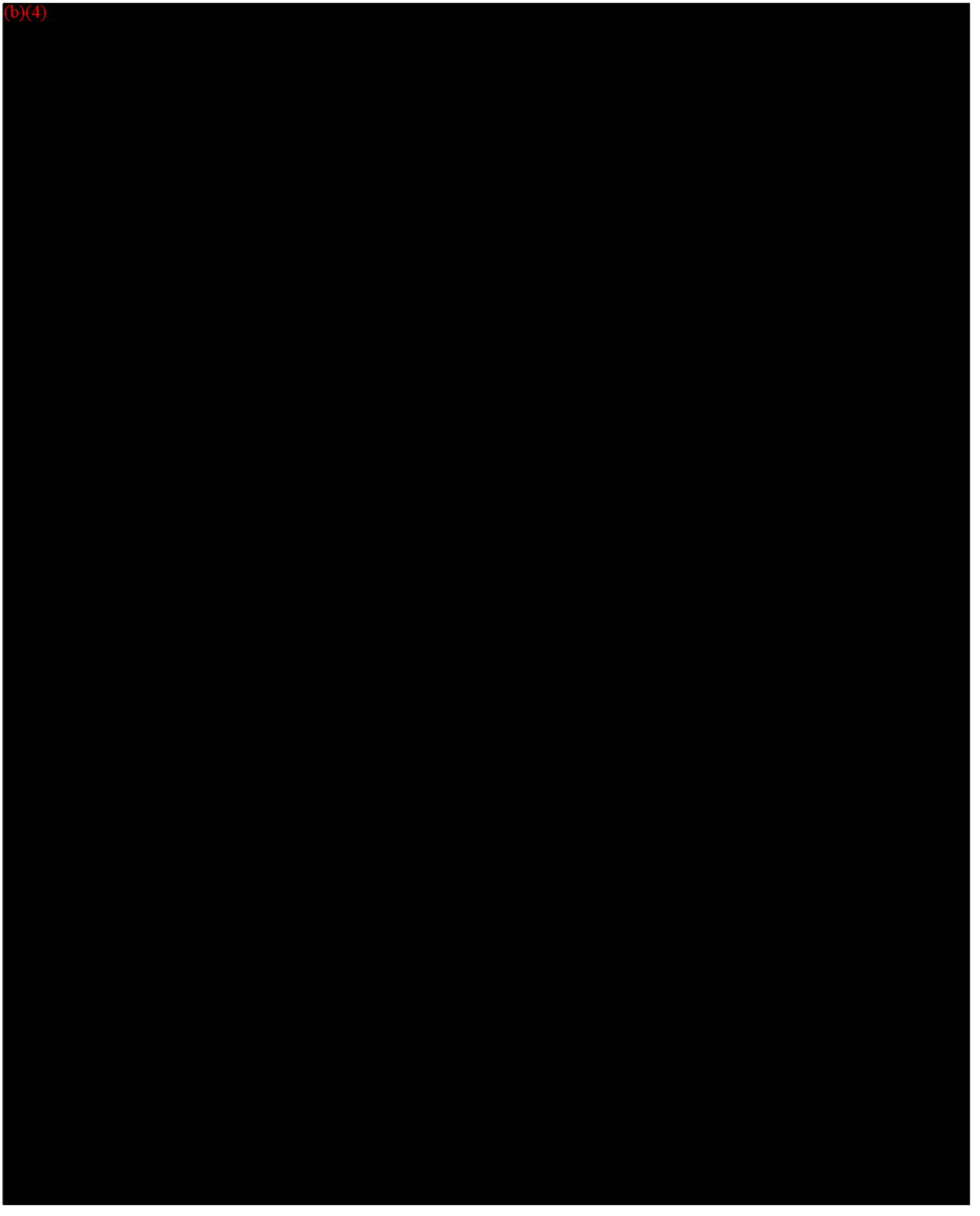

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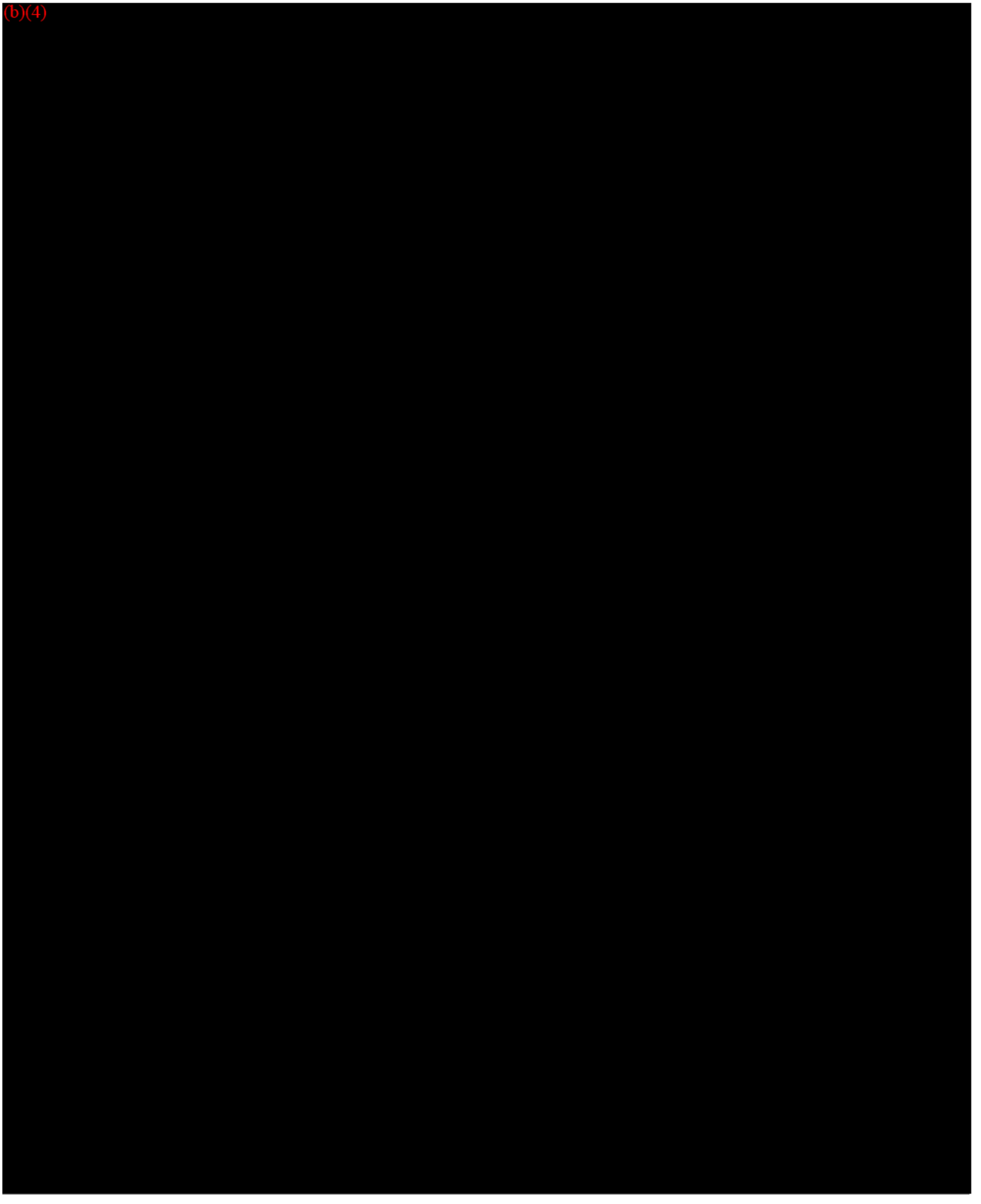

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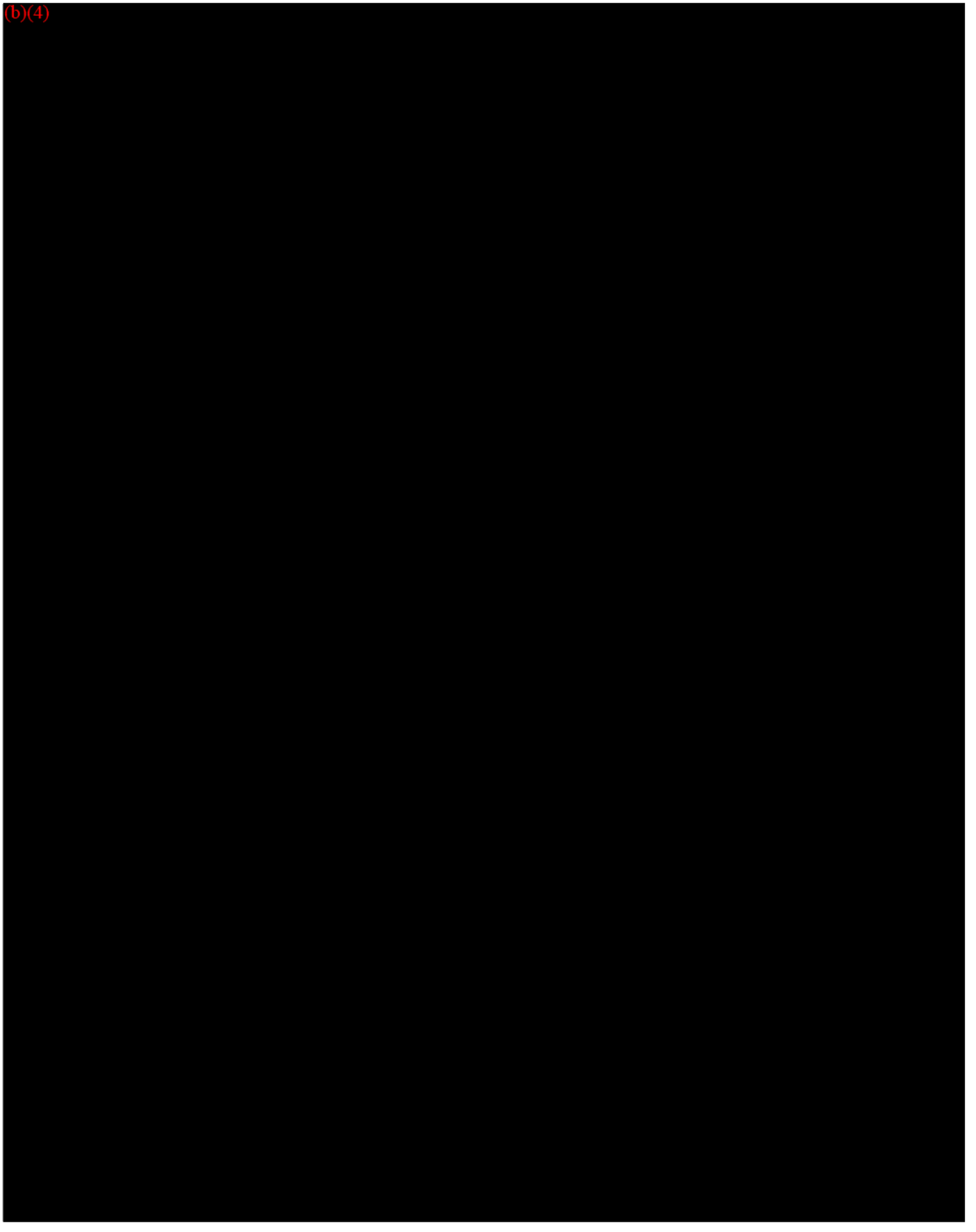

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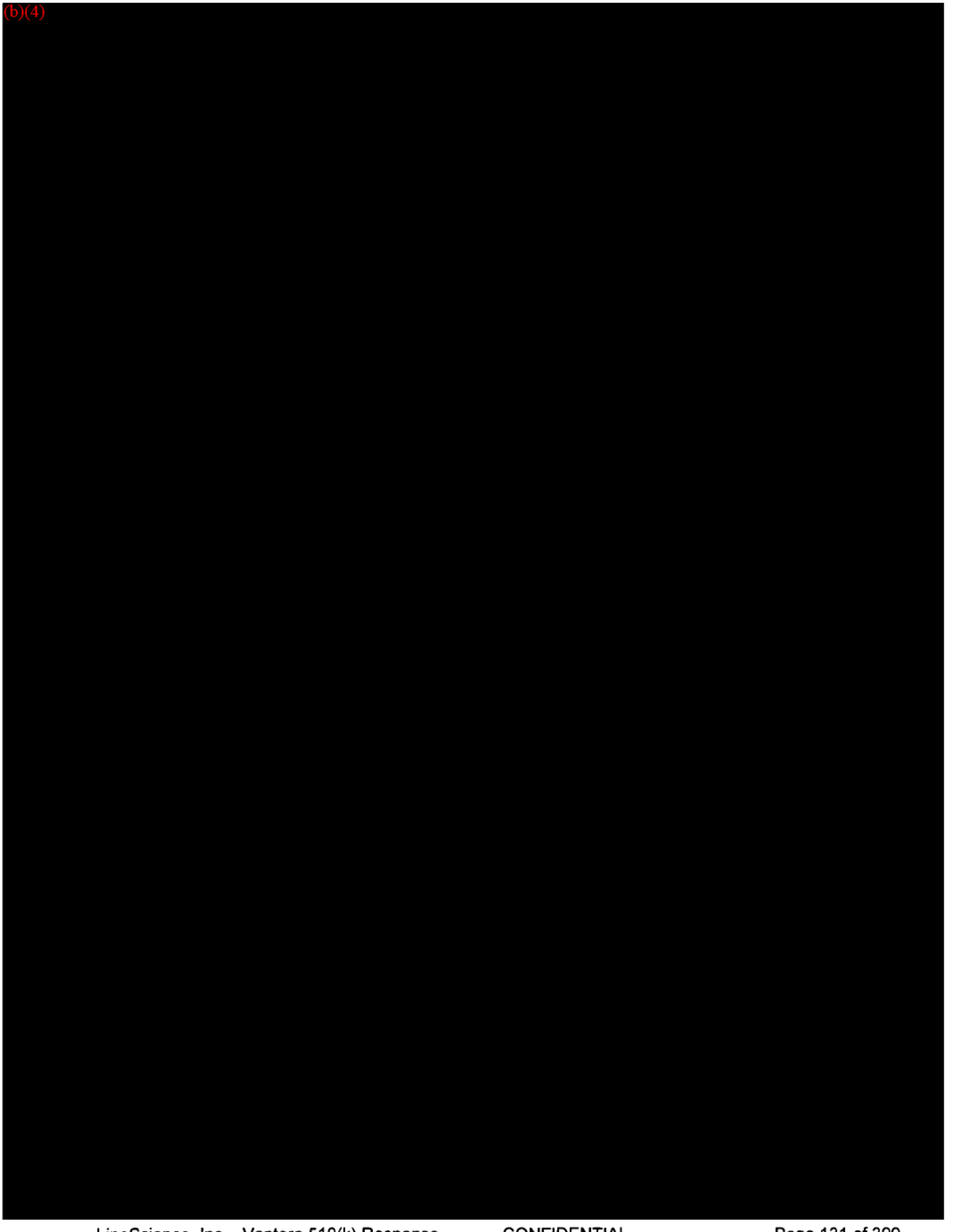

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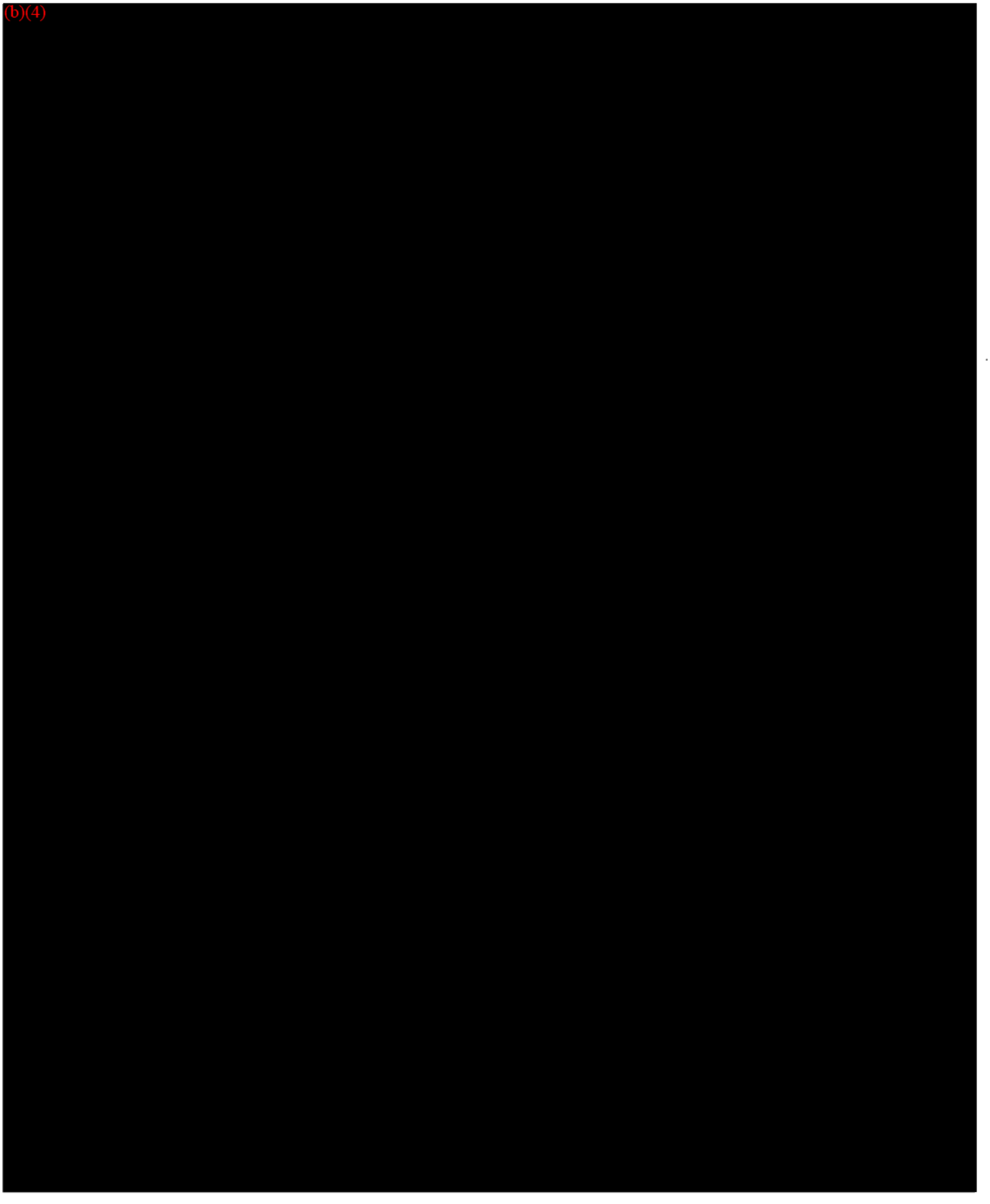

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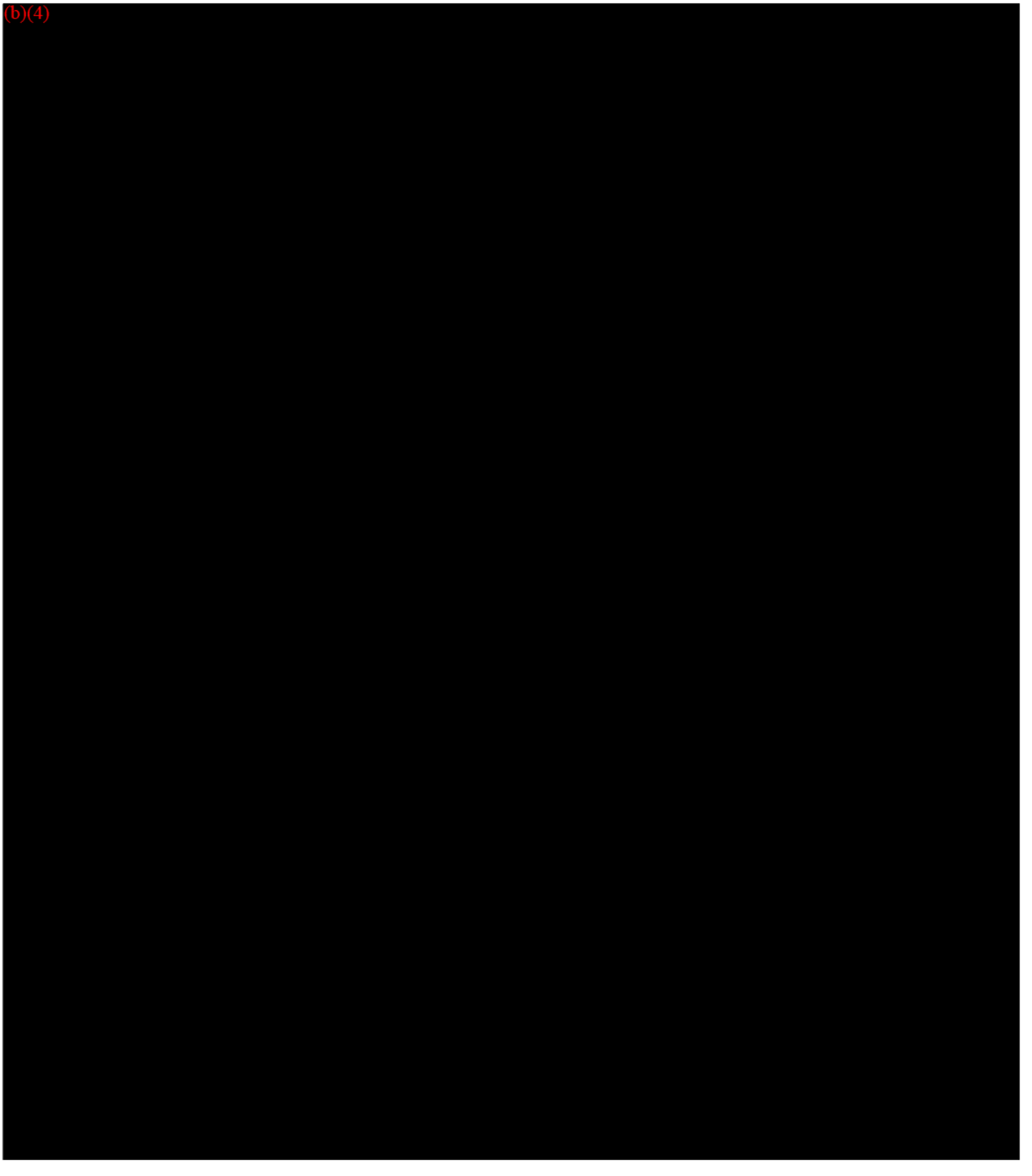

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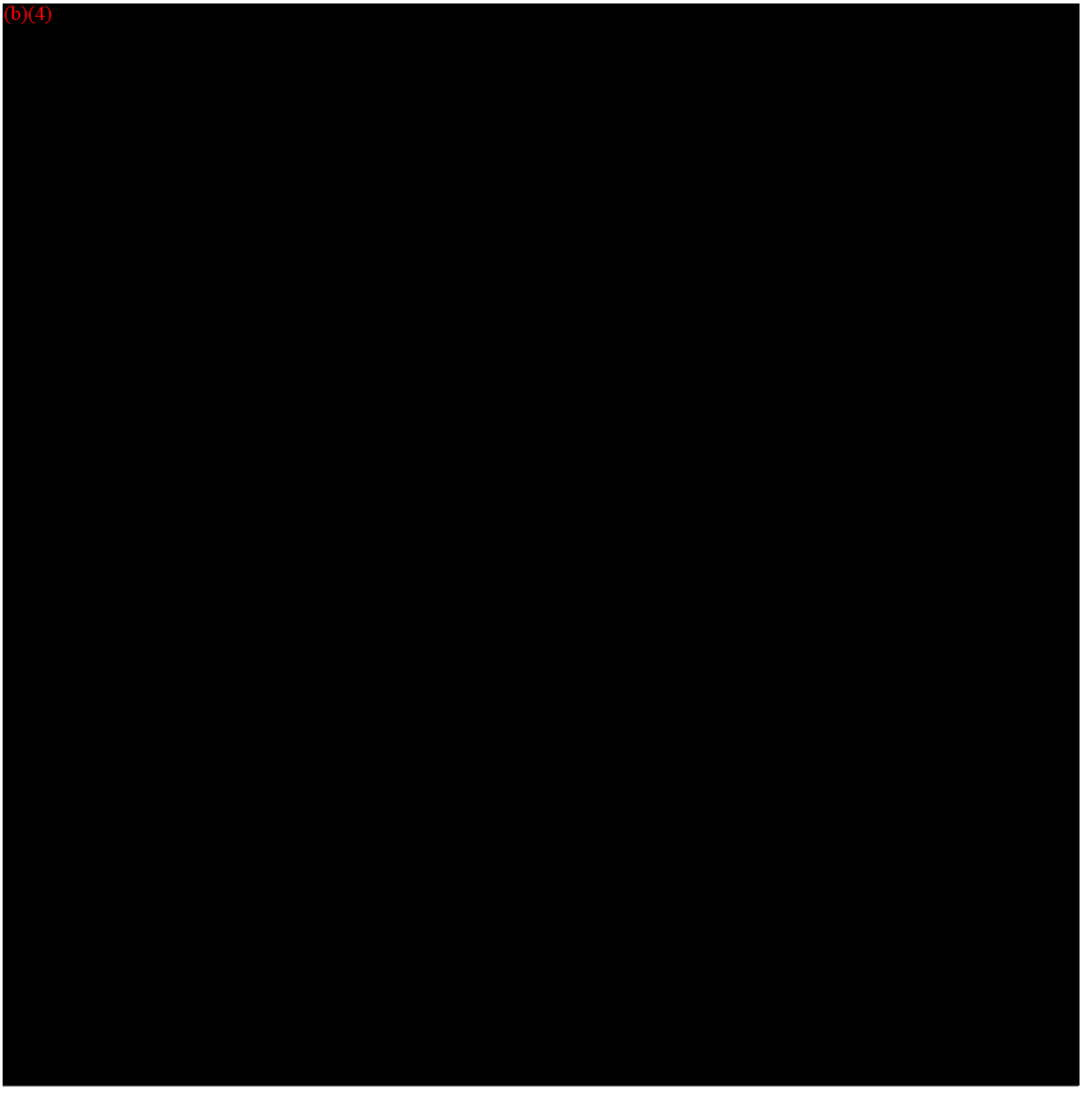


LIPOSCIENCE

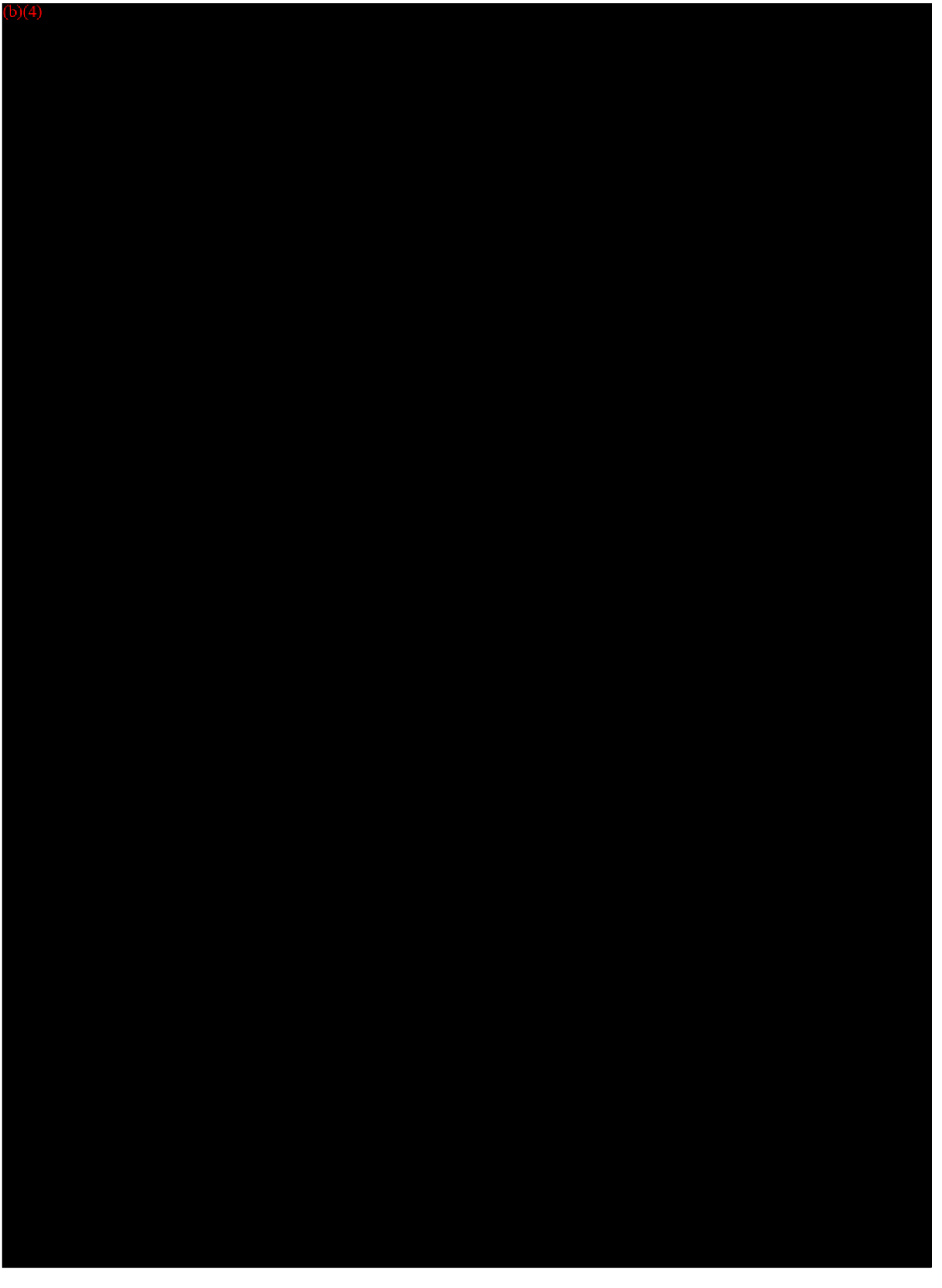
Premarket Notification
Response for K113830
Vantera® Clinical Analyzer for use with NMR
LipoProfile® test

July 27, 2012

Volume 2 of 2

Liposcience, Inc.
2500 Sumner Blvd.
Raleigh, NC 27616

Attachment 1: (b)(4) Letter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Attachment 2: 62-001-01-0615: Reference Range Study for *NMR LipoProfile* test

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APPENDIX 2: Health Questionnaire

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APPENDIX 3: Specimen Exclusion Log

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Attachment 3: Journal of Clinical Lipidology, October, 2011
"Clinical utility of inflammatory markers and advanced lipoprotein testing: Advice from an expert panel of lipid specialists

Journal of Clinical Lipidology (2011) 5, 338–367

Journal of Clinical Lipidology

Biomarkers

Clinical utility of inflammatory markers and advanced lipoprotein testing: Advice from an expert panel of lipid specialists

Michael H. Davidson, MD, FNLA, Chair*, Christie M. Ballantyne, MD, FNLA, Co-Chair, Inflammatory Biomarkers Sub-group, Terry A. Jacobson, MD, FNLA, Co-Chair, Lipoprotein Biomarkers Sub-group, Vera A. Bittner, MD, MSPH, FNLA, Lynne T. Braun, PhD, CNP, FNLA, Alan S. Brown, MD, FNLA, W. Virgil Brown, MD, FNLA, William C. Cromwell, MD, FNLA, Ronald B. Goldberg, MD, FNLA, James M. McKenney, PharmD, FNLA, Alan T. Remaley, MD, PhD, Allan D. Sniderman, MD, Peter P. Toth, MD, PhD, FNLA, Sotirios Tsimikas, MD, Paul E. Ziajka, MD, PhD, FNLA

Non-Panel Scientists: Kevin C. Maki, PhD, FNLA, Mary R. Dicklin, PhD

Baylor College of Medicine, Houston, TX, USA (Dr. Ballantyne); University of Alabama at Birmingham, Birmingham, AL, USA (Dr. Bittner); Rush University Medical Center, Chicago, IL, USA (Dr. Braun); Loyola University Stritch School of Medicine, Maywood, IL, USA (Dr. A.S. Brown); Emory University School of Medicine (Emeritus), Atlanta, GA, USA (Dr. W.V. Brown); Lipoprotein and Metabolic Disorders Institute, Raleigh, NC, USA and Wake Forest University School of Medicine, Winston–Salem, NC, USA (Dr. Cromwell); University of Chicago Pritzker School of Medicine, 515 North State Street, Suite 2700, Chicago, IL 60610, USA (Dr. Davidson); Provident Clinical Research, Glen Ellyn, IL, USA (Drs. Dicklin and Maki); University of Miami Miller School of Medicine, Miami, FL, USA (Dr. Goldberg); Emory University, Atlanta, GA, USA (Dr. Jacobson); National Clinical Research, Inc., and Virginia Commonwealth University (Emeritus), Manakin Sabot, VA, USA (Dr. McKenney); National Institutes of Health, National Heart, Lung, and Blood Institute, Bethesda, MD, USA (Dr. Remaley); McGill University, Montreal, Quebec, Canada (Dr. Sniderman); Sterling Rock Falls Clinic, Ltd., University of Illinois College of Medicine, Peoria, IL, USA (Dr. Toth); University of California, San Diego, La Jolla, CA, USA (Dr. Tsimikas); and Florida Lipid Institute, Winter Park, FL, USA (Dr. Ziajka)

KEYWORDS:
C-reactive protein;
Lipoprotein-associated phospholipase A2;
Apolipoprotein B;
Low-density lipoprotein particle concentration;

Abstract: The National Cholesterol Education Program Adult Treatment Panel guidelines have established low-density lipoprotein cholesterol (LDL-C) treatment goals, and secondary non-high-density lipoprotein (HDL)-C treatment goals for persons with hypertriglyceridemia. The use of lipid-lowering therapies, particularly statins, to achieve these goals has reduced cardiovascular disease (CVD) morbidity and mortality; however, significant residual risk for events remains. This, combined with the rising prevalence of obesity, which has shifted the risk profile of the population toward patients in whom LDL-C is less predictive of CVD events (metabolic syndrome, low HDL-C, elevated triglycerides), has increased interest in the clinical use of inflammatory and lipid biomarker assessments.

* Corresponding author.
E-mail address: **MDavidso@medicine.bsd.uchicago.edu**

Submitted July 28, 2011. Accepted for publication July 29, 2011.

doi:10.1016/j.jacl.2011.07.005

Lipoprotein(a);
Lipoprotein subfractions

Furthermore, the cost effectiveness of pharmacological intervention for both the initiation of therapy and the intensification of therapy has been enhanced by the availability of a variety of generic statins. This report describes the consensus view of an expert panel convened by the National Lipid Association to evaluate the use of selected biomarkers [C-reactive protein, lipoprotein-associated phospholipase A_2, apolipoprotein B, LDL particle concentration, lipoprotein(a), and LDL and HDL subfractions] to improve risk assessment, or to adjust therapy. These panel recommendations are intended to provide practical advice to clinicians who wrestle with the challenges of identifying the patients who are most likely to benefit from therapy, or intensification of therapy, to provide the optimum protection from CV risk.

Preamble

Since the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) I in 1988,[1] low-density lipoprotein cholesterol (LDL-C) has been the principal target of cholesterol treatment to reduce cardiovascular (CV) risk. The NCEP treatment guidelines have established LDL-C goals on the basis of risk stratification, with the lowest LDL-C targets for the patients at the greatest absolute risk for coronary heart disease (CHD) events. This strategy has successfully resulted in lower LDL-C levels and a significant reduction in the incidence of CV morbidity and mortality. Subsequently, non-high-density lipoprotein (HDL)-C goals were incorporated into the ATP III guidelines for patients with hypertriglyceridemia as a secondary target once LDL-C goals are achieved.[2] Post-hoc analyses of clinical trial datasets support the inclusion of non-HDL-C as a target of therapy, with the authors of most studies demonstrating that non-HDL-C is superior to LDL-C as a predictor of recurrent events on statin therapy.[3]

Unfortunately, measurements of non-HDL-C and the treatment to non-HDL-C goals have not been widely implemented, with surveys showing poor adherence to the recommended non-HDL-C targets[4] and major knowledge gaps on the calculation of non-HDL-C and the goals of therapy.[5] The National Lipid Association official policy has advocated the inclusion of non-HDL-C on all lipid profile laboratory reports.[6] The National Lipid Association believes that if clinicians are made more aware of a patient's non-HDL-C level, achievement of the non-HDL-C goals will improve in practice and ultimately result in further CV outcomes benefit.

Surveys of National Lipid Association members have demonstrated a major interest in the clinical utility of biomarkers to improve CV risk prediction and as potential novel targets of therapy. Three major factors are driving an increased interest in the use of biomarkers to potentially improve patient outcomes. First, although statins and LDL-C reduction reduce CV events, a significant residual risk for events remains in both primary and secondary prevention populations receiving statin therapy. The residual risk is most prominent in patients with metabolic syndrome and/or diabetes.[7,8] Second, a sharp increase in the prevalence of obesity has occurred during the last three decades, thereby markedly shifting the risk profile of the population toward patients with the metabolic syndrome features such as low HDL-C and elevated triglycerides. This is the same population at the greatest residual risk for events on statin therapy, and LDL-C is less predictive of CVD events in this group. Therefore, clinicians express considerable interest in the use of biomarkers, such as C-reactive protein (CRP), and lipid parameters, such as apolipoprotein (Apo) B or LDL particle concentration (LDL-P), that are elevated in this population and are frequently discordant with other traditional risk factors, particularly the level of LDL-C.

The Justification for the Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) was the first major clinical trial in which investigators tested the hypothesis that a novel biomarker such as CRP could be used to identify patients who would benefit from statin treatment but would have been considered "healthy" and not candidates for cholesterol-lowering therapy on the basis of existing guidelines.[9] Finally, the use of generic statins has made the cost of treatment very low and, therefore, enhanced the cost-effectiveness of the use of biomarkers to identify additional patients at increased absolute risk of CV events for whom more aggressive intervention may ultimately improve morbidity and mortality.[10,11]

The National Lipid Association convened a panel of clinical experts to evaluate the use of selected biomarkers in clinical practice as either tools to improve risk assessment or as markers to adjust therapy once a decision to treat had been made (**Table 1**). Five clinical scenarios were considered by the panel that accounted for the vast majority of patients in whom clinicians would consider the use of biomarkers. These clinical scenarios were defined as follows: (1) low risk (patients with <5% 10-year CHD event risk on the basis of NCEP ATP III Framingham risk scoring); (2) intermediate risk (patients with 5%–20% 10-year CHD event risk on the basis of NCEP ATP III Framingham risk scoring); (3) CHD or CHD equivalent (ie, diabetes, atherosclerotic CV disease [CVD], or more than 20% 10-year CHD event risk by ATP III Framingham risk scoring); (4) patients with a family history of premature CHD; and (5) patients with CVD and recurrent events despite apparently "optimal" medical therapy. Risk categories are classified in this document according to estimated Framingham 10-year CHD event risk to provide an objective standard for demarcation of low, intermediate (moderate to moderately-high), and high risk in those without CHD or CHD risk equivalents; however, the panel recognizes the role of clinical

Table 1 Summary recommendations for measurement of inflammatory markers and advanced lipoprotein/subfraction testing in initial clinical assessment and on-treatment management decisions

	Initial Clinical Assessment					
	CRP	**Lp-PLA$_2$**	**Apo B**	**LDL-P**	**Lp(a)**	**HDL or LDL Subfractions**
Low risk (<5% 10-year CHD event risk)	Not recommended	Not recommended	Not recommended	Not recommended	Not recommended	Not recommended
Intermediate risk (5-20% 10-year CHD event risk)	Recommended for routine measurement	Consider for selected patients	Reasonable for many patients	Reasonable for many patients	Consider for selected patients	Not recommended
CHD or CHD Equivalent	Consider for selected patients	Consider for selected patients	Consider for selected patients	Consider for selected patients	Consider for selected patients	Not recommended
Family History	Reasonable for many patients	Consider for selected patients	Reasonable for many patients	Reasonable for many patients	Reasonable for many patients	Not recommended
Recurrent Events	Reasonable for many patients	Consider for selected patients	Reasonable for many patients	Reasonable for many patients	Reasonable for many patients	Not recommended

	On-Treatment Management Decisions					
	CRP	**Lp-PLA$_2$**	**Apo B**	**LDL-P**	**Lp(a)**	**HDL or LDL Subfractions**
Low risk (<5% 10-year CHD event risk)	Not recommended	Not recommended	Not recommended	Not recommended	Not recommended	Not recommended
Intermediate risk (5-20% 10-year CHD event risk)	Reasonable for many patients	Not recommended	Reasonable for many patients	Reasonable for many patients	Not recommended	Not recommended
CHD or CHD Equivalent	Reasonable for many patients	Not recommended	Reasonable for many patients	Reasonable for many patients	Consider for selected patients	Not recommended
Family History	Consider for selected patients	Not recommended	Consider for selected patients	Consider for selected patients	Consider for selected patients	Not recommended
Recurrent Events	Reasonable for many patients	Not recommended	Reasonable for many patients	Reasonable for many patients	Consider for selected patients	Not recommended

Apo, apolipoprotein; CHD, coronary heart disease; CRP, C-reactive protein; HDL, high-density lipoprotein; Lp-PLA$_2$, lipoprotein-associated phospholipase A$_2$; LDL, low-density lipoprotein; LDL-P, LDL particle number/concentration; Lp(a), lipoprotein (a).

judgment in risk categorization and acknowledges that Framingham risk scoring may not be necessary for many patients with 0 or 1 major CHD risk factors.

The panel limited its assessment to the following biomarkers and lipid markers: CRP, lipoprotein-associated phospholipase A2 (Lp-PLA$_2$), Apo B, LDL-P, lipoprotein(a) [Lp(a)], and LDL and HDL subfractions. This list of biomarkers evaluated was not intended to be comprehensive, and the panel acknowledges that additional biomarkers may be used in some clinical practices. The specific biomarkers selected were those that, in the collective opinion of the organizers, have penetrated into clinical practice to at least a moderate degree, and for which sufficient evidence from epidemiological and clinical studies has accumulated for the panel to provide recommendations relevant to clinical practice (Table 2).[12–17] Additional panels may be organized in the future to address other biomarkers and/or to update recommendations for the biomarkers covered herein as new information becomes available.

The recommendations of the panel should not be considered guidelines or official policy of the National Lipid Association. They represent the consensus of opinions of clinicians considered to be experts in the field of clinical lipidology. In the development of a consensus, there are always compromises that are reached and, therefore, individuals on the panel may have points of view that are different from the consensus opinion. The expert panel believed that the recommendations should be both practical and clearly defined. Thus, the panel identified four categories of recommendations:

1. recommended for routine measurement in this population,
2. reasonable for many patients,
3. consider in selected patients, or
4. not recommended.

The panel weighed the available clinical evidence and heard testimony from other experts in the field; voting was used to establish the consensus position for each biomarker

Table 2 Laboratory values of CRP, Lp-PLA$_2$, Apo B, LDL-P, and Lp(a) according to lower-, intermediate-, and greater-risk categories, approximated from population studies

	Population-based approximations		
Biomarker	Lower risk	Intermediate risk	Greater risk
CRP, mg/L[12]	<1.0	1.0–3.0	>3.0
Lp-PLA$_2$, ng/mL[13,*]	<200	200–259	≥260
Apo B, mg/dL[14,†]	<80	80–119	≥120
LDL-P, nmol/L[15,16,‡]	<1000	1000–1559	≥1600
Lp(a), mg/dL[17,§]	<5	5–49	≥50

Apo, apolipoprotein; CRP, C-reactive protein; LDL-P, low-density lipoprotein particle number/concentration; Lp(a), lipoprotein (a); Lp-PLA$_2$, lipoprotein-associated phospholipase A$_2$.

*Values for lower, intermediate, and greater risk represent approximate tertiles of population distribution values obtained from a sample of 425 healthy men and women as described in the PLAC® Enzyme Immunoassay for the Quantitative Determination of Lp-PLA$_2$ in Human Plasma and Serum product insert information (diaDexus, Inc., South San Francisco, CA). Results from several studies have suggested that population cutpoints may vary markedly depending on the assay used.

†Values for lower, intermediate, and greater risk taken from the Framingham Offspring Study correspond approximately to Apo B population percentiles consistent with those from NCEP ATP III LDL-C cut-points of <100 mg/dL (20th percentile) and ≥160 mg/dL (80th percentile).

‡Values for lower, intermediate, and greater risk taken from the Multi-Ethnic Study of Atherosclerosis (MESA) population correspond approximately to LDL-P population percentiles consistent with those from NCEP ATP III LDL-C cutpoints of <100 mg/dL (20th percentile) and ≥160 mg/dL (80th percentile).

§Values for lower risk represent <22nd percentile and greater risk represent ≥80th percentile of the general population. Many laboratories use ≥30 mg/dL as a cutpoint for indicating an elevated Lp(a) concentration; this represents approximately the top tertile of the general population.

considered for each of the risk categories defined. Within a large population, risk for many will be similarly classified whether or not novel risk factors are included in the assessment. However, there was a consensus among the panel members that there are occasions when novel risk factor evaluation can provide useful insight into an individual patient's CV risk, particularly in cases where clinical judgment leads one to suspect that a patient may be at higher risk than suggested by traditional risk factor evaluation. The objective of this report is to provide practical advice to clinicians who wrestle with the challenges of identifying the patients who are most likely to benefit from therapy or intensification of therapy, to provide the optimum protection from CV risk.

Executive summary of recommendations

CRP: initial clinical assessment

1. In patients with low risk (10-year CHD event risk <5% on the basis of Framingham scoring), CRP measurement is not recommended for routine use but may be of value in selected patients, particularly those who have multiple mild disturbances, including those with the metabolic syndrome (**rating: "not recommended"**).
2. In patients with intermediate risk (5%–20% 10-year risk), it is recommended that CRP be measured routinely in men >50 years of age and women >60 years of age given its capacity to enhance risk prediction, especially when used with Reynolds risk scoring (**rating: "recommended for routine measurement"**).
3. In certain patients with CHD and risk equivalents, CRP measurement may be considered (**rating: "consider for selected patients"**).
4. In patients with a premature family history of CHD or in patients with established CHD with a history of recurrent events despite appropriate therapy, CRP measurement is a reasonable option to help determine if therapy should be: (1) started in the case of premature family history; or (2) intensified, or effort be made to identify other ancillary risk factors that may be impacting the progression or stability of established atherosclerotic plaque (**rating: "reasonable for many patients"**).

CRP: on-treatment management decisions

1. Among patients on treatment, there is insufficient evidence to support CRP measurement in patients with low risk and it is not recommended (**rating: "not recommended"**).
2. In patients with intermediate risk, CHD (or a CHD risk equivalent), or a history of recurrent coronary events, CRP measurement is reasonable and can help to guide the intensity of therapy (**rating: "reasonable for many patients"**).
3. Among patients with family history of premature CHD, CRP measurement can be considered and may have value, but its clinical utility in guiding therapy in this setting is less certain pending further investigation (**rating: "consider for selected patients"**).

Lp-PLA$_2$: initial clinical assessment

1. Lp-PLA$_2$ testing should generally not be performed in low-risk patients for the purpose of reclassification (**rating: "not recommended"**).
2. Lp-PLA$_2$ testing may be considered in intermediate-risk patients, as well as certain higher risk subgroups, such as those with CHD or a CHD risk equivalent, patients with family history of premature CHD, and patients with recurrent CHD events (**rating: "consider for selected patients"**).

Lp-PLA$_2$: on-treatment management decisions

1. Measurement of Lp-PLA$_2$ is not recommended for on-treatment risk management decisions in low-risk or intermediate-risk patients or in those with CHD or a

CHD risk equivalent, family history of premature CHD, or with recurrent CHD events (**rating: "not recommended"**).

Apo B: initial clinical assessment

1. In patients at low risk, <5% 10-year CHD event risk, the likelihood of markedly elevated Apo B is low. Hence, use of Apo B is not recommended in this category (**rating: "not recommended"**).
2. In patients at intermediate risk, those with premature family history, and those with recurrent events, measurement of Apo B would enable the best possible management of modifiable factors for vascular risk (**rating: "reasonable for many patients"**).
3. Once a patient with CHD or CHD risk equivalent has achieved his or her LDL-C and/or non-HDL-C goals, obtaining an Apo B measurement might be useful for determining whether further intensification of lipid-lowering therapy should be considered, as might be the case for discordant individuals with residual Apo B elevation (**rating: "consider for selected patients"**).

Apo B: on-treatment management decisions

1. There is no clear benefit of measuring Apo B in patients at low risk receiving lipid-altering therapy, and therefore it is not recommended in this group of patients (**rating: "not recommended"**).
2. In patients at intermediate risk, with CHD or CHD risk equivalent, and in those with recurrent events, measurement of Apo B is reasonable for many patients (**rating: "reasonable for many patients"**)
3. In patients with a family history of premature CHD, measurement of Apo B should be considered for selected patients (**rating: "consider for selected patients"**).

LDL-P: initial clinical assessment

1. Treatment decisions are unlikely to be altered by use of LDL-P among low-risk patients. Hence, use of LDL-P was not recommended for this patient group (**rating: "not recommended"**).
2. There is a substantial number of patients for whom LDL-C may not accurately reflect CVD risk, and data show that discordantly elevated LDL-P is more strongly associated with incident CVD risk than LDL-C. When LDL-P is discordantly elevated, consideration should be given to initiating LDL-lowering therapy. Thus, the use of LDL-P is thought to be reasonable for many patients at intermediate risk (5%–20%), those with a family history of CHD, and those with recurrent events, all of whom have the potential for discordantly elevated LDL-P (**rating: "reasonable for many patients"**).
3. Because of high CV risk, patients with known CHD or a CHD risk equivalent are candidates for aggressive lipid-altering therapy, and it is unclear whether additional LDL-P information would alter initial therapeutic decisions, but measurement might be considered for selected patients (**rating: "consider for selected patients"**).

LDL-P: on-treatment management decisions

1. Treatment decisions are unlikely to be altered by use of LDL-P among low-risk patients. Hence, use of LDL-P is not recommended for this patient group (**rating: "not recommended"**).
2. Use of LDL-P measurement is reasonable for many patients at intermediate risk treated to LDL-C and non-HDL-C goal, among patients with CHD or CHD risk equivalents on lipid-lowering therapy, and in those with recurrent CHD events, to adjudicate the adequacy of LDL lowering therapy. When LDL-P is discordantly elevated, consideration should be given to intensifying LDL lowering therapy (**rating: "reasonable for many patients"**).
3. Increased LDL-P is commonly encountered among patients with a family history of premature CHD. Once on therapy, use of LDL-P should be considered for selected patients treated to LDL-C and non-HDL-C goal to adjudicate the adequacy of LDL lowering therapy (**rating: "considered for selected patients"**).

Lp(a): initial clinical assessment

1. In patients with low risk (<5% 10-year CHD event risk), Lp(a) measurement is not recommended for routine use (**rating: "not recommended"**).
2. In patients with intermediate risk (5%–20% 10-year CHD event risk) or CHD or a CHD equivalent, it is recommended that Lp(a) measurement be considered for selected patients (**rating: "consider for selected patients"**).
3. Because elevated Lp(a) is additive to CHD risk, measurement of Lp(a) in patients with a premature family history of CHD or in patients with established CHD with a history of recurrent events despite appropriate therapy is a reasonable option (**rating: "reasonable for many patients"**).

Lp(a): on-treatment management decisions

1. Among patients with low-risk or intermediate-risk for CHD receiving treatment, there is insufficient evidence to support Lp(a) measurement and it is not recommended (**rating: "not recommended"**).
2. Lp(a) measurement may be considered for assistance with on-treatment management decisions in selected patients with CHD (or a CHD risk equivalent), premature family history, or a history of recurrent coronary events, on the basis of the rationale that aggressive LDL-C reduction is beneficial in those with elevated Lp(a) and LDL-C,

and that there is no evidence that reducing Lp(a) is harmful (**rating: "consider for selected patients"**).

LDL subfractions: initial clinical assessment and on-treatment management decisions

1. In patients with low risk (<5% 10-year CHD event risk), intermediate risk (5%–20% 10-year CHD event risk), CHD or CHD risk equivalent, premature family history of CHD in the absence of other risk factors, and in patients with established CHD who experience recurrent events despite appropriate therapy there is insufficient evidence to support LDL subfraction measurement for initial clinical assessment or on-treatment management decisions (**rating: "not recommended"**).

HDL subfractions: initial clinical assessment and on-treatment management decisions

1. In patients with low risk (<5% 10-year CHD event risk), intermediate risk (5%-20% 10-year CHD event risk), CHD or CHD risk equivalent, premature family history of CHD in the absence of other risk factors, and in patients with established CHD who experience recurrent events despite appropriate therapy there is insufficient evidence to support HDL subfraction measurement for initial clinical assessment or on-treatment management decisions (**rating: "not recommended"**).

C-reactive protein (CRP)

Does CRP predict risk, over and above traditional risk factors?

CRP is a marker of risk for CV events and reflects the intensity of inflammation.[18,19] In most cases, the term CRP indicates high-sensitivity CRP (ie, measured with a high-sensitivity assay), which is recommended for use in clinical practice. Serum high-sensitivity CRP levels of <1.0, 1.0–3.0, and >3.0 mg/L, representing approximate tertiles of values in the U.S. population, indicate lower, moderate, and greater relative risk for CV events, independent of serum LDL-C levels. CRP levels are most useful to refine risk estimates in patients with 10-year CHD event risk in the intermediate range of 5%–20%.[20]

In the Women's Health Study, CRP measurements were more predictive of CV events than lipids or apolipoproteins, including LDL-C, HDL-C, total cholesterol (TC)/HDL-C ratio, and Apo B, or other inflammatory markers such as interleukin (IL)-6 and serum amyloid A.[21] A number of prospective observational studies have demonstrated that the serum level of CRP is a strong, independent predictor of risk for myocardial infarction (MI), stroke, peripheral arterial disease, and CV mortality.[21–30]

A meta-analysis by the Emerging Risk Factors Collaboration (ERFC) of 54 prospective cohorts demonstrated that the hazard ratio (HR) for a one standard deviation change in CRP after adjustment for traditional risk factors was 1.37 (95% confidence interval [CI] 1.27–1.48), a HR that was equal to or greater in magnitude than that of non-HDL-C (1.28, 95% CI 1.16–1.40) or systolic blood pressure (1.35, 95% CI 1.25–1.45), and results were consistent in men and women (**Fig. 1**).[31] Elevated CRP has also been associated with increased vascular event rates among patients with acute coronary ischemia,[32–35] stable angina pectoris,[36] stable coronary artery disease,[37] and a history of MI.[38] In a study of 27,939 healthy women, baseline CRP measurements were predictive of CV events, including MI, stroke, and death, and risk for CV events increased in a linear fashion from the lowest to the highest serum levels of CRP.[39]

What is the physiological rationale for the link between CRP and adverse CV outcome?

Elevation in serum CRP was first associated with host immunity in patients with streptococcal pneumonia. On a molecular level, CRP is an annular, pentameric disk that belongs to the pentraxin family of proteins whose physiological role is to bind to phosphocholine present on pneumococci, oxidized LDL, and apoptotic and dying cells, suggesting it is part of the innate immune response to phosphocholine-bearing antigens. CRP is produced by the liver as part of the acute phase response.[40] During an infection, CRP binds to microbes and promotes their destruction by activating complement. CRP binds to the lectin-like oxidized LDL receptor-1 on endothelial cells[41] and is produced de novo in atherosclerotic lesions.[42]

At the present time, a clinical trial has not been completed to demonstrate that targeted, specific CRP lowering with an anti-inflammatory agent beneficially impacts CV outcomes. However, CRP has been hypothesized to directly promote atherogenesis by a number of potential mechanisms, including its role in: (1) endothelial cell adhesion molecule expression, which potentiates intravascular inflammation by increasing the influx of inflammatory white cells such as monocytes and T cells[41]; (2) reduced endothelial nitric oxide synthase expression,[43] nitric oxide release,[44] and increased coronary vasoreactivity[45]; (3) increased expression of endothelial plasminogen activator inhibitor-1, a protein that inhibits fibrinolysis and increases thrombotic risk[46]; (4) promotion of the production of endothelin-1,[47] a potent vasoconstrictor and inducer of vessel wall inflammation, abnormal cell growth, and thrombosis[48]; (5) increased monocyte chemoattractant protein-1 expression, which promotes the influx of monocytes into the subendothelial space[49]; (6) activation of complement by binding to partly degraded non-oxidized LDL cholesterol,[50] and colocalization with the terminal membrane attack complex in early atherosclerotic lesions[51]; (7) stimulation of macrophage scavenging for oxidized LDL, a principal step in foam cell formation[52]; and (8)

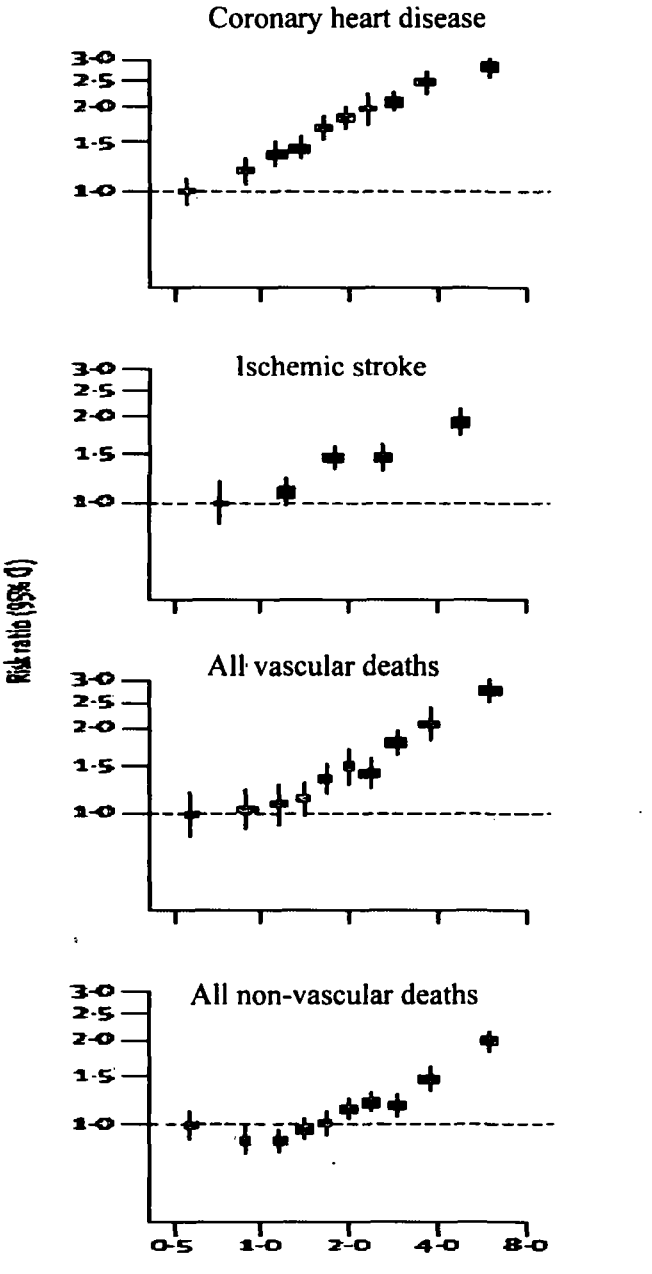

Figure 1 Risk ratios for major vascular and nonvascular outcome by quartiles of CRP concentration, adjusted for age, sex, and study, from a meta-analysis of 54 prospective cohort studies from the Emerging Risk Factors Collaboration.[31] Permission to reuse figure granted by Elsevier.

up-regulation of angiotensin type 1 receptors in vascular smooth muscle,[53] among other functions. On the basis of these investigations, CRP appears to have the potential to directly and indirectly activate inflammation and cytotoxicity, resulting in progressive vessel wall injury and atherosclerotic plaque formation. Consequently, it is possible, though not proven, that CRP may not only be a marker of CV risk, but may also directly promote its development and progression.

In which patients would CRP testing be most valuable?

Consistent with the results of JUPITER, it is appropriate to measure CRP in men at least 50 years and women at least 60 years of age who have an LDL-C <130 mg/dL and at least one other major CHD risk factor. If CRP is ≥2.0 mg/L in these patients, statin therapy for lipid lowering may be strongly considered.[54] JUPITER demonstrated benefit in patients at intermediate or greater risk on the basis of global risk scoring, whether they did, or did not, have metabolic syndrome or a family history of CHD.[55,56]

Among younger patients, there is no clear consensus as to the role of measuring CRP. As shown in the Atherosclerosis Risk in Communities (ARIC) study, the absolute risk for CV events is low in patients with low LDL-C and low CRP; however, absolute risk is greater and underestimated by Framingham scoring in patients with low LDL-C but elevated CRP.[56] Similar results were found in a post-hoc analysis of the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS).[57] Because traditional risk scoring and routine cholesterol screenings miss a significant percentage of patients at risk for events, consideration might be given to routine inclusion of CRP when evaluating global CV risk among patients with two or more major CHD risk factors in primary prevention. CRP measurement and family history for CV disease are important components of the Reynolds risk score (http://www.reynoldsriskscore.org) that are not included in the Framingham risk scoring system used in the NCEP ATP III guidelines. The Reynolds risk score has been shown to more accurately predict CV risk than Framingham risk scoring in both men[58] and women.[59]

When considering whether to measure CRP, it is important to avoid measurement in the setting of an active infection because CRP production increases as part of the acute phase response. In addition, if the patient has a malignancy or chronic inflammatory disease, CRP should not be measured for CV risk prediction. Postmenopausal hormone therapy with oral estrogen is associated with increased serum levels of CRP.[60] Moreover, because CRP shows substantial intraindividual variability (test-retest coefficient of variation ~40%), it is ideal to obtain and average at least two measurements when assessing CRP level in clinical practice.[20]

Should CRP be a target of therapy? If not, how should CRP affect treatment decisions?

1. CRP is a risk marker and is not presently considered a proven direct factor in the causal pathway for CV disease. CRP measurements assist health care providers in evaluating the adequacy of therapeutic intensity. It is not currently recommended that CRP be considered a treatment target. A clinical trial is underway which will help to determine whether the addition of an anti-inflammatory agent (interleukin-1β antagonist) in

high-risk patients after MI who continue to have elevated CRP levels will improve CV outcomes.

2. Investigators from JUPITER and other studies suggest that CRP levels predict outcomes in patients on statin therapy in both primary and secondary prevention settings. If the CRP level remains elevated with lipid therapy, then comprehensive CV risk management can be intensified through lifestyle modification and pharmacologic intervention as indicated for dyslipidemia, hypertension, insulin resistance, etc. In JUPITER, the patients who achieved the largest reductions in relative risk (RR; 79%) were those who achieved the dual targets of LDL-C <70 mg/dL and a CRP <1.0 mg/L (HR 0.21; 95% CI 0.49–0.84).[61] Patients who achieved LDL-C <70 mg/dL and CRP <2.0 mg/L achieved a 65% RR reduction for the primary composite end point (HR 0.35; 95% CI, 0.23–0.54; **Fig. 2**).[62] Among patients who achieved neither of these targets, the risk reduction with rosuvastatin was significantly attenuated to 36% (HR 0.64; 95% CI 0.49–0.84; $P < .0001$).

The potential importance of achieving dual targets for LDL-C and CRP is highlighted by additional studies. In the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction (PROVE-IT-TIMI) trial, the effects of intensive (atorvastatin 80 mg) compared with standard (pravastatin 40 mg) statin therapy on the prevention of secondary coronary events among 4162 patients demonstrated that those patients achieving an LDL-C <70 mg/dL and a CRP level <1.0 mg/L on therapy had the lowest risk for events compared with patients unable to achieve either or both of these levels.[63] These results were corroborated by the Aggrastat-to-Zocor (A to Z) trial, which compared early intensive statin treatment (simvastatin 40 mg/d for 30 days followed by 80 mg/d) to a delayed conservative statin strategy (placebo for 4 months followed by 20 mg/d simvastatin).[64] In the Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) trial, intensive lipid lowering (atorvastatin 80 mg) compared with moderate lipid lowering (pravastatin 40 mg) in 654 patients with stable coronary artery disease demonstrated that the rate of progression of coronary artery atheroma volume was significantly and independently associated with the magnitude of reduction in CRP.[65] Atheroma regression was only observed in patients with CRP less than the median, irrespective of whether achieved LDL-C was above or below the median.[66] Although there is no specific anti-inflammatory drug currently available for use in clinical practice that reproducibly reduces serum levels of CRP, patients in primary and secondary prevention settings with CRP levels ≥2.0 mg/L may benefit from intensification of both lifestyle modification (weight loss, smoking cessation, dietary modification) and statin therapy, which have been shown to lower serum levels of CRP.[54,67–70]

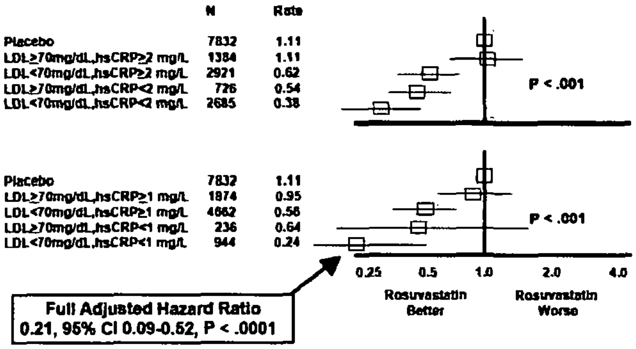

Figure 2 A prospective assessment of the effects of 20 mg of rosuvastatin versus placebo on rates of nonfatal MI, nonfatal stroke, admission for unstable angina, arterial revascularization, or cardiovascular death according to on-treatment concentrations of LDL-C and high-sensitivity CRP in JUPITER.[62] Permission to reuse figure granted by Elsevier.

What are the main areas of controversy and research questions regarding CRP and its use in clinical practice?

One major area of controversy relates to whether CRP itself is a direct contributor to the atherothrombotic process, or a marker for other processes that are within the causal pathways leading to clinical events. A second important issue is whether CRP should be a treatment target. Results from multiple statin intervention trials suggest that those with low levels of LDL-C and CRP during treatment have better CV outcomes than those with a low on-treatment level of one or the other. To date, no trial has been completed in which the policy of treating to specific target levels of CRP has been tested. Recently, a trial of an anti-inflammatory agent (interleukin-1β antagonist) that lowers CRP without reducing atherogenic lipoprotein levels has been started in post-MI patients with elevated CRP. This trial is expected to help establish whether reducing inflammation in high-risk patients, as reflected in the change in CRP concentration, leads to reduced CV morbidity and mortality.

Lipoprotein-associated phospholipase A_2 (Lp-PLA_2)

Does Lp-PLA_2 predict risk, over and above traditional risk factors?

The authors of several prospective epidemiological studies have identified Lp-PLA_2 as a significant predictor of CV events and stroke.[71,72] In both primary and secondary prevention trials, an approximate 2-fold increase in risk for CV events, after multivariate adjustment for traditional risk factors, is associated with Lp-PLA_2 in the upper tertile or quartile. Lp-PLA_2 predicts risk independent of, and complementary to, CRP.[73] Notably, in the ARIC Study, when both Lp-PLA_2 and CRP were in the top tertile, the risks for CHD events and stroke increased 4-fold and 11-fold,

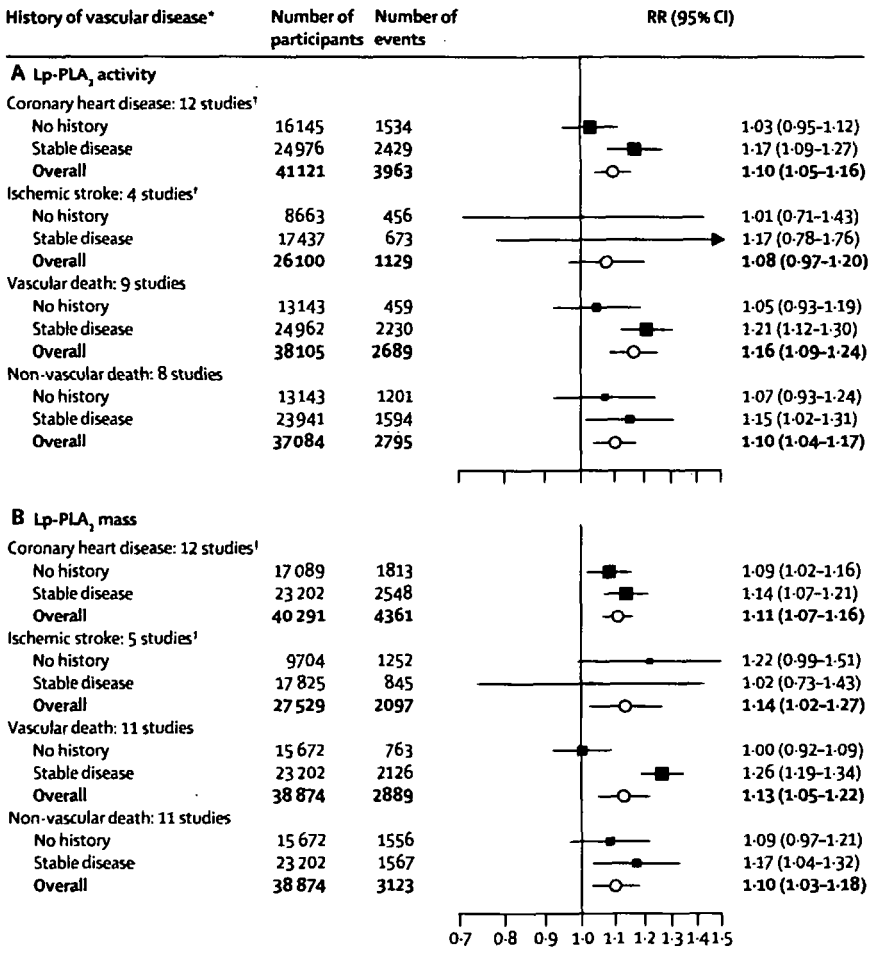

Figure 3 Risk ratios for CHD, ischemic stroke, and vascular, and nonvascular mortality per 1 standard deviation greater Lp-PLA_2 activity or mass at baseline, adjusted for several risk factors. Error bars represent 95% CIs. The sizes of the boxes are proportional to the inverse of the variance of risk ratios.[78] *Diagnosis more than 30 days before baseline of myocardial infarction, angina, other coronary heart disease, stroke (including transient ischemic attack), peripheral vascular disease, or coronary surgery (including revascularizations). †Fatal and nonfatal events. Permission to reuse figure granted by Elsevier.

respectively, compared with those in the lowest tertile for both markers.[74,75] Unlike for CHD risk, epidemiological studies fail to show a consistent relationship between elevated LDL-C and stroke risk.[76] However, elevation in Lp-PLA_2 confers approximately a 2-fold increase in both first and recurrent strokes.[77]

A recent meta-analysis of almost 80,000 patients in 32 prospective studies evaluated associations of Lp-PLA_2 mass and activity with risk of CHD, stroke, and mortality (Fig. 3).[78] RR ratios adjusted for conventional risk factors and expressed per one standard deviation increment in Lp-PLA_2 activity or mass at baseline were as follows: 1.10 (95% CI 1.05–1.16) with Lp-PLA_2 activity and 1.11 (1.07–1.16) with Lp-PLA_2 mass for CHD; 1.08 (0.97–1.20) and 1.14 (1.02–1.27) for ischemic stroke; and 1.16 (1.09–1.24) and 1.13 (1.05–1.22) for vascular mortality, respectively. The association between baseline Lp-PLA_2 and CHD risk was similar in magnitude to those for non-HDL-C and systolic blood pressure.

As a result of consistent epidemiological data showing that elevated Lp-PLA_2 predicts risk for CHD events and stroke, the NLA Biomarkers Expert Panel recommends that the measurement of Lp-PLA_2 may assist with the risk assessment of intermediate-risk and some high-risk patients.

What is the physiological rationale for the link between Lp-PLA_2 and adverse CV outcome?

Lp-PLA_2 primarily circulates bound to LDL particles, although it also resides on HDL particles, lipoprotein (a) [Lp(a)], and triglyceride-rich remnant lipoproteins. It is produced by macrophages, monocytes, T lymphocytes, and mast and liver cells. Lp-PLA_2 activity has been shown to be up-regulated in atherosclerotic lesions and in rupture-prone fibrous caps.[79,80] Lp-PLA_2 is an enzyme that is responsible for the hydrolysis of oxidized phospholipids on LDL particles within the arterial intima, thus producing two highly inflammatory mediators, lysophosphatidylcholine and oxidized fatty acids. These products result in a cascade of events that have been linked to atherosclerotic plaque formation: up-regulation of adhesion molecules, expression of cytokines, recruitment of monocytes to the

intimal space, and differentiation of monocytes into macrophages that engulf oxidized LDL, producing foam cells.[81–84] Foam cells aggregate to form a fatty streak covered by a fibrous cap. Cytokines and proteases secreted by the plaque destroy the collagen within the fibrous cap, making it prone to rupture and resulting in an acute coronary event.

Lp-PLA_2 and its byproduct, lysophosphatidylcholine, have been identified in early atherosclerosis and are associated with endothelial dysfunction.[85] Furthermore, Lp-PLA_2 expression in carotid artery plaques predicted long-term cardiac events in 162 consecutive patients who underwent elective carotid endarterectomy and were then followed for approximately 4 years. Carotid plaque expression of Lp-PLA_2 above the median was associated with markedly increased risk for cardiac events (HR 3.39; 95% CI 1.13–10.17; $P = .03$).[86]

The rationale for Lp-PLA_2 as a key inflammatory biomarker is attractive because this enzyme is produced in atherosclerotic plaques and is specifically linked to plaque inflammation, and presumably, rupture, suggesting a possible causal pathway leading to clinical events. In preclinical studies investigators have shown that inhibition of Lp-PLA_2 attenuates the inflammatory response and slows atherosclerotic plaque progression.[87] Lp-PLA_2 shows less variability than CRP, making it a practical tool for CVD risk assessment.[81] However, clinical trials are necessary to support the proposition that blocking or reducing Lp-PLA_2 activity will interrupt the sequence of events leading to atherosclerotic plaque formation and/or rupture.[88]

In which patients would Lp-PLA_2 testing be most valuable?

Recently, a consensus panel of investigators recommended how to use Lp-PLA_2 along with guideline-endorsed CVD risk assessment to better stratify individuals who might be at greater CVD risk than suggested by traditional risk factors and thus benefit from more aggressive management strategies.[89] The consensus panel endorsed the use of Lp-PLA_2 for the assessment of CHD event and stroke risk in intermediate- or moderate-risk populations, and specifically recommended testing in the following patients:

- any patient with two or more major CHD risk factors;
- any patient 65 years of age or older with one additional risk factor, given that risk for CHD events and strokes increase with age;
- smokers;
- individuals with an elevated fasting glucose; and
- patients with diagnostic criteria for metabolic syndrome who are generally at moderate risk (it has been shown that elevated Lp-PLA_2 further increases CVD risk in these patients.[88])

According to that consensus panel, moderate-risk individuals with an elevated Lp-PLA_2 level (>200 ng/mL) should be reclassified as high risk, and the LDL-C goal adjusted from <130 mg/dL to <100 mg/dL. The panel[89] also recommended Lp-PLA_2 testing for patients with known CHD or a CHD risk equivalent, such as diabetes or ischemic stroke. An elevated Lp-PLA_2 would place these patients in the very high-risk category, and therefore, the LDL-C goal is <70 mg/dL.

Results from epidemiological studies have suggested that Lp-PLA_2 predicts risk independent of, and complementary to, CRP.[73] Therefore, it might be reasonable to measure both inflammatory markers in intermediate- and high-risk individuals. Given that CRP is an acute-phase reactant, its elevation can be caused by acute infections, chronic inflammatory conditions and obesity, as well as certain medications such as oral estrogens. Lp-PLA_2, on the other hand, appears to be related specifically to vascular inflammation, shows significantly less variability than CRP, and may be causally linked to plaque rupture.

Similar to the previous consensus panel, members of the NLA Biomarkers Expert Panel recommends that Lp-PLA_2 testing may be considered in intermediate-risk patients, as well as certain greater-risk subgroups, such as those with CHD or a CHD risk equivalent, patients with family history of premature CHD, and patients with recent CHD events, to identify patients who might benefit from more intensive lipid therapy. Lp-PLA_2 testing should generally not be performed in low-risk patients for the purpose of reclassification. An elevated level of Lp-PLA_2 measured 1 month after a patient started statin therapy in PROVE IT–TIMI 22 was associated with increased CV event risk, with an adjusted HR of 1.33 (95% CI 1.01–1.74) for the top versus bottom Lp-PLA_2 quintile.[90] The association between the Lp-PLA_2 level and the primary CV event outcome appeared somewhat attenuated in the group receiving high-dose atorvastatin, HR 1.29 (95% CI 0.87−1.92), compared with the group receiving pravastatin, HR 1.63 (95% CI 1.03–2.58), but the test for interaction did not reach statistical significance. Although the on treatment data for Lp-PLA_2 level were not presented for the Heart Protection Study, the vascular protection produced by simvastatin did not vary significantly by baseline level of Lp-PLA_2.[91] Because of the paucity of data examining the predictive value of Lp-PLA_2 during lipid-modifying therapy, Lp-PLA_2 testing is not recommended for these patients.

Should Lp-PLA_2 be a target of therapy? If not, how should Lp-PLA_2 affect treatment decisions?

Although Lp-PLA_2 has been shown to be a significant predictor of risk for CHD events, stroke, and mortality in primary and secondary prevention studies, there are no randomized trials in which the authors examine the benefits of lowering Lp-PLA_2 with any specific therapies. Lipid-altering medications, including statins, fenofibrate, ezetimibe, and prescription omega-3 fatty acids, as well as weight loss, have been shown to reduce inflammatory markers, including Lp-PLA_2[92–96]; however, the degree of inflammatory marker reduction typically correlates with the extent of lipid lowering. It is currently unknown whether lowering Lp-PLA_2 per se, will have a direct benefit on CVD events and mortality.

This question may be answered in the near future by investigations of selective Lp-PLA$_2$ inhibitors that are currently in clinical development. Darapladib, a potent selective inhibitor of Lp-PLA$_2$, produced sustained inhibition of plasma Lp-PLA$_2$ activation in patients on atorvastatin therapy. In a clinical trial with 95% of patients having CHD or CHD risk equivalents, darapladib at 40, 80, and 160 mg produced dose-related reductions of 43%, 55%, and 66% in Lp-PLA$_2$ activity.[97] At the greatest dose of 160 mg of darapladib, there were changes in IL-6 and CRP at 12 weeks that suggest a possible reduction in total inflammatory burden. A study in a hyperlipidemic, diabetic pig model showed a marked reduction in atherosclerosis.[98] In a proof-of-concept trial in which the authors used intravascular ultrasound with virtual histology in 330 patients with coronary disease, darapladib prevented necrotic core expression versus placebo (P = .012) but did not significantly modify the primary endpoint (plaque deformability).[99]

On the basis of these preliminary studies suggesting a beneficial effect of Lp-PLA$_2$ inhibition on the atherosclerotic process, a large morbidity and mortality trial was initiated in 2008 to evaluate the long-term safety and efficacy of darapladib versus placebo in patients with chronic high-risk CHD, receiving standard of care, including lipid-lowering and antiplatelet therapies. In the Stabilization of Atorvastatin Plaque by Initiation of Darapladib Therapy (STABILITY) trial,[100] 15,828 patients were randomized to receive darapladib 160 mg or placebo for 3 years. The primary end point is the composite of major adverse CV events: CV death, nonfatal MI, and nonfatal stroke. Until the STABILITY Trial results are known, the NLA Biomarkers Expert Panel cannot recommend the measurement of Lp-PLA$_2$ for on-treatment risk management decisions.

What are the main areas of controversy and research questions regarding Lp-PLA$_2$ and its use in clinical practice?

The main areas of controversy regarding Lp-PLA$_2$ center on cost-effectiveness and whether the measurement of Lp-PLA$_2$ after the institution of lipid-altering therapy is warranted to help guide therapy. The results from the ongoing STABILITY trial are expected to provide evidence relevant to these questions. With the development of automated assays for Lp-PLA$_2$ mass and activity, there need to be additional studies to examine population distributions, as there has been a considerable range of median values reported in studies using different assays.[78]

Apolipoprotein B (Apo B)

Does Apo B predict risk, over and above traditional risk factors?

A wealth of epidemiological and clinical trial evidence justifies LDL as the cornerstone of lipid management. A body of evidence has evolved that supports the view that LDL-C is not the best indicator of the risk attributable to LDL because risk correlates more closely with the number of circulating atherogenic particles than with the quantity of cholesterol carried by those particles.[101–113] The LDL-P concentration is the major determinant of plasma Apo B because ~90% of the total circulating Apo B is associated with LDL particles in both normotriglyceridemic and hypertriglyceridemic patients.[114] Type III hyperlipoproteinemia, an uncommon but important disorder because it carries a very high risk of vascular disease, is one of the few exceptions because large numbers of remnant Apo B48 and Apo B100 particles account for almost half of the total Apo B particles in these patients.[115,116]

If the amount of cholesterol per LDL particle was constant, the LDL-C concentration would consistently reflect the number of LDL particles. However, the amount of cholesterol per LDL particle varies substantially.[117] In individuals whose LDL particles, on average, contain the normal amount of cholesterol, the LDL-C level will accurately reflect the LDL burden. In these patients, Apo B and LDL-C levels are concordant and are equivalent markers of risk and the adequacy of therapy. However, in individuals whose LDL particles, on average, contain less cholesterol than normal, the LDL-C concentration will underestimate the number of LDL particles. In these individuals, the Apo B concentration will more accurately reflect the number of LDL particles and LDL-related CVD risk.

Similarly, in individuals whose LDL particles, on average, contain more cholesterol than normal, the LDL-C concentration will overestimate the number of LDL particles. In these patients as well, the Apo B concentration will more accurately indicate the number of LDL particles than will the LDL-C concentration.[116] This variance in the composition of LDL particles[117] is important clinically because small, cholesterol-poor LDL particles are the dominant form of LDL in a substantial proportion of patients in all the major clinical risk groups for vascular disease. It is these groups in which Apo B level amplifies the capacity to estimate more accurately the LDL-related risk of vascular disease in an individual patient.

Thus, a high proportion of patients with diabetes or the metabolic syndrome,[118] abdominal obesity,[119] hypertriglyceridemia,[120] or with low HDL-C but otherwise-normal lipids,[121,122] will have increased numbers of LDL particles that contain less cholesterol than average. The LDL-C concentration is often normal in these patients despite an elevated level of LDL particles, and hence an elevated circulating concentration of Apo B. An increased number of cholesterol-poor LDL particles is also the hallmark abnormality of the most common familial dyslipoproteinemia associated with coronary disease, familial combined hyperlipidemia (FCH).[123–125] Notably, in familial hypercholesterolemia, LDL particles contain greater-than-average quantities of cholesterol, but both LDL-C and Apo B concentrations are markedly elevated.

In many prospective studies, investigators have demonstrated that the risk of vascular disease relates more closely

to the level of Apo B than LDL-C.[101–113] The non-HDL-C concentration reflects the sum of the cholesterol in all Apo B-containing particles and also predicts risk better than LDL-C in both normotriglyceridemic and hypertriglyceridemic individuals.[107,126] The evidence comparing Apo B and non-HDL-C as markers of risk is mixed, with results from some studies suggesting them to be equivalent and others supporting the view that Apo B is superior. A subset of the ERFC project database (22 of the 68 studies) was analyzed and the hazard ratio for non-HDL-C was equivalent to that for Apo B.[127] However, most of these studies were unpublished and, within the ERFC analysis, the hazard ratios for LDL-C and non-HDL-C were indistinguishable, a finding that contrasts with much prior experience. A more recent meta-analysis of the published studies that include risk estimates for non-HDL-C and Apo B suggests a hierarchy of outcome among the markers, with Apo B being the best predictor, LDL-C the worst, and non-HDL-C intermediate.[128]

Another advantage Apo B has over LDL-C is accuracy of measurement, a critical issue in therapeutic decision-making. The limitations of the Friedewald method used to estimate LDL-C have been well documented.[129] The introduction of direct LDL-C measurement methods may have improved precision for normolipidemic samples, but not for hyperlipidemic sera, and these assays also suffer from the disadvantage of not being standardized.[130]

The switch to direct HDL-C measurement brings with it a similar set of problems as those noted for the direct LDL-C assays, leading to error in the calculation of non-HDL-C.[129] By contrast, the measurement of Apo B is standardized, and can be performed relatively inexpensively and reliably in clinical laboratories.[129,131] As with non-HDL-C, fasting is not required for Apo B measurement, a major advantage in clinical practice.

What is the physiological rationale for the link between Apo B and adverse CV outcome?

Each lipoprotein particle secreted by the intestine or the liver contains one molecule of Apo B,[132] which is embedded within the phospholipid monolayer that encircles the particle. The Apo B molecule provides external structural integrity for the particle and, in contrast to all the other apolipoproteins, which can associate transiently with lipoproteins, Apo B stays with the lipoprotein particle for its lifetime.

Because each particle contains one molecule of Apo B, the plasma Apo B concentration is a direct indication of the total number of circulating Apo B-containing lipoprotein particles. The intestinal Apo B particles contain Apo B48, whereas the hepatic particles contain the full-length form of the protein, Apo B100.[133] Both Apo B48 and Apo B100 are recognized by most clinically available immunoassays.[129] Apo B48 particles, even postprandially, contribute minimally to the total number of Apo B particles in plasma.[129,134] Measurement of Apo B, like non-HDL-C, does not require a fasting blood draw.

Atherosclerosis is initiated and advanced by the trapping of Apo B-containing lipoprotein particles within the subintimal space of the arterial wall. The cholesterol that is deposited within the arterial wall, which leads over time to the development of a complex plaque, is transported into the arterial wall within an Apo B-containing lipoprotein particle. LDL Apo B particles are considered to be far more important than VLDL Apo B particles in driving atherogenesis because, in most cases, the serum LDL particle concentration is roughly nine times that of the VLDL particle concentration. Also, LDL particles are substantially smaller than VLDL particles, so are able to enter the arterial wall more readily.

The number of LDL particles entering the arterial wall is directly related to the concentration of LDL particles in plasma. A greater number of Apo B particles entering the arterial wall will increase the number that becomes trapped in the subendothelial space. This, in turn, increases the number of particles susceptible to modification via oxidation and other pathways, leading to unregulated uptake by macrophages, further promoting the development and progression of atherosclerosis.[135]

In which patients would Apo B testing be most valuable?

Low risk

Apo B was **"not recommended"** in this category of patients because the characteristic that defines this group, ie, <5% 10-year CHD event risk, makes the likelihood of a markedly elevated Apo B low.

Intermediate risk

In this category, Apo B received a **"reasonable for many patients"** recommendation because a large portion of the patients, if not the majority, belong to one of the classes in which discordance between Apo B and LDL-C has been well-documented. These include patients with hypertriglyceridemia, abdominal obesity, the metabolic syndrome or insulin resistance, and patients with otherwise-normal lipids but low HDL-C. In patients with LDL-C and/or non-HDL-C above NCEP ATP III cutpoints for initiation of lipid therapy, the measurement of Apo B would not be required to make the decision to initiate treatment, and therefore would not be necessary. On the other hand, given the analytical imprecision in the laboratory determination of LDL-C,[136] it could be argued that the decision to commit a patient to a prolonged course of therapy or, conversely, not to treat when treatment might be of value, should be confirmed by an independent and more reliable laboratory parameter, such as Apo B. That is a question of clinical judgment.

For those at intermediate risk with an LDL-C and/or non-HDL-C below the NCEP ATP III cutpoints for initiation of therapy, the NLA Biomarkers Expert Panel accepts that Apo B is a more reliable measure of the quantity of

LDL in plasma than LDL-C and measurement of Apo B would be reasonable to identify patients with an elevated LDL particle burden who might benefit from LDL-lowering treatment. The choices of threshold levels of Apo B for initiation of therapy have generally been determined on the basis of population percentile equivalents of the NCEP ATP III LDL-C cutpoints. For example, the Canadian Guidelines selected a level of Apo B of 100 mg/dL to correspond to an LDL-C level of 130 mg/dL.[137]

CHD or CHD risk equivalent

In CHD patients, the decision to substantially lower LDL is based on clinical criteria, and statin therapy would be indicated no matter the level of any of the markers: LDL-C, non-HDL-C or Apo B.[138] Because the decision to treat is not based on the level of any of these markers, it could be reasonably argued that it is not necessary to measure them before instituting the therapy. Once a patient has been treated to his or her LDL-C and/or non-HDL-C goal(s), obtaining an Apo B measurement would help to determine whether further intensification of lipid lowering therapy might be considered, as might be the case for discordant individuals with residual elevation in Apo B concentration despite having attained cholesterol goals.

In those with a CHD risk equivalent such as clinical evidence of non-CHD atherosclerosis or diabetes mellitus, the same argument could be made. In patients with diabetes, for example, the LDL-C concentration is often normal, and only a low or moderate dose of statin might be thought necessary to achieve target levels, but in a substantial number of these patients, Apo B is markedly elevated, notwithstanding the normal level of LDL-C. Therefore, the panel decided on a **"consider for selected patients"** recommendation for patients with CHD or risk equivalents.

Family history of premature CHD

This panel accepted the ATP III definition of a premature family history, namely of the presence of CHD before age 55 years in a male and before age 65 years in a female first-degree relative.[139]Apo B received a **"reasonable for many patients"** recommendation based, in part, on the fact that FCH is the most common atherogenic dyslipoproteinemia associated with premature CHD, far more common, in fact, than familial hypercholesterolemia. Moreover, the clinical risk associated with FCH is similar to the clinical risk associated with heterozygous familial hypercholesterolemia.

The fact that the genetic basis of FCH has not been clearly defined does not reduce its clinical importance. Until recently, a reliable diagnosis of FCH has not been possible in routine clinical care. However, a diagnostic algorithm has been developed and validated to identify individuals affected with FCH. The FCH phenotype has been defined as triglycerides >150 mg/dL and an Apo B >120 mg/dL.[124] On the basis of this definition, in a cohort presenting with premature MI, Wiesbauer et al[140] demonstrated that 38% had a lipoprotein phenotype consistent with FCH and 76% of these families were shown to have FCH. Thus, just as an individual presenting with familial hypercholesterolemia is an opportunity to identify other affected family members, so a patient presenting with FCH is an important opportunity to identify other affected family members.

Recurrent events

Apo B received a **"reasonable for many patients"** recommendation for this category of patients, whose very high level of risk requires the best possible management of all the modifiable factors for vascular risk. Accurately assessing LDL burden by measuring Apo B will often be useful for aiding difficult therapeutic choices.

Should Apo B be a target of therapy? If not, how should Apo B affect treatment decisions?

Statins reduce clinical vascular event rates in nearly every category of patients in which they have been tested. Consensus groups have recommended targets for LDL-C principally on the basis of the levels achieved in these trials for different classes of patients, matching the intensity of lipid treatment to the absolute risk for an event. However, objection has been raised to this practice because the major statin trials were designed as tests of different therapeutic regimens, not as tests of different target levels of LDL-C.[141]

Lowering of Apo B by statins is as directly related to the fundamental metabolic mechanism of statin action as is lowering of LDL-C because enhanced clearance of Apo B particles is the principal basis for the reduction in both. In addition, in none of the statin trials in which Apo B was measured was there an imbalance at baseline between the levels of Apo B in the groups compared.[142–149] No statin treatment trial has failed to find a significant relation between on-treatment Apo B and residual risk of vascular disease, whereas a number have found no significant relation between on-treatment LDL-C to the residual risk of vascular disease.[142,150,151] Such results validate the use of Apo B as a target of statin therapy.

Clinicians should be aware that statins lower LDL-C and non-HDL-C levels more than they lower Apo B.[152] Measurement of Apo B provides a more direct assessment of the residual number of atherogenic particles, which could potentially modify therapeutic decisions. In the large subgroup of patients with cholesterol-depleted LDL particles, the LDL-C level underestimates LDL particle concentration. Treatment with statins exaggerates this discordance, thus some patients at target levels of LDL-C (and non-HDL-C) still have concentrations of LDL particles above desirable levels.[153] If Apo B is measured, therapeutic adjustments can be made when such discordant patients are identified.

Although the clinical benefits of statin therapy are unequivocal, the evidence for clinical gains from combination therapy is incomplete. Adding an additional agent to

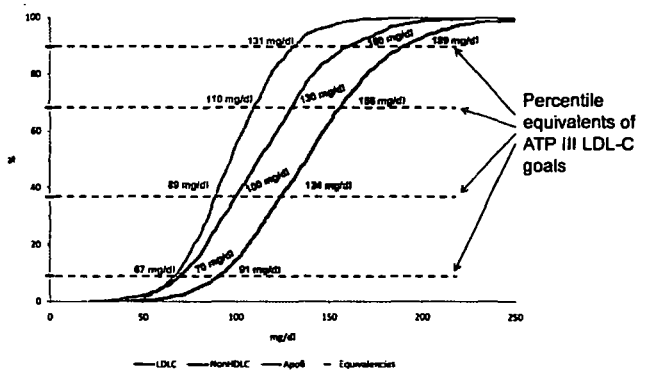

Figure 4 Cumulative distributions of Apo B, LDL-C, and non-HDL-C from National Health and Nutrition Examination Survey, 2005-2006.

statin therapy will help to further lower LDL-C, non-HDL-C, and Apo B. However, whether that results in substantial additional clinical benefit remains unknown. Until the appropriate large-scale clinical outcomes trials are completed, each clinician must use his or her clinical judgment as to whether any form of combination therapy to further lower LDL burden is warranted in a particular patient. Also, it is not universally appreciated that the relationships of LDL-C, non-HDL-C and Apo B to CV risk are curvilinear (ie, log-linear), not linear. Accordingly, risk increases and decreases exponentially upon changes in the concentration of LDL-C or Apo B. This means that the absolute gain becomes less and less as the initial levels of LDL-C or Apo B become lower and lower. Accordingly, combination therapy will be of greatest potential benefit to those who are farthest from target levels.

The American Diabetes Association/American College of Cardiology Foundation consensus panel recommended measurement of Apo B in patients at elevated cardiometabolic risk.[154] In high-risk patients, including those with lipoprotein abnormalities without diabetes or clinical CVD, but with at least two more major CVD risk factors, an Apo B target <90 mg/dL is recommended. In patients categorized as being at the greatest risk, including those with known clinical CVD, or diabetes, and at least one other cardiometabolic risk factor, an Apo B concentration <80 mg/dL is recommended. The Canadian guidelines recommend a target Apo B of <80 mg/dL in moderate-to-high risk patients as a secondary optional treatment target once LDL-C is at goal.[137]

One approach to selection of treatment goals is to use Apo B values that are equivalent to LDL-C and non-HDL-C targets based on population percentiles. **Figure 4** compares the percentile distributions and ATP III cutpoints of LDL-C, non-HDL-C, and Apo B in NHANES III. On the basis of this figure, Apo B values of 90 mg/dL and 67 mg/dL would be equivalent to LDL-C concentrations of 100 mg/dL and 70 mg/dL, respectively,[155] whereas on the basis of the Framingham Offspring Study, the equivalent values of Apo B would be 80 and 55 mg/dL, respectively.

An alternative basis for the choice of treatment goals is evaluation of the levels of Apo B achieved in trials of interventions that reduced clinical events. **Table 3** lists the mean or median baseline and on-treatment levels of LDL-C and Apo B in the major statin trials for which Apo B has been reported.[143–146,149,156–159] On-treatment levels of Apo B in these trials ranged from 67 to 98 mg/dL, compared with 55 to 115 mg/dL for LDL-C. Notably, two studies achieved mean or median on-treatment levels of Apo B well below 80 mg/dL, ie, PROVE-IT, with 67 mg/dL, and JUPITER, with 71 mg/dL. The majority of these studies, with the exception of the IDEAL study, showed a significant reduction in the primary CV event outcome variable.

Figure 5 shows the relationship between Apo B levels and CHD event rates in primary and secondary prevention studies of lipid-altering drug therapies.[160] Although subject

Table 3 Baseline and on-treatment levels of LDL-C and Apo B and RR or HR vs the comparator for the primary outcome in clinical trials of statin therapy

Study	Statin and dosage, mg/d	LDL-C, mg/dL		Apo B, mg/dL		HR or RR (95% CI) vs comparator*
		Baseline	On-treatment	Baseline	On-treatment	
LIPID[156]	Pravastatin 40	150 (130–170)	107 (NR)	132 (NR)	98 (NR)	0.76 (0.65–0.88)
AFCAPS/TexCAPS[157]	Lovastatin 20	150 (17)	115 (20)	120 (NR)	96 (NR)	0.63 (0.50–0.79)
HPS[146]	Simvastatin 40	132 (31)	80 (NR)	114 (23)	78 (NR)	0.87 (0.81–0.94)
CARDS[143]	Atorvastatin 10	118 (28)	82 (27)	117 (24)	80 (19)	0.63 (0.48–0.83)
TNT[144,149]	Atorvastatin 80	152 (NR)	75 (23)	111 (NR)	91 (21)	0.78 (0.69–0.89)
IDEAL[158]	Atorvastatin 80	122 (33)	84 (25)	119 (NR)	90 (NR)	0.89 (0.78–1.01)
PROVE-IT[159]	Atorvastatin 80	106 (89–128)	62 (50-79)	102 (NR)	67 (NR)	0.84 (0.74–0.95)
JUPITER[145]	Rosuvastatin 20	108 (94–119)	55 (44-70)	108 (NR)	71 (NR)	0.56 (0.46–0.69)

AFCAPS/TexCaps, Air Force/Texas Coronary Atherosclerosis Prevention Study; Apo, apolipoprotein; CARDS, Collaborative Atorvastatin Diabetes Study; CI, confidence interval; HPS, Heart Protection Study; HR, hazard ratio; IDEAL, Incremental Decrease in End Points through Aggressive Lipid Lowering; JUPITER, Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin; LDL-C, low-density lipoprotein cholesterol; LIPID, Long-term Intervention with Pravastatin In Ischemic Disease; NR, not reported; PROVE-IT, Pravastatin or Atorvastatin Evaluation and Infection Therapy; RR, relative risk; SD, standard deviation; SEM, standard error of the mean; TNT, Treating to New Targets.

Values are mean (SD) or median (interquartile limits) values.

*Hazard ratio (HR) or relative risk (RR) and 95% confidence intervals (CI) for the primary cardiovascular event outcome for the statin group indicated vs its comparator group (placebo or less-aggressive statin therapy).

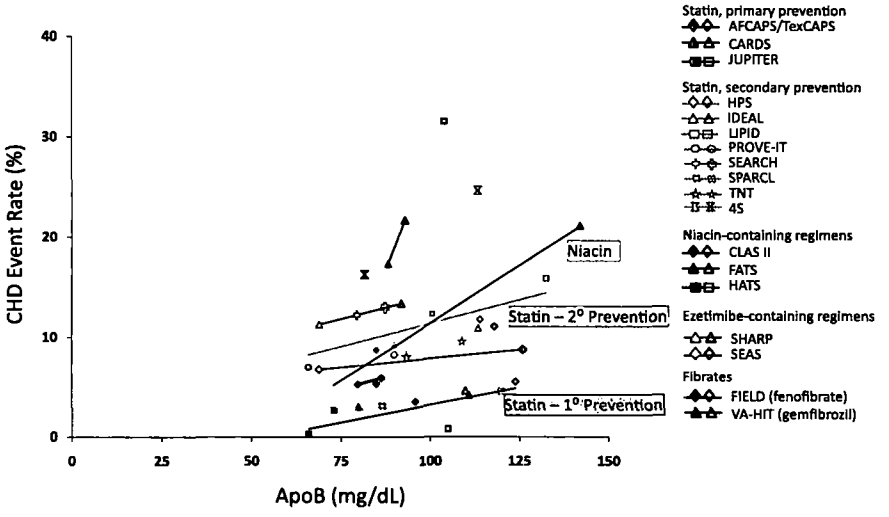

Figure 5 Relationship between mean Apo B concentration and CHD event rate in primary and secondary prevention trials with lipid-altering drug therapies. Statin trials are shown in red and purple, niacin (nicotinic acid) in blue, fibrates (fibric acid derivatives) in green, and ezetimibe in orange. Filled symbols represent the treated group, and empty symbols represent the control or placebo group.[160] AFCAPS/TexCAPS, Air Force/Texas Coronary Atherosclerosis Prevention Study; CARDS, Collaborative Atorvastatin Diabetes Study; CLAS-II, Cholesterol-Lowering Atherosclerosis Study; FATS, Familial Atherosclerosis Treatment Study; FIELD, Fenofibrate Intervention and Event Lowering in Diabetes; HATS, HDL Atherosclerosis Treatment Study; HPS, Heart Protection Study; IDEAL, Incremental Decrease in End Points Through Aggressive Lipid Lowering; JUPITER, Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin; LIPID, Long-Term Intervention With Pravastatin in Ischemic Disease; PROVE-IT, Pravastatin or Atorvastatin Evaluation and Infection, high-dose atorvastatin group; 4S, Scandinavian Simvastatin Survival Study, simvastatin group; SEARCH, Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine; SEAS, Simvastatin and Ezetimibe Aortic Stenosis, simvastatin-ezetimibe group; SHARP, Study of Heart and Renal Protection; SPARCL, Stroke Prevention by Aggressive Reduction in Cholesterol Levels; TNT, Treating to New Targets; VA-HIT, Veterans Affairs High-Density Lipoprotein Intervention Trial.

selection was not based on Apo B for the majority of these studies, none of the trials showed a significant imbalance between groups for baseline Apo B concentration. Also, these studies varied with regard to the therapeutic regimen tested, clinical population, and Apo B assay used. Nevertheless, a clear and approximately linear association is present, suggesting that a lower on-treatment Apo B concentration is associated with a lower CHD event rate, as has been shown previously for LDL-C and non-HDL-C.[161,162] The association is particularly robust for statin therapy, which has the largest evidence base for risk reduction.

Thus, although data on the effects of lowering Apo B to values <80 mg/dL are limited, the available results from clinical trials are consistent with the potential for further risk reduction. Accordingly, in patients at very high risk, it may be reasonable to consider more aggressive lowering of Apo B to <70 mg/dL. Additional research is needed to more clearly define optimal treatment targets for Apo B, as well as LDL-C and non-HDL-C.

What are the main areas of controversy and research questions regarding Apo B and its use in clinical practice?

The major areas of controversy regarding the use of Apo B in clinical practice relate to the relative merits of Apo B versus non-HDL-C for assessing risk and adequacy of treatment, as well as patient and clinician awareness and knowledge regarding Apo B. The panel concluded that previous controversies regarding measurement accuracy, standardization, and availability of measurement at relatively low cost on automated chemistry analyzers, were no longer of concern.

The majority view of the NLA Biomarkers Expert Panel was that the available evidence clearly supports the conclusion that Apo B is a better indicator of risk and treatment adequacy than LDL-C. However, its superiority over non-HDL C for these purposes has been less well established. In epidemiological studies that have compared Apo B with non-HDL-C for risk prediction, a majority suggest Apo B to be superior or equivalent to non-HDL-C, whereas very few have found superiority for non-HDL-C. Although the results of the analysis by the Emerging Risk Factor Collaboration suggested equivalence of Apo B and non-HDL-C for risk prediction,[127] a more recent meta-analysis that included a larger number of studies showed superiority of Apo B over non-HDL-C and LDL-C.[128]

The issue is complicated because the potential superiority of Apo B to non-HDL-C (and LDL-C) may not be constant across all subgroups of the population. Both LDL-C and non-HDL-C may underestimate atherogenic particle burden in subsets of the population in whom the cholesterol content of LDL particles is lower than average (greater Apo B than predicted by non-HDL-C or LDL-C concentrations), such as those with hypertriglyceridemia, the metabolic

syndrome, diabetes, or low HDL-C. More studies are needed to better define risk in "discordant" patients whose Apo B (or LDL-P) level is higher or lower than would be predicted based on measurement of lipoprotein cholesterol (LDL-C and non-HDL-C) concentrations.

Because measurement of Apo B is associated with additional cost and complexity compared with the standard lipoprotein lipid profile, whereas non-HDL-C can be calculated from the standard lipoprotein lipid profile at essentially no additional cost, important questions remain regarding whether Apo B should be incorporated into routine clinical evaluation,[163] or reserved for measurement in subgroups for whom the prevalence of discordance is high. Research is needed to further model the cost-effectiveness of routine versus targeted use of Apo B measurements for risk assessment, as well as for evaluation of residual risk and treatment adequacy in patients receiving lipid-altering therapies.

As reviewed previously, there is also debate about the methods that should be used for establishing Apo B treatment goals. Lipid-altering drug therapy often reduces non-HDL-C and LDL-C to a greater degree than Apo B. Thus, more aggressive therapy would be required to attain Apo B levels that correspond to population percentiles similar to those for the recommended LDL-C and non-HDL-C treatment goals. More aggressive therapy is associated with incremental costs and risks, which must be balanced against potential therapeutic gains. Thus, additional work is needed to develop and test models that justify treatment targets.

Finally, education of clinicians regarding the value and clinical application of new treatment targets, such as Apo B, remains a significant challenge. The magnitude and difficulty of the task has been illustrated by the experience following introduction of non-HDL-C into treatment guidelines. A decade after the NCEP ATP III report, clinician knowledge and use of non-HDL-C treatment goals in clinical practice remains low.[164]

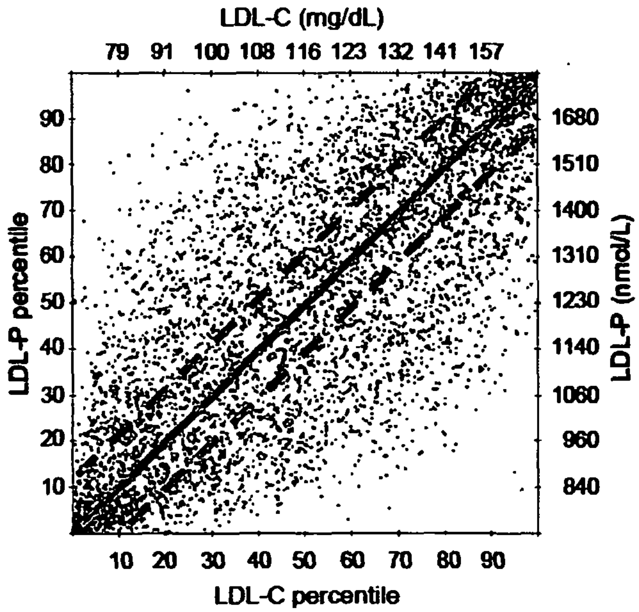

Figure 6 Relationship of LDL-C and LDL-P levels given in percentile units. The dashed lines bracket discordant LDL-C and LDL-P values defines in those with ± 12 percentile units.[173] Permission to reuse figure granted by Elsevier.

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Low-density lipoprotein particle number/ concentration (LDL-P)

Does LDL-P predict risk, over and above traditional risk factors?

LDL measurements have two important clinical applications: (1) risk assessment, with LDL levels used, along with other risk markers, to identify patients at increased risk of CVD, and (2) risk management via LDL lowering, with target levels serving as treatment goals and indicators of the success of LDL-lowering therapies. The quantitative measure of LDL used traditionally for both of these applications is LDL-C, the amount of cholesterol carried in a person's LDL particles. However, the cholesterol content of LDL particles is not constant, varying more than 2-fold between individuals.[165–168] Furthermore, the cholesterol content of a given patient's LDL particles is not fixed, but can change over time in response to lipid-altering treatments.[169]

An alternative way to quantify LDL is to assess the concentration of LDL particles, either by measures of Apo B or LDL-P.[170] For many patients, levels of LDL-C and LDL-P (as well as Apo B) are concordant. But for many others, because of the variability of the cholesterol content of LDL particles, LDL-C and LDL-P levels are discordant (one LDL measure being higher or lower than the other on the basis of population percentiles; Fig. 6).[165,171–174]

In the general population, ~50% of subjects demonstrate discordance between LDL-C and LDL-P defined as a differential in population percentile of 12% or more (Fig. 7).[173] Individuals with elevated triglycerides or low HDL-C manifest progressively greater elevations of LDL-P concentrations at a given level of LDL-C.[166,175] In observational studies of patients with type 2 diabetes mellitus or metabolic syndrome and LDL-C <100 mg/dL (<20th percentile), discordantly elevated LDL-P levels greater than the 20th percentile (>1000 nmol/L) occur in 75% of subjects.[172,174] Similar results have also been shown for patients with type 2 diabetes mellitus and LDL-C <70 mg/dL.[172] In addition, discordance between LDL-C and LDL-P levels frequently occurs in patients receiving statin therapy because statins lower the LDL-C concentration to a greater degree than the LDL-P concentration.[169]

When one evaluates evidence bearing on the potential clinical utility of a reference standard laboratory measure

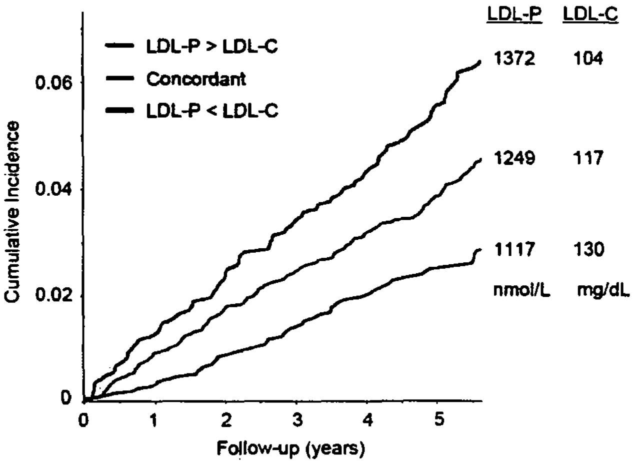

Figure 7 Cumulative incidence of cardiovascular events in subgroups with concordant or discordant levels of LDL-C and LDL-P, from proportional hazards models adjusted for age, sex, and race.[173] Permission to reuse figure granted by Elsevier.

(LDL-C) versus a new measure (LDL-P), it is useful to focus attention on cases of disagreement (discordance) between the measures.[176] To address questions regarding the practical implications of concordance versus discordance in LDL measures, this NLA Biomarkers Expert Panel report considered specific clinical circumstances to appraise the potential utility of LDL-P in clinical practice. Recently, an American College of Cardiology Foundation/American Heart Association task force issued recommendations in which the use of lipoprotein measures beyond a standard fasting lipid profile for CV risk assessment in asymptomatic adults was not recommended.[177] However, the report did not examine CV outcomes when alternate LDL measures (LDL-C vs LDL-P) are discordant. Although similar outcome associations are observed for the two measures when LDL-C and LDL-P are concordant, CV risk is more strongly associated with LDL-P when these measures are discordant.[167,173]

What is the physiological rationale for the link between LDL-P concentration and adverse CV outcome?

The key role played by LDL particles in the pathogenesis of CHD is well established. LDL particles move into the arterial wall via a gradient-driven process; the greater the circulating concentration of LDL particles, the greater the rate of passive diffusion into the arterial wall.[178–180] Once inside the intima, LDL particles that bind to arterial wall proteoglycans are retained, oxidized or otherwise modified, and subsequently taken up by macrophages to form foam cells.[181] When the serum LDL-P level is low (ie, fewer LDL particles are present in the circulation), fewer particles enter the arterial wall resulting in less propensity for initiation and promotion of atherosclerosis.[181]

In which patients would LDL-P testing be most valuable?

Use of LDL-P concentration in initial clinical assessment

Low risk (<5% 10-year CHD event risk)

It is the consensus of the NLA Biomarkers Expert Panel that treatment decisions are unlikely to be altered by use of LDL-P among low risk patients. Hence, measurement of LDL-P was **"not recommended"** for this patient group.

Intermediate risk (5–20% 10-year CHD event risk)

It is the consensus of the NLA Biomarkers Expert Panel that there are a substantial number of patients for whom LDL-C may not accurately reflect CVD risk. On the basis of the data showing that discordantly elevated LDL-P is more strongly associated with incident CVD risk than LDL-C level,[167,173] measurement of LDL-P is thought to be **"reasonable for many patients."** When LDL-P is discordantly elevated, consideration should be given to initiating or intensifying LDL lowering therapy. Conversely, a more conservative treatment approach could be considered for patients with lower LDL-P values than predicted based on their LDL-C (or non-HDL-C) concentrations. Populations known to manifest increased prevalence of discordance (elevated LDL-P for the level of LDL-C or non-HDL-C) include patients with metabolic syndrome,[171,174] as well as those with low HDL-C and/or elevated triglycerides.[165–167]

CHD or CHD risk equivalent

Because of high CV risk, patients with known CHD or a CHD risk equivalent are candidates for aggressive lipid-altering therapy. Given the clinical benefit of treating these patients with appropriate medical therapy, it is unclear whether additional LDL-P information would alter initial therapeutic decisions. Hence, it is the consensus of the NLA Biomarkers Expert Panel that use of LDL-P should be **"considered for selected patients only"** to identify individuals who might benefit. An example of such a patient might be an individual with type 2 diabetes in the absence of other major CHD risk factors who has LDL-C <100 mg/dL and non-HDL-C <130 mg/dL before treatment. In this setting, discordantly elevated LDL-P is commonly present[172] and could reasonably be used to justify more aggressive LDL lowering.

Family history of premature CHD (male <55 years, female <65 years)

Increased LDL-P concentration is often encountered among patients with a family history of premature CHD, including patients with FCH.[182,183] Because of the presence of cholesterol-depleted LDL particles, LDL-C levels are frequently unremarkable and fail to indicate the presence and degree of elevated LDL-P. Hence, it is the consensus of the NLA Biomarkers Expert Panel that measurement of LDL-P would be **"reasonable for many patients"** with a family history of premature CHD. When LDL-P is

discordantly elevated, consideration should be given to initiating LDL-lowering therapy.

Recurrent CHD events

Despite therapeutic lifestyle and pharmacologic therapy, some patients continue to have CHD progression and recurrent CHD events. Given the potential for discordantly elevated LDL-P among such individuals, it is the consensus of the NLA Biomarkers Expert Panel that use of LDL-P would be **"reasonable for many patients"** with recurrent CHD events. Discordantly elevated LDL-P could lead to more aggressive LDL lowering therapy which might reduce risk for future events.

Use of on-therapy LDL-P concentration to aid in clinical management

Lowering LDL is a key strategy in managing CVD risk. The authors of numerous clinical trials of statin agents, which up-regulate LDL receptors, resulting in reduced levels of circulating LDL-P, have shown significant reductions in CVD events among a wide range of patients. Although these data collectively reveal that greater LDL reduction is significantly associated with greater relative CVD event reduction, statin trials were not designed to evaluate the impact of adjusting individual therapy to achieve a specific LDL-C or LDL-P target of therapy. Rather, statin trials have generally used a fixed dose of statin compared with an alternative dose or placebo without titration to a specific treatment goal.

Consistent with data showing that CHD risk tracks with LDL-P, not LDL-C, when these two measures are discordant,[167,173] post-hoc analyses demonstrate that on-trial levels of LDL-P may be more predictive of residual risk than LDL-C.[184,185] In addition, given that statin therapy reduces LDL-C and non-HDL-C to a greater extent than it lowers LDL-P,[169] recent expert recommendations suggest that LDL-P may provide a better assessment of on-treatment residual risk than LDL-C or non-HDL-C measurement.[186] Thus, it was suggested that intensification of therapy would be a reasonable consideration when residually elevated LDL-P concentration is present. To adjudicate response to therapy, LDL-P targets were proposed as an optional therapeutic goal (in addition to LDL-C and non-HDL-C). LDL-P values advocated as targets of therapy were selected based on population equivalent levels for LDL-C targets in the Framingham Offspring cohort (<20th percentile for very high and high risk patients [LDL-P <1100 nmol/L], <50th percentile for moderately high- and moderate-risk patients [LDL-P <1440 nmol/L]).[170,186] Slightly lower population equivalent LDL-P levels have been reported from the Multi-Ethnic Study of Atherosclerosis (MESA; LDL-P values <1000 nmol/L [20th percentile], <1300 nmol/L [50th percentile]).[170,173]

Low risk (<5% 10-year CHD event risk)

It is the consensus of the NLA Biomarkers Expert Panel that treatment decisions are unlikely to be altered by use of LDL-P among low risk patients. Hence, use of LDL-P was **"not recommended"** for this group.

Intermediate risk (5–20% 10-year CHD event risk)

Because of the heterogeneity of the cholesterol content of LDL particles, and frequent LDL-P elevation among patients on lipid lowering therapy,[169] it is the consensus of the NLA Biomarkers Expert Panel that measurement of LDL-P would be **"reasonable for many patients"** at intermediate risk treated to LDL-C and non-HDL-C goal to adjudicate the adequacy of LDL lowering therapy. When the LDL-P concentration is discordantly elevated, consideration should be given to intensifying LDL lowering therapy. Conversely, a more conservative approach could be considered for patients with low LDL-P values.

CHD or CHD risk equivalent

Because of LDL-P heterogeneity among CHD or CHD risk equivalent patients on lipid-lowering therapy, it is the consensus of the NLA Biomarkers Expert Panel that use of LDL-P would be **"reasonable for many patients"** treated to LDL-C and non-HDL-C goal to adjudicate the adequacy of LDL lowering therapy.

Family history of premature CHD (male <55 years, female <65 years, first-degree relative)

As previously noted, increased LDL-P is commonly encountered among patients with a family history of premature CHD, including patients with FCH. Because of the presence of cholesterol-depleted LDL particles, LDL-C levels are often unremarkable and fail to indicate the presence of elevated LDL-P concentration. Once on therapy, it is the consensus of the NLA Biomarkers Expert Panel that measurement of LDL-P should be **"considered for selected patients"** treated to LDL-C and non-HDL-C goal to adjudicate the adequacy of LDL lowering therapy.

An example of such a selected patient could be a patient with significant family history of premature CHD and LDL-P elevation on lipid-lowering therapy. In this setting, LDL-P would be reasonable to adjudicate the adequacy of LDL-lowering therapy.

Recurrent CHD events

Given the very high risk inherent to patients with recurrent CHD events, it is the consensus of the NLA Biomarkers Expert Panel that use of LDL-P would be **"reasonable for many patients"** treated to LDL-C and non-HDL-C goal to adjudicate the adequacy of LDL lowering therapy.

Should LDL-P be a target of therapy? If not, how should LDL-P affect treatment decisions?

If elevated LDL-P is present in patients at LDL-C and non-HDL-C goals, intensification of therapy would be a reasonable consideration. Furthermore, LDL-P has been

proposed as an optional therapeutic goal with LDL-P targets advocated at population equivalent levels used for LDL-C targets (<20th percentile for very high and high risk patients [LDL-P <1100 nmol/L], <50th percentile for moderately high- and moderate-risk patients [LDL-P <1440 nmol/L]).[170,186] Medications routinely used for lipid optimization have well documented effects on LDL-P.[187] Because of changes in the cholesterol content of LDL particles on therapy, some treatments lower LDL-C more than they lower LDL-P concentration (statins, statin combination with ezetimibe and bile acid sequestrates), whereas other therapies lower LDL-P more than they lower LDL-C concentration (niacin, fibrates, or statin combination with niacin or fibrates). Accordingly, clinicians have several options for adjusting medication selection, dosage or combination therapy in response to elevated LDL-P.

What are the main areas of controversy and research questions regarding LDL-P and its use in clinical practice?

As is the case for Apo B concentration, which is also a reflection of the number of circulating atherogenic particles, the superiority of LDL-P concentration to non-HDL-C for CVD risk stratification and for guiding therapy has not been fully documented. Accordingly, the cost-effectiveness of using LDL-P in clinical practice, as an adjunct to or replacement of the traditional cholesterol measures, has not been established. Furthermore, the relative merits of measuring LDL-P versus Apo B remains uncertain and, at present, the decision about which to use remains a matter determined by availability, cost and clinician preference. The greatest usefulness of LDL-P (and Apo B) appears to reside in subgroups of patients for whom LDL-C, and to a lesser degree, non-HDL-C, do not provide a reliable indication of the burden of circulating atherogenic particles. In such patients, available data and expert panel recommendations support consideration of LDL-P (or Apo B) as a target of therapy (in addition to LDL-C and non-HDL-C) to adjudicate the adequacy of LDL-lowering therapy. Population equivalent values <20th percentile (<1100 nmol/L) for very high and high risk patients, or <50th percentile (<1440 nmol/L) for moderately high- and moderate-risk patients have been advocated for this purpose. Additional research is needed to more clearly define optimal treatment targets for LDL-P. Given the prevalence and magnitude of discordance between cholesterol and particle number measures of LDL burden, additional research is needed to more clearly define settings in which a policy of treating to LDL-P (or Apo B) goals might produce more favorable outcomes than the alternative of treating to LDL-C and non-HDL-C goals.

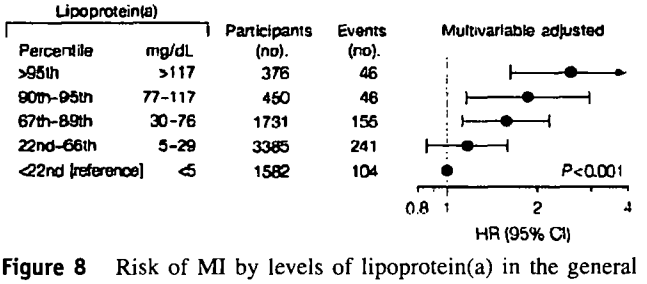

Figure 8 Risk of MI by levels of lipoprotein(a) in the general population assessed from the 1991–1994 examination of Copenhagen City Heart Study (n = 7524). HRs were adjusted for cardiovascular risk factors, and *P* value is for trend of HR [increasing lipoprotein(a) levels].[191,192] Permission to reuse figure granted by Oxford University Press.

Lipoprotein (a)

Does lipoprotein (a) [Lp(a)] predict risk, over and above traditional risk factors?

Lp(a) has positive predictive power that is additive to other measures of lipoprotein risk factors and to the classical "Framingham Risk Factors."[188–190] According to a recent review of the available evidence by Nordestgaard et al,[191] Lp(a) is specifically associated with increased risk for CHD in a continuous nonthreshold manner (**Fig. 8**).[191,192] Furthermore, the association between Lp(a) and CHD risk is independent of LDL-C, non-HDL-C, and the presence of other CV risk factors.[191]

What is the physiological rationale for the link between Lp(a) and adverse CV outcome?

Lp(a) represents a modification of LDL by addition of the "lipoprotein antigen," a protein made in the liver that binds to LDL in the plasma compartment and forms a disulfide bond with Apo B (**Fig. 9**).[193,194] The lipoprotein antigen is highly variable in its molecular weight because of the duplication of a sequence in the coding region of the gene that creates repeat amino acid sequences.[195] The large number of alleles causes a high variability of the molecular weight of Lp(a) in the population (from approximately 300,000 to 800,000 Daltons).[193] Variation in the promoter combines with the sequence differences to create highly variable plasma concentrations (approximately 1000-fold).[193] Lp(a) collects in the arterial wall where it is taken up by scavenger receptors on monocyte/macrophages.[196–199] It also binds to fibrin and may interfere with the conversion of plasminogen to plasmin.[194,200,201] This would, in theory, enhance clotting triggered by endothelial damage or plaque rupture, providing for a larger thrombus, a greater probability of arterial blockage, and a resulting acute clinical event. It may also promote monocyte adhesion to the endothelium, and carry a significant amount of potentially atherogenic oxidized phospholipids in human plasma.[196–199]

The molecular weight of apolipoprotein (a) can vary from approximately 300,000 to more than 800,000 D, depending on the number of K-IV units produced by the allele of a given genotype. This variability in structure changes the properties of Lp(a) and affects the mass in the

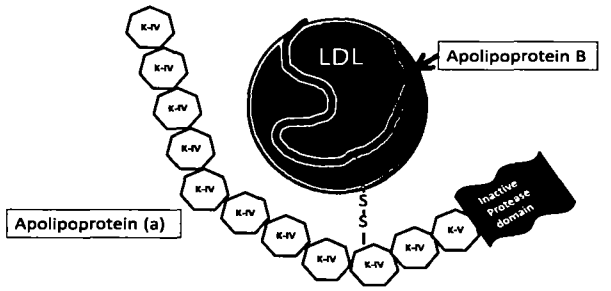

Figure 9 Diagram of Lp(a) structure. Lp(a) is composed of a LDL-P to which the apo(a) is attached by a disulfide bond through a cysteine side chain in Apo B. The apo(a) contains three basic regions depicted in the figure. From the carboxyl end, there is an inactive protease domain that is preceded by a series of folded structures that are reminiscent of a Danish pastry referred to as a kringle. Two different kringle structures are found in apo(a). This recapitulates the structure of plasminogen which has an initial active protease region preceded by five different forms of kringle structures designated by Roman numerals (I through V). Apo(a) contains a kringle V and a highly variable number of kringle IV repeats. There are no structures of the plasminogen type kringle I through III. The kringle IV repeats in apo(a) have sequence variability producing some 10 different types (KIV-1 through KIV-10). The disulfide bond with Apo B exists between a KIV-9 component in apo(a). KIV-7 and KIV-8 have non-covalent binding properties for regions of Apo B.

plasma of individuals. Smaller molecules are associated with higher synthesis rates in population data and it is the number of molecules of Lp(a) that seems to be the strongest determinant of related CVD risk.

In which patients would Lp(a) testing be most valuable?

Elevated plasma concentrations are controlled primarily by features of the Lp(a) gene.[202] Therefore, a very strong family history of vascular events, suggesting an autosomal dominant pattern, should lead to assessment.[192,203] Because elevated concentrations are additive to risk,[192] any patient with early disease that is not explained by the composite of other risk factors should be assessed. However, because family history is often inaccurate and the impact of other risk factors is variable, one could argue that anyone presenting with vascular disease should have this measurement. Because it is a very stable parameter, unaffected by diet and most drugs, a single measure that is well within normal limits (<25 mg/dL) is usually adequate to rule out Lp(a) as an important contributor to CVD risk in an individual patient. Many laboratories use ≥30 mg/dL as a cutpoint for indicating an elevated Lp(a) concentration; this represents approximately the top tertile of the general population.

Should Lp(a) be a target of therapy? If not, how should Lp(a) affect treatment decisions?

Lp(a) can be reduced by niacin therapy and, in women, by estrogen therapy.[204,205] A variety of other compounds can change Lp(a), but none is truly suitable as therapeutic agents.[206] The reduction of events in patients so treated has not been determined to relate specifically to changes in Lp(a). Therefore, although there is a strong theoretical reason to believe that lowering an elevated Lp(a) concentration would be beneficial, the clinical rationale for lowering Lp(a) with these agents has not been established.

Retrospective evidence suggests that aggressive reduction of LDL-C has a very significant effect on those with both elevated Lp(a) and elevated LDL-C.[207] Therefore, many have recommended more aggressive management of LDL-C, with treatment to lower target values in patients with elevated Lp(a).[207] Because there is no evidence that reducing Lp(a) is harmful, some lipidologists will use niacin in the effort to treat other lipoprotein abnormalities and to also achieve a lower Lp(a) value.

What are the main areas of controversy and research questions regarding Lp(a) and its use in clinical practice?

The absence of clear evidence that treating Lp(a) will change risk has prevented recommendations that this be used in screening all patients. The occurrence of high risk related to this is relatively uncommon; however, the authors of several studies have suggested that values sufficient to add significant risk occur in up to one fourth of the population.[191]

Important clinical questions remaining to be answered include the following:

1. Will reduction of plasma levels in those with elevated plasma concentrations reduce recurrent clinical events?
2. Will pharmacologic reduction of Lp(a) levels among individuals without manifest disease but high Lp(a) concentrations result in lower risk of CV events?
3. Can we develop a specific inhibitor of the synthesis of the "little a" protein such as an antisense oligonucleotide specific for the mRNA would provide a tool for specific reduction without changing other parameters. Because other current agents that reduce Lp(a) markedly alter other lipoprotein concentrations, they are not interventions that can give a clear answer to these questions.

Low-density lipoprotein subfractions

Do LDL subfractions predict risk, over and above traditional risk factors?

LDL particles are heterogeneous in size, density, and cholesterol/lipid content. Multiple analytic methods have been developed to classify LDL particles into various subfractions.[208–210] These subfractions can be individually quantitated or can be expressed as LDL particle patterns depending on the size of the predominant subfraction (Pattern

A or B if large or small LDL particles predominate, respectively). A gold standard for such analyses does not exist, and few comparative studies have been performed with highly variable statistical analysis methods.[210–212] Correlations between analytic methods for determination of LDL size vary widely and concordance in identifying LDL patterns ranges from 7% to 94%.[211,212] Furthermore, comparability of methods appears to vary by type of patient population.[212]

Studies have linked large LDL particles to atherosclerosis in nonhuman primates,[213] in patients with familial hypercholesterolemia (who have an elevated concentration of predominantly large LDL particles),[214] in participants of the population-based MESA study,[215] in normolipidemic men with CHD,[216] and among patients after MI in the Cholesterol And Recurrent Events (CARE) study.[217]

Predominantly small LDL particles are often present in patients with CHD, in individuals with type 2 diabetes mellitus, in those with low HDL-C and high triglycerides, and in individuals with insulin resistance and other features of the metabolic syndrome.[208] Many studies document links between small dense LDL particles and atherosclerotic CVD.[208–210,218–222] However, these statistical associations between small, dense LDL and CV outcomes are either significantly attenuated or abolished when the analyses are adjusted for the overall number of circulating LDL particles (LDL-P) either by adjustment for Apo B levels or by adjustment for nuclear magnetic resonance-derived LDL-P.[208,210]

What is the physiological rationale for the link between LDL subfractions and adverse CV outcome?

All lipoprotein particles in the LDL fraction are atherogenic, independent of size. LDL particles become trapped in the arterial wall and are internalized by macrophages through scavenger receptors on the macrophage surface, resulting in foam cell formation, activation of these foam cells and expansion of the inflammatory response.[223] It has been proposed that small, dense LDL particles are more atherogenic than larger particles due to longer residence time in plasma, increased susceptibility to oxidation, enhanced arterial proteoglycan binding, and increased permeability through the endothelial barrier.[208,209]

In which patients would LDL subfraction testing be most valuable?

The NLA Biomarkers Expert Panel was unable to identify any patient subgroups in which LDL subfractionation is recommended.

Should LDL subfraction be a target of therapy? If not, how should LDL subfractions affect treatment decisions?

Several investigators have suggested that lifestyle change and pharmacologic treatment can change LDL particle distribution.[208,209,224,225] However, such shifts are always accompanied by changes in LDL-C concentration and/or change in LDL-P, and often by changes in other lipoprotein fractions (eg, HDL-C and triglyceride levels) or nonlipid risk factors (eg, weight loss, improved insulin sensitivity, improved blood pressure with lifestyle modification). To date, there is no evidence that the shift in LDL subfractions directly translates into change in disease progression or improved outcome.

What are the main areas of controversy and research questions regarding LDL subfractions and its use in clinical practice?

Major areas of uncertainty can be summarized as follows:

- There is no agreed-upon gold standard for measurement of LDL subfractions and comparability of methods is limited.
- There are no studies to formally assess the incremental risk prediction achieved by measurement of LDL subfractions above and beyond traditional lipid measures and nonlipid risk factors.
- There are no prospective studies to show that a treatment strategy of changing LDL subfractions is superior to traditional lipid-lowering therapy in terms of atherosclerosis progression or CV morbidity and mortality.

High-density lipoprotein subfractions

Do HDL subfractions predict risk, over and above traditional risk factors?

HDL particles are heterogeneous in size, charge, density, and cholesterol/lipid content, and contain a large number of surface proteins which determine metabolic fate and function.[226] Although many aspects of reverse cholesterol transport have been elucidated in recent years, other antiatherosclerotic functions of HDL remain poorly understood.[227] Several analytic methods have been developed to classify HDL particles into various subfractions, but only recently has a unified nomenclature been proposed.[226]

HDL-C levels are strongly inversely associated with CV outcomes in population-based studies.[228] Most, but not all, analyses suggest that both baseline and on-trial HDL-C levels are also prognostically useful among patients on lipid-lowering therapy.[229–232] A number of studies have

shown that HDL subfractions also correlate with risk,[226,233,234] whereas others have failed to find a relationship.[235]

What is the physiological rationale for the link between HDL subfractions and adverse CV outcome?

HDL particles are involved in reverse cholesterol transport and have additional antioxidant and anti-inflammatory properties believed to be antiatherogenic.[226,227]

In which patients would HDL subfraction testing be most valuable?

The NLA Biomarkers Expert Panel was unable to identify any patient subgroups in which HDL subfractionation would be recommended.

Should HDL subfractions be a target of therapy? If not, how should HDL subfractions affect treatment decisions?

Several investigators have suggested that lifestyle change and pharmacologic treatment can change HDL particle distribution and the HDL proteonome,[226,236] but such changes are always accompanied by a change in HDL-C concentration and/or in HDL particle number, and often by changes in other lipoprotein fractions (eg, LDL-C levels and triglyceride levels) or nonlipid risk factors, especially when changes are achieved with comprehensive lifestyle modification. To date, there is no evidence that such a shift in HDL subfractions translates into change in disease progression or improved outcome.

What are the main areas of controversy and research questions regarding HDL subfractions and its use in clinical practice?

Major areas of uncertainty can be summarized as follows:

- HDL structure, metabolism, and function are very complex and not well understood.
- There is no consensus regarding a gold standard for measurement of HDL subfractions and comparability of methods is limited.
- There are no studies to formally assess the incremental risk prediction achieved by measurement of HDL subfractions above and beyond traditional lipid measures and non-lipid risk factors.
- There are no prospective studies in which authors demonstrate that a treatment strategy of changing HDL subfractions is superior to traditional lipid-lowering therapy in terms of atherosclerosis progression or CV morbidity and mortality.

Financial disclosures

The January 2011 National Lipid Association (NLA) consensus conference on inflammatory markers and advanced lipoprotein testing was supported by unrestricted grant funding from the following companies: Abbott Laboratories, Atherotech Diagnostics Laboratory, Berkley Heart Lab, Inc., Boston Heart Diagnostics, diaDexus, Inc., LipoScience, Merck & Co., Inc., and Spectracell Laboratories.

The NLA would like to thank each company for its support of this endeavor. In accordance with the National Lipid Association Code for Interactions with Companies, the NLA maintained full control over the planning, content, quality, scientific integrity, implementation, and evaluation of the consensus conference and this inflammatory markers and advanced lipoprotein testing consensus document. All related activities are free from commercial influence and bias.

Dr. Davidson has received research grants from Abbott Laboratories, Daiichi Sankyo, GlaxoSmithKline, Merck & Co. and Roche. Dr. Davidson has received consulting fees from Abbott Laboratories, Aegerion Pharmaceuticals, Amgen, AstraZeneca, Atherotech Inc., Daiichi Sankyo, DTC MD, Esperion, GlaxoSmithKline, Intelligent Medical Decisions, Kinemed, LipoScience, Merck & Co, Novo Nordisk, Roche, Sanofi-Aventis, Synarc, Takeda Pharmaceuticals, and Vindico Medical Education. Dr. Davidson has received honoraria related to speaking from Abbott Laboratories, GlaxoSmithKline and Merck & Co. Dr. Davidson has served on the Board of Directors of DTC MD, Omthera, Professional Evaluation Inc., and Sonogene.

Dr. Ballantyne has received research grants from Abbott Laboratories, AstraZeneca, Bristol-Myers Squibb, diaDexus Inc., GlaxoSmithKline, Kowa Pharmaceuticals, Merck & Co., Novartis Pharmaceuticals, Roche, Sanofi-Synthelabo, and Takeda Pharmaceuticals. Dr. Ballantyne has received consulting fees from Abbott Laboratories, Adnexus, Amylin Pharmaceuticals, AstraZeneca, Bristol Myers-Squibb, Esperion, Genentech, GlaxoSmithKline, Idera Pharmaceuticals, Kowa Pharmaceuticals, Merck & Co., Novartis Pharmaceuticals, Omthera, Resverlogix, Roche, Sanofi-Synthelabo, and Takeda Pharmaceuticals. Dr. Ballantyne has received honoraria related to speaking from Abbott Laboratories, AstraZeneca, GlaxoSmithKline, Merck & Co., Sanofi-Synthelabo, and Takeda Pharmaceuticals.

Dr. Jacobson has received consulting fees from Abbott Laboratories, Amarin Pharmaceuticals, AstraZeneca, GlaxoSmithKline and Merck & Co.

Dr. Bittner has received research grants from Abbott Laboratories, National Institutes of Health, Spirocor, Roche, GlaxoSmithKline, Gilead, and Pfizer Inc.

Dr. Braun has received honoraria related to speaking from the American Heart Association and the Preventive Cardiovascular Nurses Association. Dr. Braun has received salary support from the National Institutes of Health.

Dr. Alan S. Brown has received honoraria related to speaking from Abbott Laboratories, Forest Laboratories and Daiichi Sankyo.

Dr. W. Virgil Brown has received consulting fees from Abbott Laboratories, Amgen, Anthera, Genzyme, Pfizer Inc., LipoScience, and Merck & Co. Dr. W. Virgil Brown has received honoraria related to speaking from Abbott Laboratories, LipoScience, and Merck & Co.

Dr. Cromwell has received consulting fees from Isis Pharmaceuticals, LabCorp, and Health Diagnostics Laboratory. Dr. Cromwell has received research grants from Isis Pharmaceuticals. Dr. Cromwell has received honoraria related to speaking from Abbott Laboratories, LipoScience, Merck & Co., and Merck Schering Plough.

Dr. Goldberg has received research grants from Abbott Laboratories, GlaxoSmithKline and Roche. Dr. Goldberg has received consulting fees from GlaxoSmithKline, Daiichi Sankyo, and Pfizer Inc. Dr. Goldberg has received honoraria related to speaking from Daiichi Sankyo, GlaxoSmithKline, and Merck & Co.

Dr. McKenney has no relevant disclosures.

Dr. Remaley has received research grants from AlphaCore Pharmaceuticals, Kinemed, and VirxSys Inc.

Dr. Sniderman has received research grants from AstraZeneca. A. D. S. has received honoraria related to speaking from Merck & Co.

Dr. Toth has received consulting fees from Abbott Laboratories, AstraZeneca, GlaxoSmithKline, Kowa Pharmaceuticals, Pfizer Inc., and Merck & Co. Dr. Toth has received honoraria related to speaking from Abbott Laboratories, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Pfizer Inc., Merck & Co., and Takeda Pharmaceuticals.

Dr. Tsimikas has received consulting fees from ISIS, Merck & Co., Genzyme/Sanofi and Quest. Dr. Tsimikas has received honoraria related to speaking from Merck & Co. Dr. Tsimikas has received research grants from Merck & Co. and Pfizer Inc. Dr. Tsimikas has received equity interest from Atherotope.

Dr. Ziajka has received honoraria related to speaking from Abbott Laboratories, AstraZeneca and Merck & Co. Dr. Ziajka has received research grants from Genzyme.

Dr. Maki has received research grants from Abbott Laboratories, Amarin Pharmaceuticals, Atherotech, BioSante Pharmaceuticals, Cargill, Coca-Cola, Dairy Research Institute, Fermenich, GlaxoSmithKline, Kao Corporation, Kellogg Co., Monsanto, National Starch/Corn Products, Ocean Spray, Omthera, PepsiCo, Pharmavite, Shaklee, Solae, Trygg Pharmaceuticals and Welch's. Dr. Maki has received consulting fees from Abbott Laboratories, Cargill, Dairy Research Institute, General Mills, GlaxoSmithKline, Omthera, PepsiCo, Pharmavite and Trygg Pharmaceuticals. Dr. Maki has received salary support from Biofortis.

Dr. Dicklin has received research grants from Abbott Laboratories, Amarin Pharmaceuticals, Atherotech, BioSante Pharmaceuticals, Cargill, Coca-Cola, Dairy Research Institute, Fermenich, GlaxoSmithKline, Kao Corporation, Kellogg Co., Monsanto, National Starch/Corn Products, Ocean Spray, Omthera, PepsiCo, Pharmavite, Shaklee, Solae, Trygg Pharmaceuticals and Welch's. Dr. Dicklin has received consulting fees from Abbott Laboratories, Dairy Research Institute, General Mills, GlaxoSmithKline, Omthera, PepsiCo, Pharmavite, and Trygg Pharmaceuticals. Dr. Dicklin has received salary support from Biofortis.

Acknowledgments

We thank Biofortis-Provident Clinical Research for writing and editorial assistance.

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Attachment 4: EDTA Plasma vs Serum Differences in Cholesterol, High Density Lipoprotein Cholesterol and Triglycerides as Measured by Several Methods

CLIN. CHEM. 40/11, 2068–2092 (1994) • Lipids and Lipoproteins

EDTA-Plasma vs Serum Differences in Cholesterol, High-Density-Lipoprotein Cholesterol, and Triglyceride as Measured by Several Methods

Iraj Behsehti, Linda M. Wessels, and John H. Eckfeldt[1]

To investigate EDTA-plasma/serum (P/S) differences, we collected paired samples from 25 volunteers and measured total cholesterol (TC), triglyceride (TG) and high-density-lipoprotein cholesterol (HDLC), using the Cobas FARA, Ektachem 700, DuPont Dimension, and Baxter Paramax Analyzers. The mean (SD) P/S ratios for TC, HDLC, and TG concentrations were, respectively: 0.980 (0.0171), 1.063 (0.0704), and 0.961 (0.0363) for Paramax; 0.976 (0.0189), 1.034 (0.1091), and 0.950 (0.0657) for Dimension; 1.003 (0.0221), 1.059 (0.0304), and 0.988 (0.0179) for Ektachem; and 0.993 (0.0162), 1.063 (0.0830), and 1.013 (0.0410) for Cobas. We conclude that P/S ratios vary by analytical methods, and that HDLC ratios tend to be larger in magnitude and in the opposite direction from TC and TG. Both effects lead to significant biases in computed disease risk.

Indexing Terms: *sample collection/variation, source of/inter-method comparison/heart disease/risk factors*

Accurate risk assignment for coronary heart disease requires both accurate and precise blood lipid measurements. Consequently, the Lipid Standardization Panel of the National Cholesterol Education Program (NCEP) has assigned accuracy (bias) and precision targets for these analytes.[2] Goals for laboratory accuracy and precision of measurements of total cholesterol (TC) were promulgated in 1988 (*1*) as 5% and 5%, respectively, both to be reduced to 3% by 1992. Modern automated instruments appear to have quite adequate precision to meet even the more-stringent 1992 precision goal for TC (*1*). Formal accuracy and precision goals for triglycerides (TG) and high-density lipoprotein cholesterol (HDLC) are not yet published. Estimating actual inter-laboratory accuracy (bias) for all of these analytes is difficult, because "matrix effects" in most of the materials used in interlaboratory proficiency-testing surveys make a simple comparison of interlaboratory performance by use of lyophilized proficiency-testing fluids potentially unreliable and potentially misleading (*2–4*). However, for laboratories that participated in the 1989 College of American Pathologists (CAP) General Chemistry Survey, in which a pooled frozen serum proficiency-testing material was used, results indicate that the vast majority (~92%) apparently met the total error goal for TC of 8.9%, i.e., 3.0% + (1.96 × 3.0%), derived from the 1992 NCEP separate accuracy and precision targets (*2*).

Proficiency testing, even with proficiency-testing fluids that ideally mimic fresh human serum, can measure only a laboratory's within-laboratory analytical performance. It cannot measure pre- or postanalytical factors that may also markedly effect a patient's laboratory test result. Among the many nonanalytical factors that influence a patient's blood lipid results (*5*), one of the more important preanalytical factors that can introduce systematic bias in determinations of lipids and lipoproteins is specimen type, namely, serum vs EDTA-plasma. Both specimen types have been widely used in large research studies: e.g., the Coronary Primary Prevention Trial (*6, 7*) analyzed EDTA-plasma; the Helsinki Heart Study, serum (*8*). More recently, serum appears to have become the more widely used and recommended specimen (*9, 10*), although some investigators still consider EDTA-plasma preferable, particularly when lipoprotein and apolipoproteins are to be analyzed (*10*).

Because both EDTA-plasma and serum are used widely for lipid analyses, plasma/serum (P/S) differences have been the subject of several studies. An early report indicated that EDTA-plasma TC concentrations averaged ~3% lower than those in simultaneously collected serum (*11*), and the first NCEP Adult Treatment Panel report, which decided on clinical decision cut-points for serum TC [5.18 and 6.22 mmol/L (200 and 240 mg/dL)], recommended that EDTA-plasma TC results be multiplied by 1.03 for interpretation by NCEP guidelines (*9*). The observed 3% difference was attributed to in vitro fluid shifts between plasma and erythrocytes in the presence of EDTA. A later study found a P/S TC difference of 4.7% and attributed the larger bias to an increase of ~50% in EDTA concentration in more-recently manufactured commercial evacuated blood-collection tubes (*12*).

Less has been published on EDTA-plasma vs serum biases in HDLC and TG determinations. In addition, formal accuracy and precision goals for these two analytes are yet to be published by the NCEP Laboratory Standardization Panel. However, preliminary analytical performance goals for accuracy and precision of HDLC determinations have been selected as 10% and 6%, respectively, by 1994 and 5% and 4% by 1998 (M. Kimberly, Cholesterol Reference Method Laboratory Network, Centers for Disease Control and Prevention, personal communication). In some earlier reports from the Lipid Research Clinic laboratories on the effect of

Department of Laboratory Medicine and Pathology, University of Minnesota, Box 609 UMHC, Minneapolis, MN 55455-0392.
[1] Corresponding author. Fax 612-625-6994, E-mail eckfe001@maroon.tc.umn.edu.
[2] Nonstandard abbreviations: P/S, EDTA-plasma/serum; TC, total cholesterol; TG, triglyceride; HDLC, LDLC, and VLDLC, high-, low-, and very-low-density lipoprotein cholesterol, respectively; NCEP, National Cholesterol Education Program; and CAP, College of American Pathologists.
Received July 5, 1994; accepted August 19, 1994.

manganese ion concentration and EDTA-plasma vs serum on HDLC results, a reasonably complete precipitation of apolipoprotein B-containing lipoprotein particles was found to require greater manganese concentrations for EDTA-plasma samples than for serum samples (*13*, *14*). Nevertheless, the P/S bias for HDLC analyzed by the Lipid Research Clinics chemical-extraction method on the AutoAnalyzer II was reportedly <1% (*15*). The average P/S ratio for TG has been reported to be between 0.97 (*11*) and 0.95 (*15*), close to the P/S ratios reported for TC.

The P/S biases for the major lipid and lipoprotein fractions that are used for prediction of atherosclerotic disease risk and for therapeutic decisions appear to be as great as the proposed maximum analytical bias under NCEP Laboratory Standardization Panel guidelines. Thus, we decided to investigate more systematically the P/S biases for a centrifugal analyzer method we planned to use for several upcoming NIH-funded multicenter research studies for which specimens were to be assayed in our laboratory. At the same time, we decided to investigate some of the other commonly used clinical methods.

Materials and Methods

Subjects and Specimens

The study population consisted of 25 apparently healthy individuals (6 men and 19 women; ages 25–60 years, average 39.5 years). The study was approved by our institutional review board. After an overnight fast, ~15 mL of venous blood was collected with a butterfly needle and a 30-mL plastic syringe. The blood was mixed in the syringe for few seconds and then aliquoted into evacuated 7.0-mL (blood volume) blood-collection tubes (Vacutainer Systems; Becton-Dickinson, Rutherford, NJ) that contained either no anticoagulant (prod. no. 6431) or disodium EDTA designed to give a final concentration in blood of 4.46 mmol/L (prod. no. 6452, lot no. 4C020). This plastic syringe technique was used to eliminate any temporal effects on lipid concentration from tourniquet application. The EDTA-anticoagulated samples were cooled to 4°C without delay. Samples collected without anticoagulant were allowed to clot at room temperature for 45 ± 10 min. Cellular components were removed from both sample types by centrifugation at 1500*g* at 60 ± 15 min after venipuncture. Separated serum and plasma specimens were then stored at 4°C for ≤48 h before analysis.

Lipid Analyses

TC, HDLC, and TG were measured in each serum specimen and in each plasma specimen in duplicate. To minimize the impact of run-to-run variability, we always assayed the matched EDTA-plasma and serum pairs from a given volunteer in the same analytical batch. Analytical methods used included:

1) Cobas FARA. Cholesterol oxidase-based reagent (prod. no. 236691) and glycerol oxidase-based TG reagent (prod. no. 701912) were supplied by Boehringer Mannheim (Indianapolis, IN). We used the HDLC method of Warnick et al. (*16*), combining 0.50 mL of serum or plasma with 50 μL of a solution containing 0.50 mol/L magnesium chloride and 10 g/L dextran sulfate (average molecular mass 50 kDa; Genzyme, Cambridge, MA; prod. no. 70-5801-00), vortex-mixing ~10 s, incubating for 10 min at room temperature, and centrifuging (1500*g*, 10 min) before analyzing cholesterol in the supernate.

2) Ektachem 700. The reagent slides for cholesterol (prod. no. 168-8290), TG (prod. no. 164-8088), and HDLC precipitation reagent (prod. no. 146-32356) were supplied by Kodak (Rochester, NY) and used as directed by the manufacturer. In the Kodak HDLC method 0.50 μL of serum or plasma is combined with a premeasured amount of HDLC reagent to yield 0.91 g/L dextran sulfate (50 kDa) and 45 mmol/L magnesium chloride in the final precipitation mixture. After vortex-mixing for ~10 s, incubating 10 min, and centrifuging (1500*g*, 10 min), the supernate cholesterol is analyzed with the same total cholesterol slides, calibrated specifically for HDLC analysis.

3) DuPont Dimension. The TC (prod. no. DF-27), TG (prod. no. DF-69), and HDLC (prod. no. DF-47) reagents were supplied by DuPont (Wilmington, DE) and used as directed by the manufacturer. The DuPont HDLC method combines 0.250 mL of serum or plasma with 50 μL of 6.0 mmol/L phosphotungstic acid; after vortex-mixing (~5 s), incubation (room temperature, 5 min), and centrifugation (1500*g*, 20 min), the cholesterol in the supernate is assayed.

4) Paramax. The reagent kits for all three analytes were supplied by Baxter Travenol (Chicago, IL) and used as directed by the manufacturer. The Baxter HDLC method combines 0.50 mL of serum or plasma with 100 μL of 6.59 mmol/L phosphotungstic acid, vortex-mixes (~10 s), incubates (10 min), and centrifuges (1500*g*, 10 min), and then analyzes cholesterol in the supernate.

5) TC was quantified in our laboratory by the modification of the original Abell–Kendall method that is currently used at the Centers for Disease Control and Prevention (*16*).

During this study our laboratory's primary methods for TC, HDLC, and TG analysis for multicenter research studies were as listed above for the Cobas FARA. These methods were continually standardized via the National Heart, Lung, and Blood Institute/Centers for Disease Control and Prevention's Lipid Standardization Program.

Computations were performed on a Macintosh IIsi computer with Excel software (Microsoft, Redmond, WA) for computation of the means of duplicates and calculated low-density lipoprotein cholesterol (LDLC) concentrations with the Friedewald et al. equation (*17*). Statistical analyses were also performed on the Macintosh IIsi with Statview II (BrainPower, Calabasas, CA). The mean and SD for P/S ratio for calculated LDLC for a given method were derived by computing a calculated LDLC for each volunteer's EDTA-plasma, computing a calculated LDLC for that same volunteer's matched se-

rum, dividing the EDTA-plasma calculated LDLC result by its matched serum result, and finally computing the mean and SD from the 25 individual LDLC P/S ratios.

Results and Discussion

Table 1 shows the mean (SD) concentrations of the various lipids and lipoproteins measured in serum and in EDTA-plasma as well as the mean (SD) P/S ratios for the 25 volunteers for each of the analytical methods used. The lipid and lipoprotein concentrations were what would be expected for a healthy, reasonably young population.

We found several results in Table 1 quite interesting. First, the mean P/S ratio for TC is statistically different across analytical methods. The original difference between EDTA-plasma and serum TC was reported to be ~2–3% when TC was analyzed by chemical extraction methods (*11, 15*). Cloey et al. (*12*), using a cholesterol oxidase-based method for TC, later reported a TC P/S difference of 4.7%. They attributed their observed increase in the P/S bias to an increase in the amount of disodium EDTA in the collected blood from ~3.0 mmol/L in older EDTA blood-collection tubes to 4.5 mmol/L in more modern commercially available EDTA-containing tubes, a change that occurred in the mid-1980s. However, our findings indicate that the P/S ratio for TC for some analytical methods is statistically different (two-tailed, unpaired Student's *t*-test) from that for the Abell–Kendall method (0.984): Cobas ratio 0.993 ($P = 0.02$); Ektachem ratio, 1.003 ($P = 0.0002$); Paramax ratio, 0.980 ($P = 0.40$); Dimension ratio, 0.978 ($P = 0.08$). We consider very unlikely that the Abell–Kendall TC reference method with its extraction step would be affected by changing the sample matrix from EDTA-plasma to serum. Thus, we believe the Abell–Kendall P/S ratio should very closely approximate the true P/S ratio for TC concentration. Because some of the other analytical methods yield P/S TC ratios that are statistically very significantly different from the Abell–Kendall TC P/S ratio, we suggest that part of the observed change in P/S bias reported by Cloey et al. in 1990 is a result of the change in their analytical method for TC—from a chemical extraction method to an enzymatic method—rather than the difference being entirely due to an increased EDTA concentration in blood-collection tubes.

Our observed P/S ratios for TG with three of the four methods we assessed tend to be in the same direction and roughly the same order of magnitude as previously reported (*11, 15*). For three of the TG methods, the TG P/S ratios are statistically very significantly different from the P/S ratio for TC (0.984) by Abell–Kendall analysis: Paramax ratio, 0.961 ($P = 0.005$); Dimension ratio, 0.950 ($P = 0.005$); Ektachem ratio, 0.988 ($P = 0.32$); and Cobas ratio, 1.013 ($P = 0.001$). Although it is probable that the true TG concentration in EDTA-plasma vs serum may actually differ, the fact that the P/S ratios for TG differ in a statistically significant fashion from the Abell–Kendall TC P/S ratio, and from each other, can be explained, we believe, only if the clinical enzymatic TG methods recover TG differently from EDTA-plasma than from serum. Because there are no widely available or accepted reference or definitive methods for TG, distinguishing unequivocally the magnitude of analytical recovery biases vs true systematic differences in TG concentration in EDTA-plasma vs serum is not possible.

Our original primary purpose for beginning this study was to investigate carefully the EDTA-plasma vs serum difference for HDLC methods. It is interesting to note

Table 1. Measured serum concentration, EDTA-plasma concentration, and P/S concentration ratios for total cholesterol, HDL-cholesterol, triglycerides, and calculated LDL-cholesterol determined by various analytical methods.

Method	Specimen or ratio	Cholesterol	HDLC	Triglycerides	Calculated LDLC
		Mean (SD), mmol/L[a]			
Paramax	Serum	5.02 (1.04)	1.37 (0.42)	1.50 (1.29)	2.96 (1.09)
	EDTA-plasma	4.93 (1.04)[b]	1.44 (0.40)[b]	1.45 (1.26)[b]	2.82 (1.11)[b]
	P/S ratio	0.980 (0.0171)	1.063 (0.0704)	0.950 (0.0363)	0.94 (0.0642)
Dimension	Serum	5.29 (1.08)	1.43 (0.40)	1.39 (1.34)	3.29 (1.18)
	EDTA-plasma	5.17 (1.07)[b]	1.47 (0.40)	1.31 (1.25)[b]	3.10 (1.16)[c]
	P/S ratio	0.976 (0.0189)	1.034 (0.1910)	0.950 (0.0557)	0.94 (0.0850)
Ektachem	Serum	5.13 (1.00)	1.39 (0.38)	1.53 (1.39)	3.04 (1.08)
	EDTA-plasma	5.15 (1.03)	1.47 (0.39)[b]	1.50 (1.32)[d]	3.00 (1.11)
	P/S ratio	1.003 (0.0221)	1.059 (0.0304)	0.969 (0.0179)	0.979 (0.0399)
Cobas	Serum	5.05 (1.04)	1.33 (0.39)	1.44 (1.26)	3.06 (1.09)
	EDTA-plasma	5.01 (1.01)[d]	1.40 (0.39)[b]	1.43 (1.22)	2.95 (1.07)[b]
	P/S ratio	0.993 (0.0162)	1.063 (0.0830)	1.013 (0.0410)	0.961 (0.0306)
Abell–Kendall	Serum	5.04 (1.06)			
	EDTA-plasma	4.96 (1.04)			
	P/S ratio	0.984 (0.0113)			

[a] Cholesterol mmol/L concentration can be converted to mg/dL by multiplying by 38.6 and triglyceride (as triolein) mmol/L concentration to mg/dL by multiplying by 88.5. n = 25 each.

[b–d] Significantly different from serum mean by the same analytical method by paired, two-tailed Student's *t*-test: [b] $P < 0.001$; [c] $0.001 < P < 0.01$; [d] $0.01 < P < 0.05$; others are not significant ($P > 0.05$).

that the P/S bias for HDLC is in the opposite direction from that for TC. Furthermore, the P/S bias for HDLC in some methods is as large or larger than the proposed maximum allowable *analytical* bias for HDLC. Substantial and analytical method-specific P/S ratios for HDLC are not totally unexpected. The exact manganese concentration is known to be an important variable for the manganese–heparin HDLC methods used by the Lipid Research Clinics; and, as expected, increasing the manganese concentration leads to lower HDLC results (*14*). In fact, the 46 mmol/L manganese chloride concentration in the mixture used for the Coronary Primary Prevention Trial to precipitate LDLC and very-low-density lipoprotein cholesterol (VLDLC) (i.e., apolipoprotein B-containing lipoproteins) was probably somewhat low; it has since been suggested (*18*) that 92 mmol/L manganese would have been more appropriate for EDTA-plasma, which was the specimen type used in that landmark drug study. The problem created by the presence of EDTA is that chelated metal ions do not participate effectively in the precipitation of LDLC and VLDLC by metal ion-containing HDLC reagents (e.g., manganese–heparin and magnesium–dextran). The differences in VLDLC and LDLC precipitation efficiency between EDTA-plasma and serum seem to have been partially forgotten in the late 1980s and '90s. Many manufacturers' package inserts (e.g., Baxter Paramax, DuPont Dimension) and clinical laboratories list both EDTA-plasma and serum as "acceptable" specimen types for HDLC quantification without discussing the preanalytical biases introduced by the type of collection tube. Interestingly, Kodak's package insert indicates that HDLC in EDTA-plasma is 0.06–0.08 mmol/L (2.2–3.2 mg/dL) higher than in simultaneously collected serum and references a 1985 study on a magnesium–50-kDa dextran sulfate method performed on the Ektachem 400 (*19*). The P/S bias in that study is amazingly close to what we have found in 1994 with the Ektachem 700. Also noteworthy is the fact that the P/S biases for all of our HDLC methods significantly exceed the early report that EDTA-plasma and serum are "virtually identical" with the Lipid Research Clinic's manganese–heparin precipitation method and the AutoAnalyzer II TC method (*15*).

Because the EDTA-plasma HDLC result tends to be biased high compared with serum while its TC tends to be biased low, the LDLC concentration computed by using the Friedewald equation (*17*) is quantitatively biased even lower. This situation in turn further increases the low bias of the EDTA-plasma LDLC/HDLC ratios, which are widely used as the starting point for calculations of coronary disease risk estimations. For example, the LDLC/HDLC ratio for an individual's EDTA-plasma averages only ~88.5%, 91.3%, 92.4%, or 90.4% of the ratio that would have been determined had serum been collected and analyzed by the Paramax, Dimension, Ektachem, or Cobas, respectively. Also, one should remember that partial filling of EDTA-containing blood-collection tubes would be expected to increase quite markedly the magnitude of the observed P/S biases in measured and calculated lipids and lipoproteins, and in the coronary disease risk computed from them.

In conclusion, if one considers the laboratory standardization efforts being spent to reduce analytical bias to <3% for TC and <5% for HDLC, it is clear that laboratories and clinicians should be cognisant of the comparably large preanalytical biases introduced by changing between serum and EDTA-plasma samples. Furthermore, manufacturers of diagnostic reagents and instruments for TC, TG, and HDLC—and the clinical laboratories that use them—should provide information of the exact quantitative biases introduced by use of EDTA-plasma, rather than serum, if they consider EDTA-plasma acceptable for these analyses.

We thank Nancy Wallace at Park Nicolet Medical Center in Minneapolis, MN, for performing all Baxter Paramax analyses and Mary Richardt in the University of Minnesota's Boynton Health Service for performing all DuPont Dimension analyses.

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Attachment 5: Varian Magnet Test Release Documentation

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Attachment 6: 99-102-00-PI Vantera Package Insert
91-145-00-P13 LDL-P Value Assignment Card
Floor Vibration Specificaion

NMR LIPOPROFILE test

NMR *LipoProfile*® test on Vantera® Clinical Analyzer by LipoScience

For *In Vitro* Diagnostic Use Only

INTENDED USE

The *NMR LipoProfile*® test by LipoScience, used with Vantera® Clinical Analyzer, an automated NMR spectrometer, measures lipoprotein particles to quantify LDL particle number (LDL-P), HDL cholesterol (HDL-C), and triglycerides (TG) in serum and plasma using nuclear magnetic resonance (NMR) spectroscopy. LDL-P and these NMR-derived concentrations of triglycerides and HDL-C are used in conjunction with other lipid measurements and clinical evaluation to aid in the management of lipoprotein disorders associated with cardiovascular disease.

SUMMARY AND EXPLANATION

Lipoprotein (HDL, LDL, and VLDL) particles play key roles in atherogenesis and their concentrations in plasma or serum are important cardiovascular disease (CVD) risk factors. For clinical use, lipoprotein levels are traditionally estimated by measuring one or more of their lipid constituents. The cholesterol within LDL and HDL particles (LDL-C and HDL-C) is used to approximate serum or plasma LDL and HDL levels, while total plasma triglycerides approximate VLDL levels. The *NMR LipoProfile*® test by LipoScience employs a novel automated process to measure NMR signals from LDL, HDL, and VLDL particles simultaneously [1]. The detected lipoprotein signals are proportional in amplitude to the numbers of lipoprotein particles emitting the signals, enabling a calculation of their concentrations. LDL is reported in terms of particle numbers (LDL-P) providing another measure of a patient's LDL level.

Lipoproteins that interact with the arterial wall set in motion the cascade of events leading to atherosclerosis [2]. LDL is the major atherogenic lipoprotein and is identified in ATP III guidelines as the primary target of treatment for reducing coronary heart disease risk [3]. According to a report from the American Diabetes Association (ADA) and American College of Cardiology (ACC), measurement of LDL-C may not accurately reflect the true burden of atherogenic LDL particles, especially in those patients with the typical lipoprotein abnormalities of cardiometabolic risk [4]. The ADA/ACC report also states that measurements of apolipoprotein B or LDL-P may more closely quantitate the atherogenic lipoprotein load. [4] Thus, they may aid in the management of patients with elevated risk of CVD. LDL-P measured by the *NMR LipoProfile*® test by LipoScience has been shown to be a determinant of CVD risk in two prospective case-control studies [5, 6].

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Attachment 7: (b)(4) Procedure for Labeling and Characterizing Vantera Trueness Control

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Appendix A-Batch Record

VANTERA TRUENESS CONTROLS-EVALUATION

PRODUCT-FROM SUPPLIER					
PART/ITEM NUMBER	LOT NUMBER	EXPIRATION DATE	QTY RECEIVED	RETAIN QTY	SUPPLIER ID #

BATCH RECORD APPROVAL

DEPARTMENTAL REVIEW	By:	Date:
QC REVIEW (If Applicable)	By:	Date:

QUALITY ASSURANCE FINAL REVIEW

___ ACCEPT: The attached Batch Record has been reviewed and found to be complete, accurate, and within set specifications. This lot is now approved for release.

___ REJECT: The attached Batch Record has been reviewed and found to be in non-compliance of set specifications and therefore rejected. All associated products and materials will be handled in accordance with QSOP0139.

By: _____ Date: ____/____/____

LINE CLEARANCE- LIPIDS CONTROL EVALUATION	DATE: ____/____/____	COMPLETED BY
Verify that all required equipment is clean and ready for use. Any required calibration and/or scheduled maintenance operations are current.		
Verify that the work area is clean. All extraneous materials from previous		

lots have been removed from the area.	

EVALUATION NOTES:

- Personnel must wash their hands prior to entering work area and immediately after leaving the work area.
- Place all reagents and materials to be used in a controlled, segregated area. Open and close these reagents and materials only after they are inside this area.
- Wear a lab coat, safety glasses, or other personal protective equipment (PPE) as needed.
- Care must be taken during the addition of individual reagents to reduce the potential for foaming/splash.
- Use approved techniques to transfer reagents.

Receipt of Product-Lipid Controls
Date:___/___/___

The following steps are to be performed sequentially unless otherwise noted.

STEP #	INSTRUCTIONS	INITIAL
1	Verify product type, lot number, expiration date, and volume received. Product Type: Vantera Trueness Control Level 1 Lot Number: _____ Exp. Date: _____ Volume Received: _____ Product Type: Vantera Trueness Control Level 2 Lot Number: _____ Exp. Date: _____ Volume Received: _____ Product Type: Vantera Trueness Control Level 3 Lot Number: _____ Exp. Date: _____ Volume Received: _____	
2	**VISUAL INSPECTION** Perform visual inspection. Inspect product looking for broken or leaky seals, broken vials, etc. Accept/reject criteria for product sampling may be obtained by accessing SQC Online and entering the following information under military standard MIL-STD-105E: • Batch size – number of items in that batch • AQL%- Acceptable Quality Level (1%) • Type of inspection (see chart below) Submit data. Print a copy of results and transfer information into chart below Qty Inspected: _____ Qty Rejected: _____	

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Attachment 8: (b)(4) Procedure for Value Assignment for Vantera Lipoprotein Controls

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Attachment 9: MFG0300 Manufacturing Procedure – NMR Reference Standard (DRAFT)

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Attachment 10: (b)(4) - Stability Protocol Trueness Control and Lipoprotein Control

Stability Protocol for Vantera Trueness Controls and Lipoprotein Controls		
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Approvals

Signature denotes the individual has read, understands, and agrees with the content of this document.

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Confidential	Page Number: 1 of 10

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Attachment 11: CLIA Categorization Score Card

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Attachment 12: Raw Data Sets

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Attachment 13: 510(k) Summary

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Attachment 14: Declarations of Conformity and Summary Reports

Section 10: Declarations of Conformity and Summary Reports

Table of Contents

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