

IN THIS ISSUE

2 • Regulatory Updates

- EU GMP Annex 1
- USP <788>

3 • Powder Filling

7 • DataAnalyst Application Note

• Product Spotlight

- Airnet II
- Lasair III
- APSS 2000
- DataAnalyst

NEXT ISSUE PREVIEW

- Particle Loss in Transport Tubing

UPCOMING EVENTS

- **ISPE New England Chapter
BioPharma 2010** May 6
- **Particle College** August 10-11

CONTACT US

www.pmeasuring.com
info@pmeasuring.com
1.800.238.1801
1.303.443.7100

SYSTEM SUPPORT

support@pmeasuring.com

REGULATORY UPDATES

EU GMP Annex 1 portion for the monitoring of Capping Machines came into effect 1st March 2010. This now requires that the capping activities for all sterile products, not just those freeze dried products, be maintained under a Grade A zone quality air envelope.

Read more....page 2

USP <788> has been reviewed and a new guidance document issued to clarify the testing requirements. USP <1788> is a document that aims to give additional information for the qualification of a suitable instrument and test environment for the USP <788> tests.

Read more...page 2

POWDER FILLING - WHERE AND WHEN TO MONITOR

The very act of powder filling in a RABS enclosure will create a dust cloud so big that any particle counter operating in that area will just become saturated and of no use. It may also create such a problem that it will take a few hours before the particle counter can be used again because of the long purge cycle required to clean out any contamination.

Read more....page 3

MAXIMIZING THE BENEFITS OF THE LASAIR®III AND LASAIR II

Why DataAnalyst?

DataAnalyst is Particle Measuring Systems® supporting software package for the Lasair III and Lasair II particle counters. The software allows for secure downloading, archiving and reporting that is fully compliant with all secure data transfer requirements including 21 CFR part 11. *Read more....page 7*

PRODUCT SPOTLIGHT



Airnet® II Particle Sensor

The Airnet II Particle Sensor is the latest continuous monitoring sensor offering a small footprint with unparalleled performance and data transmission capabilities while meeting the specifications of ISO 21501-4. [\(click to read more\)](#)



Lasair® III Particle Counter

The Lasair III Particle Counter with flow rates from 28.3 LPM to 100 LPM is ISO 21501-4 compliant while providing a large IR touch screen to control the intuitive user interface. [\(click to read more\)](#)



APSS 2000

The APSS-2000 Syringe Sampling System sizes and counts suspended particulate matter in a wide range of liquids and meets or exceeds all current USP, EP, and JP requirements. [\(click to read more\)](#)



DataAnalyst

DataAnalyst software connects easily to these airborne particle counters and allows for downloading, archiving and reporting that are fully compliant with all secure data transfer requirements. [\(click to read more\)](#)

REGULATORY UPDATES

EU GMP Annex 1

EU GMP Annex 1 portion for the monitoring of Capping Machines came into effect 1st March 2010. This now requires that the capping activities for all sterile products, not just those freeze dried products, be maintained under a Grade A zone quality air envelope. To that effect all crimp capping activities should be performed as a “clean” activity, only if the crimp capping is performed within the aseptic core does the process need to be maintained as a sterile activity. All transfers from the aseptic core to the crimp capping machine must be done under unidirectional air flow meeting Grade A with the crimp capping machine located in a Grade C maximum room. The **Lasair III** Particle Counter and **Airnet II** Particle Sensor products are used to increasingly verify the room cleanliness of these transfer areas. Where portable laminar flow carts are used to transfer products between Filling lines and Lyophilizers and Aseptic zones to Crimp Capping activities Particle Measuring Systems has a reliable Wi-Fi controller system for all particle and microbial sampling needs.

USP <788>


USP<788> has been reviewed and a new guidance document issued to clarify the testing requirements. USP <1788> is a document that aims to give additional information for the qualification of a suitable instrument and test environment for the USP <788> tests. It is essentially a re-release of the 2007 document showing the tolerances for calibration and resolution of suitable instrumentation, the requirements for a ‘suitably’ calibrated instrument does not go away, however methods for determining what constitutes ‘suitable’ are addressed. The new **APSS 2000** Syringe Sampling System fully meets the interpretation of the new ruling and can be used to test both USP <788> and USP <789> products.

UPCOMING EVENTS


COME SEE US! ISPE New England Chapter BioPharma 2010 - May 06, 2010 - Warwick, Rhode Island

New England BioPharma 2010 will feature a wide variety of vendors, educational tracks surrounding “Battle Tools for a Brighter Future”, and keynote presentations by Dr. David M. Dooley, President, University of Rhode Island and Dr. John L. LaMattina, former Senior Vice President, Pfizer Inc. and President, Pfizer Global Research & Development.

Start Making Better Contamination Monitoring Decisions Today!



PARTICLE COLLEGE August 10-11, 2010
presented by Particle Measuring Systems Boulder, Colorado





5475 Airport Boulevard, Boulder, Colorado 80301-2339
303.443.7100 1.800.238.1801 Fax: 303.546.7380
Customer Service Center 1.877.475.3317
Instrument Service 1.800.557.6363

POWDER FILLING – WHERE AND WHEN TO MONITOR

The very act of powder filling in a RABS enclosure will create a dust cloud so big that any particle counter operating in that area will just become saturated and of no use. It may also create such a problem that it will take a few hours before the particle counter can be used again because of the long purge cycle required to clean out any contamination.

There are rules for powder filling issued by both the FDA and EU GMP standards.

The EU GMP Annex 1 Regulations state:

“8. Cleanrooms and clean air devices should be routinely monitored in operation and the monitoring locations based on a formal risk analysis study and the results obtained during the classification of rooms and/or clean air devices.

9. For Grade A zones, particle monitoring should be undertaken for the full duration of critical processing, including equipment assembly, except where justified by contaminants in the process that would damage the particle counter or present a hazard, e.g. live organisms and radiological hazards. In such cases monitoring during routine equipment set up operations should be undertaken prior to exposure to the risk. Monitoring during simulated operations should also be performed. The Grade A zone should be monitored at such a frequency and with suitable sample size that all interventions, transient events and any system deterioration would be captured and alarms triggered if alert limits are exceeded. It is accepted that it may not always be possible to demonstrate low levels of $\geq 5.0 \mu\text{m}$ particles at the point of fill when filling is in progress, due to the generation of particles or droplets from the product itself.”

Clause 8 will be discussed in the section *Risk Analysis of Sample Points*. First look at the following part of Clause 9: *“except where justified by contaminants in the process that would damage the particle counter or present a hazard, e.g. live organisms and radiological hazards. In such cases monitoring during routine equipment set up operations should be undertaken prior to exposure to the risk. Monitoring during simulated operations should also be performed.”*

The regulations are quite clear here. If the particle counter does not provide useful information during the process, or may become damaged, then you need to validate a process based upon simulated operations and use that process at the beginning and end of each batch run.

In practice, this means that the validation of the process to determine the environmental control must be done with operators ‘pretending’ to fill actual bottles, bags, vessels or whatever container of final product is made. The bottles/bags will move into the RABS and the operator will move their hands around in a normal manner as if powder was flowing and the particle counter is turned ON for this whole duration. It is would recommend at least for 40-60 minutes of simulation is required. This then establishes a baseline for which you know the particle contamination of the activity before actual product is introduced.

Then at the start of the batch the operator turns ON the particle counter, runs it for say 30 minutes prior to filling in order to prove two things: 1) the baseline originally established in the ‘simulated’ run is replicated and 2) no adverse conditions are produced as a result of setting up the equipment.

Then the particle counter is turned OFF.

The only information available to ensure that process conditions have not changed are the

differential pressure results and the airflow velocity results. If these do not change, it is acceptable to believe the particle conditions have not changed and any presence of particles is only as a result of the product itself – which is acceptable.

Then filling begins (with the particle counter turned OFF).

When filling is finished the particle counter should be turned back ON again. This will demonstrate that no residual contamination exists and that the environment was able to restore baseline conditions. Run this post-test for about 30 minutes.

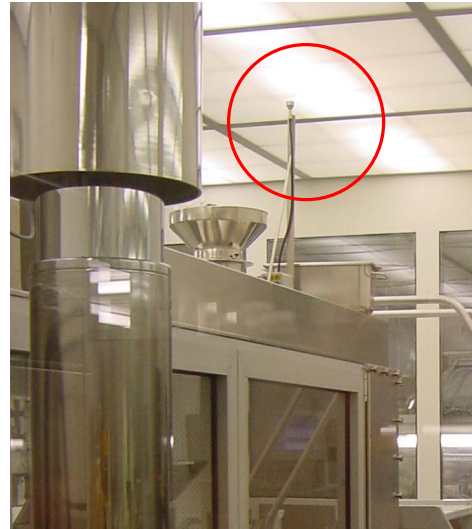
The FDA also has a similar philosophy:

“Some operations can generate high levels of product (e.g., powder) particles that, by their nature, do not pose a risk of product contamination. It may not, in these cases, be feasible to measure air quality within the one-foot distance and still differentiate background levels of particles from air contaminants. In these instances, air can be sampled in a manner that, to the extent possible, characterizes the true level of extrinsic particle contamination to which the product is exposed. Initial qualification of the area under dynamic conditions without the actual filling function provides some baseline information on the non-product particle generation of the operation.”

Guidance for Industry Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice, Food and Drug Administration, September 2004

It is very important to establish baseline results. Please do not underestimate this requirement in the light of no actual particle counting taking place during the fill.

All of this said, there are customers that insist on having a sample point mounted in such a location that it is not interfered with by the particles. An image of one such application is shown below. You will notice the sample point is just 2 inches away from the HEPA filter inlet and provides no additional confidence of control – only that the 2” area of the filter is working correctly.



Risk Analysis of Sample Points

The next concern is, “Where should a sample point be placed?”, especially when reviewed in accordance with Clause 8 of the EU GMP Annex 1 Regulations:

“8. Cleanroom and clean air devices should be routinely monitored in operation and the monitoring locations based on a formal risk analysis study and the results obtained during the classification of rooms and/or clean air devices.

Particle Measuring Systems has historically used a judgment approach that is based upon our experience in installing systems we have sufficient experience with in environmental monitoring systems and process flow knowledge. This allows us to determine where the sample point should go, without empirical proof of a location. This is sound, given our experience and the rationale documentation that justifies our claim.

Cleanroom classification is essentially an exercise in proving that the room meets specifications for both cleanliness and uniformity. Much of the standard is used to prove that not only does the cleanroom meet a particle count concentration, but that the concentration is evenly distributed in all areas – that there are no dirty areas or, conversely,

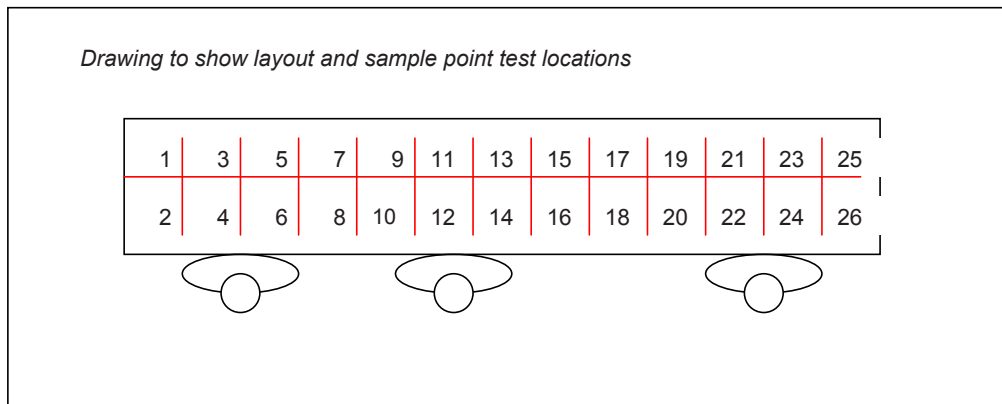
areas, that are too clean. So if we believe that the room is essentially uniform, where are the worst cases? And if there are areas of higher counts, they cannot be so high as to be considered "worst," as this flies against the requirements for uniform, 95% UCL (Upper Control Limit).

The idea of using the data from a classification exercise is not to determine a worst case scenario, but to use the data to verify the room is uniform. If the room is not uniform, then you should take steps to make it uniform.

We then move on to empirically-based information to determine a sample location within the RABS or background area.

Refer to the grid in the Particle Measuring Systems application note *Choosing the Most Suitable Non-viable Sample Point Locations* (http://www.pmeasuring.com/wrap/filesApp/app79/file_1/pharma_app79.pdf). Within the RABS, apply the grid to the area within the filling zone. The grid may need to be a 5 x 2 and not a 3 x 3 or 4 x 4, given the shape of the filler machine. I would also only measure at a single height, given the constraints of the machine – choose 300mm above the base plate of the machine in particular example,

Risk Assessment to Determine Sample Point



Assessment of critical nature

1= not critical; 2 = low critical; 3 = moderate critical; 4 = very critical

	1	2	3	4	5	6	7	8	9	10	11	12	13
RANK	2	3	3	4	3	4	2	2	2	3	4	4	3
	14	15	16	17	18	19	20	21	22	23	24	25	26
RANK	4	2	3	2	2	2	3	3	4	3	4	2	3

You will notice where the sample is close to an operator it gets more critical – this is just guidance and each exercise may have other factors – doors, access, restriction to operators, activities etc.

Results of particle survey

	1	2	3	4	5	6	7	8	9	10	11	12	13
0.5	125	156	222	134	144	245	111	134
5.0	1	0	0	0	1	1	0	0
	14	15	16	17	18	19	20	21	22	23	24	25	26
0.5										
5.0										

Results x risk factor

	1	2	3	4	5	6	7	8	9	10	11	12	13
0.5	250	468	666	536	432	980	222	268
5.0	2	0	0	0	3	4	0	0
	14	15	16	17	18	19	20	21	22	23	24	25	26
0.5										
5.0										

From this you will notice that location **6** is very critical based upon results times risk and then followed by locations **3 & 4**. It is important then that location **6** has a sample point located in its section. (Location is dependent on access.)

Author

Mark Hallworth

mhallworth@pmeasuring.com or Particle Measuring Systems, 5475 Airport Boulevard, Boulder, CO.

Mark Hallworth is the Life Science Market Manager for Particle Measuring Systems, Boulder, CO, USA. Mark has managed the design, installation and validation of over 200 environmental monitoring system projects worldwide. He has designed several products specific for pharmaceutical environmental monitoring, including particle counters for explosive and corrosive areas and 21 CFR part 11 compliant software for batch test and release. He currently lectures for the PDA, ISPE and other international pharmaceutical societies on environmental monitoring and GMP compliance design and validation. Mark recently was awarded the IEST James Mildon award for "significant contributions to the advancement and increase of knowledge in the field of contamination control".

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Application Note

DataAnalyst: Maximizing the Benefits of the Lasair® III and Lasair II

Why DataAnalyst?

DataAnalyst is Particle Measuring Systems® supporting software package for the Lasair® III and Lasair II particle counters. The software allows for secure downloading, archiving and reporting that is fully compliant with all secure data transfer requirements including 21 CFR part 11. While the software is not designed for real time data viewing or facility monitoring (Particle Measuring Systems' FacilityNet software would be the appropriate solution for this need), it offers a time plot feature that allows users to view trends. DataAnalyst is the perfect solution for customers who value the robust features of the Lasair III and II and want the same data viewing capability away from their instrument and also offers long term data storage and the ability to create various reports, including cleanroom certificates.

The program will support a multitude of installation configurations, from a single base station to integrated networks of multiple Lasair III or II particle counters connected to a LAN for distribution and reporting. From a single work station, you can:

- Download data from any Lasair III or Lasair II on your network
- View data trends
- Generate multiple reports
- Archive your data in a secure format

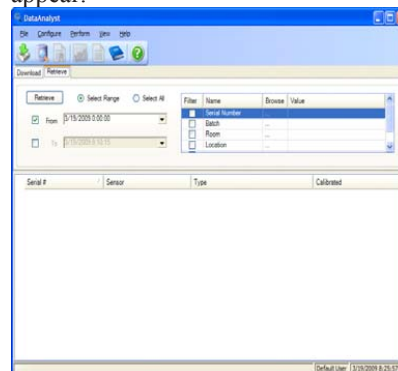
Data from instruments throughout a facility can be downloaded to the network for data viewing by multiple users. Alternatively, you can download the Lasair III data via the USB data download and upload to your workstation or to the network.

Installing DataAnalyst

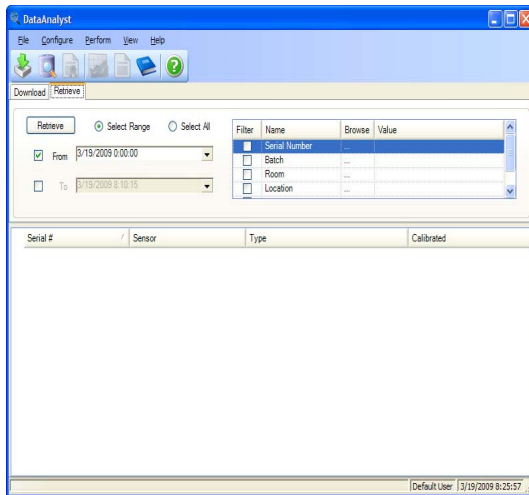
Each Lasair III and Lasair II Particle Counter is shipped with a 30 day trial version of DataAnalyst on CD. Particle Measuring System also offers this same trial version at <http://www.pmeasuring.com/particleCounter/software/DataAnalyst>. Please note that the file is large (over 100 MB) and will take some time to download. These trial versions are fully functional copies of the software. Running the CD or clicking the download link will walk you through the complete installation process. Upon software purchase, a USB key is supplied which allows for continued use of the software.

Using DataAnalyst with Networked Lasair III or Lasair II

Your Lasair III or Lasair II can be connected to your network via the Ethernet connection on the back of the machine or via the optional wireless connection feature. Your network administrator must assign a static IP address which you can configure into your particle counter on the Network screen. Open DataAnalyst via the icon on your desktop, and the following screen will appear:



Navigating the Main Toolbar



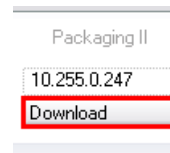
The main toolbar offers several options for the user. From configuring individual or group security settings to customizing the way your data is displayed, you can create the reports that you need using DataAnalyst. The most commonly used functions are available in the toolbar as well as via icons on the main menu.

There are two options to gather data – data download (via networked Lasair particle counters or secure USB download) or data retrieval. The Download tab allows you to locate an instrument currently on the network and download data directly from the particle counter. The Retrieve tab allows you to access previously downloaded data (from USB or networked instruments) and create reports or certifications.

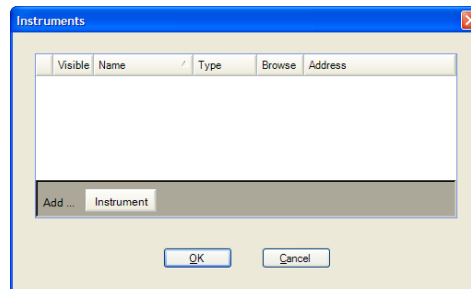
Downloading from Networked Lasair Aerosol Particle Counters

First, select the Download tab.

If you have already configured an instrument, select the Download button below the instrument you want to store the data for (as shown below).

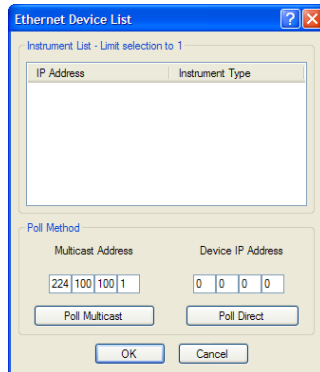


If this is the first time you are using Data Analyst, select Add→Instrument, you will see an Instruments box pop up that does not list any options. If this is the case, select Add→Instrument. If you have used the Download feature previously, any of the instruments you had added will be shown. If it is an instrument you have not added before, select Add→Instrument.



After selecting Add→Instrument a new row will appear. You can enter a name for the particle counter by clicking in the cell and select the type of download from the drop down menu. Select Ethernet.

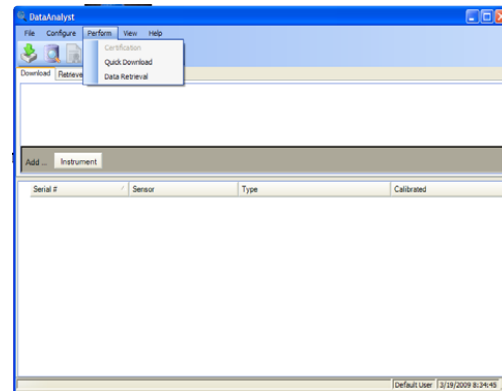
To find the instrument on the network, select Browse and the following window opens:



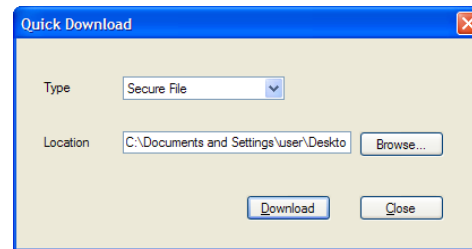
In order to locate your instrument, you can either enter the specific IP Address of your instrument (you can find this on the Network screen on the Lasair III or II), or, if you are looking to add multiple instruments, it may be more convenient to poll the Multicast address. The Multicast address can be found on the Network screen of the Lasair III or Lasair II particle counter or on your computer.

Once you have added the IP address and name of the instrument you can select OK to close the dialog. The newly configured instrument is now added to the toolbar and you can now download the data from the instrument by selecting the Download button.

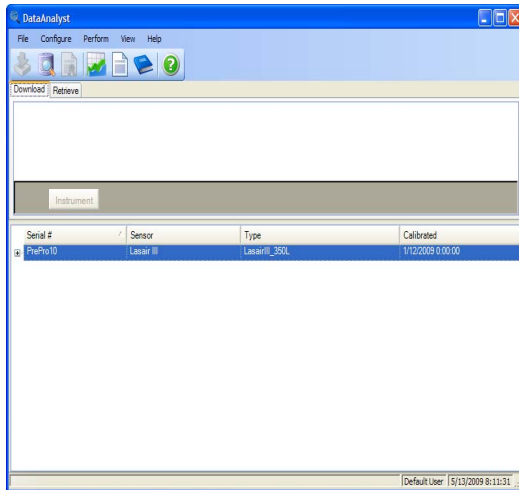
Using DataAnalyst with USB Data Download



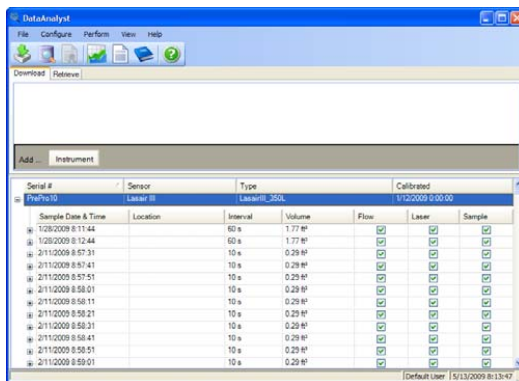
As shown in graphic above, select Quick Download from the Perform menu. Select Secure File and click the Browse button to find the file on your USB drive. The secure file will have the file extension “.sec”. Once you have located your file, click Download.



After your data has been downloaded, the instrument will show on the main DataAnalyst screen, shown below:



By clicking on the plus sign (+) next to the Serial Number, the data from the instrument will be shown.



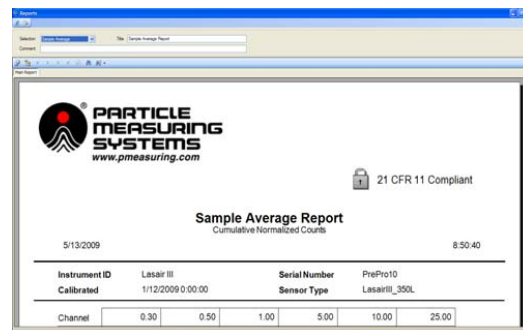
The data is now stored! Next, reports can be generated from this data.

Generating Reports

The comprehensive reporting structure works with specific inputs from the particle counter and filters sampling data based upon location, date/time or in the case of the Lasair III, product batch information. Reports can be generated to meet industry requirements and configured to include raw data, tabular data, statistical and graphical formats. The reporting tool can also be configured to give various report formats, including certification to ISO14644, FDA/EU GMP, or FS209 standards. Reports are generated using Crystal Reports, so the user can either customize these reports themselves or work with Particle Measuring Systems to have custom reports created.

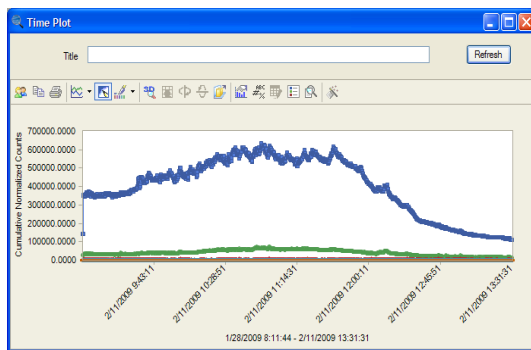
To create a report, select View→Reports.

The default report, the Sample Average Report, will load automatically. Other reports can be chosen from the drop-down menu. Users will notice the 21 CFR 11 Compliant stamp on the top of each report indicating that the data storage is secure.



Generating Time Plots

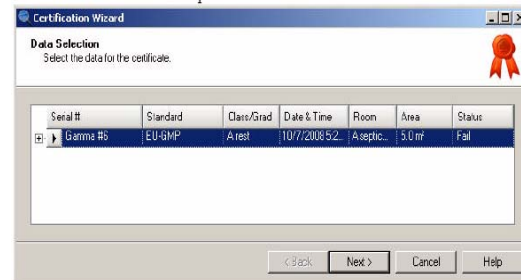
During different processing activities, the particle counts in a room can vary significantly. In order to minimize the potential for particulate contamination, it is necessary to understand the causes of particle generation. Time plots are an excellent way to gain further understanding of a process and can show periodic particle count changes to indicate how those events can be prevented in order to mitigate the risk of a particle event affecting product quality. DataAnalyst offers a tool for viewing the data from Lasair IIs and IIIs over time. From the main menu, select View→Time Plot and the following window will open:



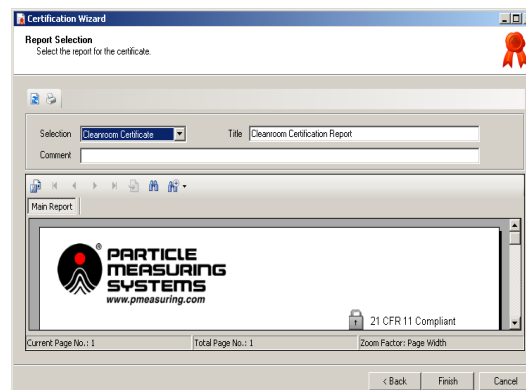
The toolbar on this window offers many options, from altering the colors, or scale, and offering labeling capabilities to identify any excursions on your plot.

Generating Cleanroom Certificates

Perhaps the most valuable capability of DataAnalyst is the ability to create cleanroom certificates. From the main menu, select Perform→Certification. The window below will open:



Users will then be allowed to select any of the data created from utilizing the certification capability of the Lasair III or Lasair II. The certificate that is generated will be to the same standard as used when in Certification mode in the Lasair II or III Particle Counter. For example, if you selected the ISO standard when certifying your cleanroom with your Lasair Particle Counter, DataAnalyst will provide a certificate detailing the testing to that particular standard. Available standards that are included in the Lasair firmware are: ISO 14644-1, EC GMP Annex #1, and FS209E. After selecting the data to be used, the following report will display:



DataAnalyst is a robust program that provides extended functionality over the user friendly interface of the Lasair III and Lasair II to provide users with valuable reporting tools to further the capabilities of their microcontamination monitoring program.

Author

Rebecca Thompson

rthompson@pmeasuring.com

303.443.7100 x253

Rebecca is an Application Engineer at Particle Measuring Systems. She has a B.S. in Chemical Engineering from the University of Colorado.

App 80 200704

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