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Subject: Manufacturer's Letter

To Whom It May Concern:

ADInstruments Inc. is the manufacturer of the **Lab Chart 8 Pro Software** included in **Q23-123598** and directly distributes all items.

The PowerLab data acquisition systems, LabChart 8 software, associated software analysis modules, and other equipment, have a number of features other competing data acquisition systems cannot match. In order to fulfill any competing bid, the specifications below must be met by any comparable systems from different manufacturers.

The data recording software must in general duplicate familiar laboratory instruments such as Chart recorders, Polygraph recorders, storage oscilloscope, X-Y plotter etc. This single piece of software must be capable of controlling hardware settings, programming analog outputs, as well as collecting and analyzing data.

Additional requirements for the software capabilities include the ability to connect to and stream data from specific hardware devices manufactured. The manufacturers of these devices and specific equipment include:

- Danish Myo Technology (DMT)
- Data Sciences International (DSI)
- Delsys Inc.
- Equivital Inc.
- Kent Scientific Corporation
- Nintendo Wii Balance Board
- Oxford Optronix

Provision must be included to allow storage of settings for use as experimental setup templates. The data recording software must be available for Macintosh OS X & Windows 10, 8, 7. Data collected under one operating system must be capable of being read by corresponding software on an alternative platform. Other requirements are listed below:

- The system provides control over color, graph size, and graph scaling must be available.
- 32 Software Channels must be available for collecting raw data, or creating channel calculations.
- The hardware must provide a digital interface for controlling other laboratory hardware with TTL signals. These signals must be able to be produced both manually, and using an automatic, event based and easily programmable interface.
- Data may be viewable as a continuous chart recording, or viewed in oscilloscope/event/sweep based format. Both viewing formats are available simultaneously. Data may also be played as a sound and saved as a QuickTime movie.
- A method must be provided for automating recording and analysis protocols by recording a set of control steps and then playing these back. These “macros” must be able to be saved along with settings for use as templates. The produced “macros” must be editable using a common scripting language.
- User-defined events should be able to be acted upon by the software, including sending analog or digital signals to other devices, automatic annotations of the data, or triggering an alarm for the user.
- Data should be displayed continuously as it is being recorded and should allow recording to be started and stopped without having to start a new file.
- Channel calculations should be available to calculate certain desired parameters in real time, plotting the results next to raw data channels. Available channel calculations include: Cyclic Rate, Cyclic Max, Cyclic Min, Cyclic Height,  $\frac{1}{3}$  Cyclic Max Minus  $\frac{2}{3}$  Cyclic Min, Cyclic Period, Cyclic Frequency, Cyclic Event Count, Cyclic Mean, Integrals of Various Types, Derivative, Smoothing, Digital Filters, Spectral Analysis, and custom arithmetic calculations. All of these calculations must show results in real time.
- The software must allow the user an easy method for extracting numerical information from the graphical interface. Calculations provided for this numerical interface include: Mean, Standard Deviation, Standard Error, Number of Points, Max Value, Min Value, Time at Max, Time at Min,
- Max-Min, End-Start, RMS,  $\frac{1}{3}$ Max- $\frac{2}{3}$ Min, Timing Parameters, Annotation Information, Derivative, Integral, Cyclic Parameters, Spectral Analysis, and XY Calculations.
- The system should provide a simple method for a two-point calibration for the signal in user-defined units.
- Raw recorded data should always be maintained by the competing systems. Calculations on raw data must be performed so that the raw data is always preserved.

- Support for transfer of data in graphical or numeric formats to other applications such as spreadsheets and word processing or graphing programs. Formats available include: ASCII text, IGOR, Binary, MATLAB, EDF and others. Images and graphs must be exportable in formats that are modifiable in other applications.
- Should have the ability to append data to previously recorded files.
- Online spectral analysis should be utilized to create power spectrum density plots in real time via a real-time Fast Fourier Transforms.
- Print a selection or an entire file, print Zoom and XY windows.
- A cost free Reader version of the software must be available for download for purposes of collaboration with individuals who do not own a fully licensed version.
- The software must be upgradeable to Good Laboratory Practice requirements, including the facilitation of 21 CFR Part 11 compliance.

Further standard analysis features are available in this system that must be matched by competing systems. These include:

- Cardiac Axis
  - Automates the calculation of the frontal plane electrocardiograms and the vectorcardiogram. It can also automate the instantaneous cardiac vector display.
- Non-Invasive Cardiac Output
  - Enables the real-time estimation of cardiac output from a Non-Invasive Blood Pressure device designed for human subjects. It implements published and widely accepted algorithms for the following parameters: Cardiac Output, Stroke Volume, and Total Peripheral Resistance.
- Multi-point and Glucose Calibration
  - Allows linear and non-linear calibration for more than 2-points. This extends to the calibration of a glucose telemetry implant.
- Spirometry
  - Allows the derivation of a number of respiratory parameters based on airflow. This includes volume, VE, VT, Frequency, PIF, PEF, FVC, FEV1. It also allows the generation of flow-volume plots and spirometry reports.

Additional Analysis tools are required which can automatically, offline or online, analyze parameters from specific recording applications. These Applications include:

#### Blood Pressure

- The software should have the ability to automatically detect, analyze, and report a set of cardiovascular parameters from arterial or ventricular pressure signals, either online or offline
- The software should display calculated Blood Pressure parameters as continuous data on separate channels. Raw data is unaltered by any calculation ensuring that recorded data can be reanalyzed anytime.

- A method of classifying and selecting good data and eliminating artifacts will be provided.
- Waveform averaging of pressure waves will be available.
- A numerical spreadsheet logs all calculated pressure parameters in real time. Table rows are linked to various analysis windows. Highlighting a row will automatically show the corresponding beat in the graphical interface.
- The analysis software dialog allows easy configuration of detection and analysis parameters for ventricular or arterial pressure recordings. The detection algorithm uses minimum cycle height and duration, with each detected cycle labeled and specific waveform parameters automatically calculated. Cycle averaging and isovolumic relaxation (Tau) options are also set in the dialog.
- Parameters Calculated on the ventricular cycle include
  - Maximum Pressure
  - Minimum Pressure
  - End Diastolic Pressure (EDP)
  - Maximum  $dp/dt$  Mean Pressure
  - Maximum-Minimum Pressure
  - Systolic Duration
  - Diastolic Duration
  - Cyclic Duration
  - Heart Rate
  - Maximum  $dp/dt$
  - Contractility Index
  - Minimum  $dp/dt$
  - Isovolumic Relaxation Period Average  $dp/dt$
  - Tau
  - Pressure Time Index
- Calculated Arterial Parameters include
  - Systolic Pressure
  - Diastolic Pressure
  - Dicrotic Notch Pressure
  - Mean Pressure
  - Pulse Pressure
  - Ejection Duration
  - Non-Ejection Duration
  - Cycle Duration
  - Heart Rate
  - Time to Peak

## ECG Analysis

- Allows real-time analysis of incoming ECG analysis.
- Analysis of ECG data from any species and includes tailored ECG Analysis algorithms for human, rat, rabbit, mouse and other animal models.
- Settings are customizable for optimal identification of ECG waveforms.
- Automatic detection and averaging of ECG cycles with the option to average a specified number of beats, or all the beats across a specified time period or in a block.
- A method is provided for identifying ectopic beats and other cardiac arrhythmias by identifying noise-contaminated waveforms and waveforms with abnormal QRS shapes or RR intervals. Beats can be included or excluded from analysis.
- A graphical window is provided for viewing averaged waveforms, reducing the effects of noise or movement artifacts and to compare effects on the ECG before and after experimental intervention.
- Provides automatic logging and displaying of selected ECG parameters of start, end, amplitude and PQRST interval times in tabular and graphical format.
- A numerical spreadsheet produces parameters that can be exported to other graphing or statistical programs. Available parameters includes:
  - P, Q, R, S, T amplitudes
  - Time intervals such as RR, PR, JT,QT and QTc
- Automatic generation of Analysis Plots from calculated parameters:
  - QT/RR Plot (QT Interval versus RR Interval)
  - QT/Time Plot
  - RR/Time Plot
  - Waterfall Plot
- All data viewing options are linked to provide easy navigation to points of interest with any manual edits performed marked in red.

## Analysis of Peaks

- Detects and analyzes multiple peaks in recorded waveforms.
- Suitable for a wide range of signals.
- Calculates and reports a wide range of peak parameters such as height, area, width, various slope values, and others.

- Allows analysis in real time and after recording.
- Provides default analysis settings for various signal types.
- Useful graphical display of calculated parameters as continuous signals in separate channels in real time.
- Detects positive or negative peaks.
- Provides automatic peak detection of an entire channel or a selection within a channel.
- Analysis presets suitable for general and specific types of waveforms includes:
  - General
  - Evoked Responses
  - Population Spikes
  - Synaptic
  - Action Potentials
  - Cardiac Action Potentials
- The software provides options for user determination, including:
  - Detection: Determines how stimulus artifacts and peaks are detected
  - Calculations: Set boundaries for the calculation of peak parameters
  - Table Options: Custom selection of calculated parameters to be displayed in a numerical table.
- A graphical representation of peaks is provided, this allows:
  - Display of each individual peak and its parameters
  - Display of waveform cursor coordinates
  - Allows scaling of the display
  - Display of parameter summary information
- The numerical spreadsheet displays calculated parameters for all detected peaks:
  - Must be able to export contents as text file that can be opened in other applications
  - Allows selection of parameters to be displayed
- Linking of all graphical and numerical views to allow easy and quick navigation of particular peak information.

#### Analysis of Extracellular Spikes

- Advanced spike discrimination and data analysis in real time or after recording.
- Two discrimination methods
  - Template matching allows the user to define a template waveform and determine

groups based on how well other waves match the template

- Freehand selection for precise selection of spikes
- Automatic indication and examination of changes in neural firing rate.
- Multi-channel, multi-unit analysis allows comparison of any physiologic measures recorded.
- Channel calculations displaying properties of the defined unit(s) such as frequency.
- User configuration allows
  - Data source selection
  - Extracted waveforms detection threshold, pretrigger and total trigger period
  - Template matching options
- Six specialized histogram windows:
  - Rate Meter plots the spike firing rate against time
  - Amplitude displays a histogram of spike amplitudes from different populations
  - Interspike Interval displays a histogram of interspike intervals distribution
  - Peristimulus Time Histograms examines changes in neural firing rates due to a repeated stimulus
  - Autocorrelation Histogram detects periodicity in an individual unit or any inherent periodicity in spike
  - Cross-correlation Histogram detects periodicity or temporal dependence of two physiologic parameters

#### Analysis of Metabolic or Exercise Function

- Specialized analysis of metabolic function, including online and offline analysis of data.
- Perform metabolic measurements and analysis of respiratory gas.
- Automatic calculations of:
  - VE expired minute volume (L/min)
  - VO<sub>2</sub> oxygen consumption (L/min)
  - VCO<sub>2</sub> carbon dioxide production (L/min)
  - RER respiratory gas ratio
- Real time tabulation and graphical plot display of metabolic calculations.
- Eight options for viewing results of the metabolic calculations:
  - A window for providing average numerical data over time.
  - VE(BTPS) vs VO<sub>2</sub>
  - VE(BTPS) vs VCO<sub>2</sub>
  - VCO<sub>2</sub> vs VO<sub>2</sub>

- RER vs Time
- VO2 vs Time
- VCO2 vs Time
- VE(BTPS) or VI(ATPS) vs Time
- User configurable options include:
  - General preferences: Averaging time (data logging) and recording time (duration of experiment) settings
  - Subject details: name, age, weight, height, gender, id number, comments
  - Environment settings: Expired/inspired, atmospheric and air conditions
  - Channel Setup
  - Calibration preferences: settings for automated first and second gas calibrations
  - Report generation: Users can choose what they want to be included in report
  - Metabolic graphs and calculations are compiled into a report that can be printed or exported to other programs for further analysis.

#### Cardiac Output

- The software allows plotting of temperature versus time to give a thermodilution curve.
- Able to calculate both upwardly- and downwardly-displayed thermodilution curves.
- Analyze recordings in the duration of 5 seconds to 10 minutes.
- Automatic calculation of Cardiac output in mL/min
  - Baseline temperature
  - Area under the thermodilution curve
  - Baseline slope correction
- User configurable settings allows the user to define the parameters used in the calculation of cardiac output such as injection volume and temperature.
- Correction factor option to account for variation in instrument/experimental conditions.
- Correction of baseline drift is managed by a user configurable option. Correction factor would be automatically inserted in the cardiac output calculation.
- Tail Fitting range to specify portion of the thermodilution curve which an exponential curve is calculated and extrapolated to return to baseline value.
- Capture tab allows the user to mark the selected thermodilution curve with Cardiac Output values and the addition of a comment and resulting cardiac output values on the selected thermodilution curve.
- Easy exportation of cardiac output values to other programs for further statistical analysis.



## Micro-vessel Normalization & Dose Response Curves

- Provides micrometer setting for achieving desired pre-tension conditions by determining vessel normalized internal circumference.
- Online and offline determination of tissue effective pressure.
- Allows the user to enter different micrometer settings that sequentially stretch the tissue and record exerted force by the vessel wall.
- Automatic display of an exponential curve plotting measured tissue's internal circumference versus resting wall tension.
- Separate window for different channel so individual tissue end points (determination of tissue length) and wire diameter can be entered to generate individual curve.
- Automatically ends when effective pressure exceeds 100 mmHg (13.3kPA). Effective pressure is an estimate of the pressure which would be necessary to extend the vessel to the measured internal circumference.
- User configurable settings allows for the selection of:
  - Microscope eyepiece calibration and Target pressure (effective pressure)
  - IC1/IC100 ratio
  - Online averaging time
  - Force reading delay when automated feature is used
  - Sound playing option is available when delay time expires
- Automatic calculation of:
  - Tissue length (from calibrated eyepiece and microscope)
  - Wall tension (from measured force divided by wall length from which effective pressure is calculated).
  - IC100 (Point on curve corresponding to 100 mmHg using Laplace's equation)
  - IC1 (From IC100 value and user defined IC1/1C100 ratio)
  - Vessel internal circumference
  - Final micrometer reading for standardizing each piece of tissue
- The Force/Tension button allows users to record new experiment data using force (mN) or tension (mN/mm) units.
- Generation of a printable report containing results of the normalization procedure. Dose/Drug Response
- Real time and offline analysis.

- Automatic and manual display of single or multiple dose response curve calculations.
- Calculates EC50 and Hill Slopes.
- Extensive set of response calculation methods:
  - Average
  - Maximum
  - Maximum-Minimum (Response Height)
  - Integral (Area)
  - Minimum
- Optional baselines, flat and sloping.
- Numerical Spreadsheet provides centralized setup, display and data management functionality.
- Graphical view allows inspection and manual adjustment of calculation region and optional baseline for each response.
- Separate Graphical view displays parameters of fitted sigmoid curves and provides for simultaneous display of multiple curves with optionally fixed top, bottom and hill-slopes.
- Data can be exported in XML and tab-delimited text format for use in other applications.

#### Heart Rate Variability

- Detection and analysis of R waves & RR interval variation in ECG in real-time or offline, and must use the Lomb Periodogram nonparametric method for unevenly sampled tachograms.
- Must be available for animal and human cardiovascular studies and allow both time domain and frequency domain parameter calculations.
- Automatically classify beats as normal, ectopic or artifact from user select interval classification limits.
- Exclude artifacts or include beats in the analysis on an individual basis.
- Option to add R waves or delete R waves which have incorrectly created short artifacts.
- Automatic generation of clinically accepted statistical parameters.
- Specialized analysis plot windows derived from RR interval data includes:
  - Poincaré Plot
  - Period Histogram
  - Delta NN Histogram

- Tachogram plots
  - Spectrum
- Automatic generation of exportable and printable report displaying information about data recording, details of subject, and statistical results.
- All windows are linked for immediate update when modifications are performed.

#### Ventricular Pressure-Volume Loops

- Graphical view of Pressure Volume (PV) loops in animal experiments, both large and small, provides for
  - Examination individual loops.
  - Selection or exclusion loops from analysis.
  - Calculation and display End-systolic and end-diastolic PV relationships.
  - Choose linear, quadratic or exponential regression fits for the ESPVR and EVDPR.
- A workflow in the software must be provided to guide the user through all components of a typical PV Loop experiment, including set-up, data collection, and analysis. This includes separate protocols, including:
  - Small mammal
  - Large mammal
  - Echo Volume Fit
- The software may support both left-ventricular and right-ventricular analysis through sinusoidal pressure fit and loop tangent fit methods.
- A numerical spreadsheet is provided for
  - A wide range of hemodynamic parameters are calculated and displayed on a loop-by-loop basis. Parameters included are:
    - Stroke Work
    - Cardiac Output
    - Stroke Volume
    - Maximum Volume
    - Minimum Volume
    - End-Systolic Volume
    - End-Diastolic Volume
    - Max Pressure

- Min Pressure
- Mean Pressure
- Developed Pressure
- End-Systolic Pressure
- End-Diastolic Pressure
- Heart Rate
- Ejection Fraction
- Arterial Elastance
- Maximum Power
- Max Value of  $dP/dt$
- Min Value of  $dP/dt$
- Min value of  $dV/dt$
- Pressure at max of  $dV/dt$
- Pressure at max of  $dP/dt$
- Volume at max  $dP/dt$
- Volume at min  $dP/dt$
- Pressure Volume Area
- Potential Energy
- Cardiac Efficiency
- Tau
- Choose which parameters are displayed in the table.
- Calibration:
  - Cuvette calibration can be computed and applied to the volume channel; settings files with known volumes of common cuvettes are supplied.
  - Saline calibration allows the parallel volume correction factor to be calculated and applied to the volume channel.
- Plots and linear regression information can be displayed for:
  - preload-recrutable stroke work (PRSW).
  - $dP/dt$  max vs EDV.
  - PVA vs EDV.

- PVA vs ESP

- Tools are provided to analyze separate data regions within a data file, and save and recall the settings of each analysis for easy comparison of results.

#### Simultaneous Video Recording

- Simultaneously record and synchronize a streaming video with recorded data.
- Suitable for use with a wide range of video cameras or capture cards.
- Automatic separate storing of movie and recorded data.
- Video playback maintains time synchronicity allowing easy illustration of visual/physical changes associated with mechanical recording.
- Preview window showing live preview from the camera useful for initial setting of image quality.
- User configurable settings allows for selections including
  - Recording: Basic recording settings including selection between video and/or audio recordings. Automatic scanning of computer for available disk space free for recording use and notifies the user regarding the possible length of recording
  - Devices: Selection of available devices and adjust video and audio settings. Video settings such as zooming, focusing, and exposure can be set manually. These can be saved for subsequent experiments using the same devices
  - Synchronization: Synchronizes recording devices with LabChart to allow frame-accurate video/data recordings, by accounting for the delay between the recorded video and the data. (Please note that synchronization is dependent on the communication interface and computer performance. Hence a manual synchronization adjustment is provided).
  - Cache: Allows selection of temporary location in hard disk to store recorded movie files and allocation of free disk space in computer to store movie recording.
- A marker is displayed to link instantaneous data with specific movie frames. Alternatively, users can scroll within the movie and correlate each point in the movie with the corresponding point in the data file.

For further information or questions regarding the above quote, please contact ADInstruments at 888-965-6040.

Sincerely,

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