TECHNICAL PAPER

Understanding Particle Counter Technology and the risks of data integrity of particle counts.

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Understanding Particle Counter Technology and the risks of data integrity of particle count data and the importance of ISO 21401-4 Calibration.

Abstract

Airborne Particle Counters are widely used in Cleanrooms to monitor for signs of cleanroom air contamination and in most cases the particle count data is used to make critical process decisions. Today's Portable particle counters have come a long way with the advent of laser diode technology, older generation cumbersome helium neon lasers also referred to as HeNe's have been phased out in favor of smaller, lighter and feature packed new technology Portable Particle counters with touchscreens and automatic certification reports that comply to many of today's Cleanroom Certification standards. In effect these devices have so much computing technology embedded that they really need to be validated to ensure they meet your process requirements and with so much focus on Data Integrity and the FDA's ALCOA approach this paper takes a deep dive into Particle Counter technology more than we have ever seen previously which will help to assist decision makers in making informed choices when considering which option/model is best for their process when data integrity is of paramount importance to them.

It is important to also acknowledge the advantages of an ISO 21501-4 calibration. ISO 21501-4 is a major particle counter calibration standard and one of the most complete guidelines and it is important that particle counters are calibrated to meet this standard as this calibration allows for better accuracy and reliability which in turn mitigates data integrity issues by verifying count data is as accurate as it can be, therefore it is important to understand the relationship between ISO 14644-1:2015 and ISO 21501-4:2007. Overall the objective of this article is to increase your knowledge in Particle Counting technology so you are more aware and experienced as particle counters play such an important role in the front line of defense against contamination in your Cleanroom.

Airborne Particle Counter Technology and critical parameters

Particle Counters measure what we cannot see. To get some perspective a 0.5µm particle is about 200 times smaller than the diameter of a strand of your hair. Refer to fig.1 to get a perspective of particle sizes which particle counters count and you will begin to understand the importance of particle counter technology. In order to count particles laser light is used to reflect light off of the particles as they pass through the laser beam. Airborne particle counters using laser diode technology count particles by collecting scattered light inside the sensor of the particle counter. This scattered light occurs when a

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particle goes through the “view volume” of the sensor. The view volume is the target location in the sensor where the laser beam and the flow path converge. The laser light generated from the laser diode crosses the view volume and particles are directed through the view volume by an internal air pump. The flowrate of the internal pump is controlled by a feedback loop and a mass flow controller which keeps the flowrate constant. There are a few options when choosing a Portable Particle Counter when it comes to flowrate. The options are typically 1CFM, 50L/min and 100L/min. A 1CFM flowrate will pull a $1m^3$ volume of air in under 36 minutes. A 50L/min flowrate will take 20 minutes and a 100L/min flowrate will take 10 minutes to sample a $1m^3$ volume of air.

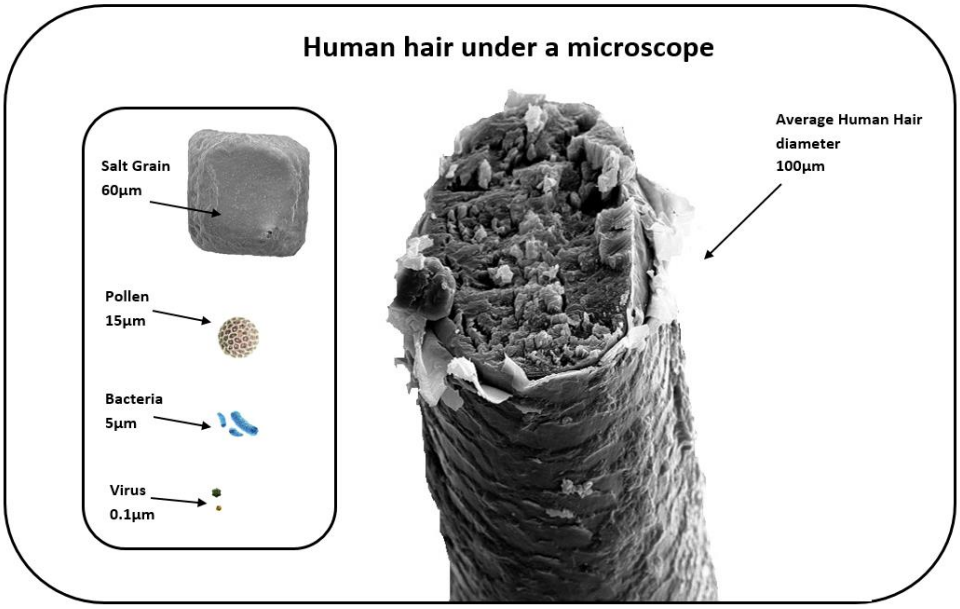

Fig.1 Sizes of particles compared to human hair

The importance of an accurate flowrate - The particle counter sensor is tuned into the flowrate and so sample flow plays a critical role in the accuracy of the particle sizing. If the flow is too slow the particle dwells longer in the view volume and scatters more light and is perceived as a large particle than it actually is. If the flowrate is higher than nominal flow then the particle dwell time in the view volume is less and the light energy picked up by the photodetector is less than normal and the particle is perceived as a smaller particle than it actually is. Streetlights that magically switch on when it gets dark at night and switch off in the morning when it gets light are triggered by photodetectors. The photodetectors change in resistivity based on light intensity or lack of is used to trigger the on/off switch for the street light. The photodetector inside a particle counter sensor is more advanced and basically converts the scattered laser light into electrical energy in the millivolt (mV) range. The amount of light scattered is proportional to the size of the particle. Big particles scatter more light than small particles. This is the fundamental conversion of a physical particle into electrical energy that can be measured. Once measured the mV signal is captured then threshold comparators size the particle and the sized particles fall into different size ranges which are displayed on the particle counter as count data at different sizes. If the flow rate is not within specified tolerance then sizing errors can occur.

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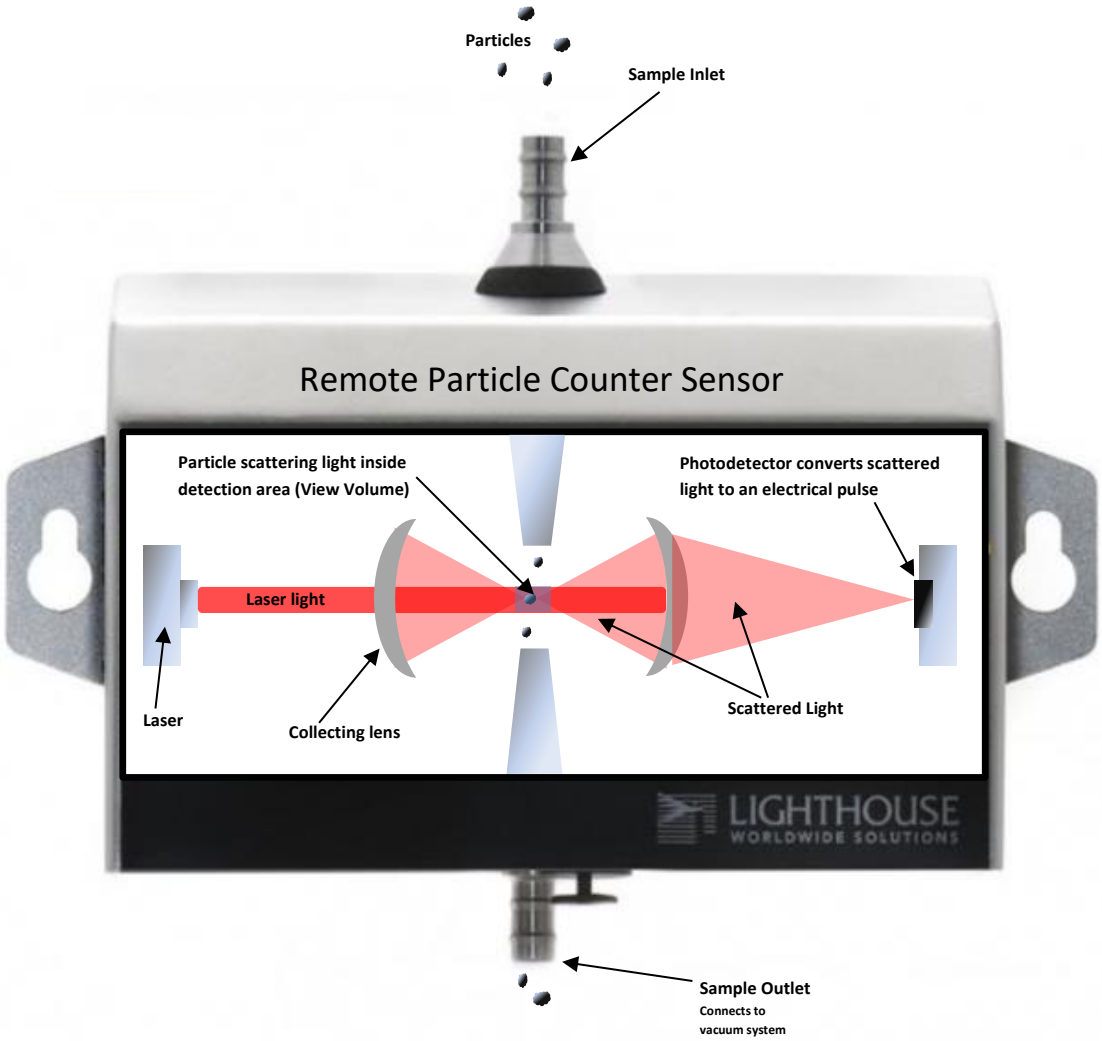
Laser integrity and alignment - If the laser light is not running at its optimum intensity then there is an accuracy error factor that comes into play. Laser health should be monitored consistently and error signals communicated if laser levels drop below optimum ranges. If the laser is not illuminated at its nominal working range then there is the possibility of some small particles passing through the view volume undetected. Laser Alignment is also a critical factor. If the laser is not aligned correctly then the particle count accuracy will be wrong as miss-alignment will also have the same effect of missing particles and the overall result will be inaccurate particle counts. Therefore laser health and alignment is critical and your particle counter should alarm on laser intensity issues and regular service should pick up miss alignment problems which mostly occur under heavy handling of the particle counter.



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Photodetector Health – The photodetector converts the scattered light as photons into electrical pulses by creating a charge for each received photon. As the amount of scattered light increases with the particle's size and the scattered photons arrive at the same time, a current pulse proportional to the particle's size is generated. If a photodetector is defective, some less technologically advanced particle counters will continue reporting zero counts and no scattered light will be picked up and therefore no counts will be registered. Even if particles are present they will go through the particle counter sensor undetected. In normal cleanroom environments reporting of zero counts for several hours is not uncommon. There is a false sense of security if the photodetector is not monitored. Therefore using a particle counter with advanced technology that monitors the photodetectors health mitigates from false zero counts. This issue is difficult to detect especially when you expect to see zero counts. Routine testing can detect if a photodector is faulty if the particle counter does not signal an error to the user.

Fig.2 Particle Counter Self Diagnostics

Sensor Contamination – One of the biggest problems with particle counter data integrity occurs when contamination builds up around the sensors optics and mirrors. This normally happens during cleaning operations when the inlet is not capped, causing cleaning solution to coat the optics, which cause the sensor to fail calibration. If you are on annual calibrations and there is a calibration failure, then how confident are you in your data for the last 12 months? A particle counter that monitors sensor health is a good choice and assists in sending out service notifications when background contamination becomes an issue. These advanced instruments can mitigate failed calibrations and assist in maintaining data integrity. These sensors can be pulled from service, tested and recalibrated before failed calibration issues could potentially ground your batches.

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Location Identification – are you 100% sure that the particle counter is in the right location? Is the location ID built into the remote sensor? Are we sure that after the unit comes back from service that it has been put back in the right location? Human error plays a major role and it has been shown that mistakes can occur and remote particle counters coming back from service are mistakenly placed at the wrong location. What does this mean? Well, as the data coming from the sensor is picked up from the EMS from the wrong location, a small mistake can have a huge impact and lead to major data integrity issues. Look for remote particle counters with technology where the location ID is embedded in the location mounting bracket rather than the particle counter. This way, any remote particle counter can be inserted and the data will be confirmed from the right location 100% of the time.

Check your Particle Counter sensor health regularly by comparison tests, zero count filter testing and using internal particle counter self-diagnostics as well as maintaining routine ISO 21501-4 calibrations.

Fig.3 Verify your Particle Counter sensor health

Data Storage Redundancy – Having data records backed up on the remote particle counter assures redundancy in case a software issue occurs in the transmission of real time data. Choosing a particle counter with sufficient buffering in data collection will enable critical data to be downloaded at a later stage back into the monitoring system software. Redundancy is a major advantage as the data becomes more critical.

Audit Trail – In order to follow the ALCOA standard, an audit trail built into the equipment or software is an absolute must. (21CFR11 in monitoring systems are required). Seek particle counter technology with built in audit trails to satisfy ALCOA requirements for who, when, what and where events.

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User Security Levels – The system must conform to 21CFR11 guidelines. Up to three security levels from operator to manager and administrator must be available with the usual compliant parameters such as password length, password aging and password control**.** User security levels are a 21cfr11 requirement and particle counters should have the ability to manage and control user access.

System Validation – A complete validation of the data records must be conducted by verifying the accuracy of the data to the location of where the data is generated. This is a must do exercise and should be rolled into the Installation and Operational Qualifications IQ/OQ protocols. Seek vendor IQ/OQ protocols and always conduct a Performance Qualification (PQ) to verify operational accuracy before going into production.

ISO 21501-4 Calibration Standard and its significance in data accuracy

ISO 21501-4 has been around for 10 years and the recent update to ISO 14644-1:2105 (Cleanrooms and associated controlled environments — Part 1: Classification of air cleanliness by particle concentration) requires airborne particle counter calibrations to be completed following ISO 21501-4. The table below defines the parameters of ISO 21501-4.

Parameter	Tolerance	Comments
Calibration particles	± 2.5 %	Mono-disperse spherical particle with a known mean particle size that is traceable to an international standard and where the standard uncertainty of the mean particle size is equal to or less than ± 2.5%.
Verification of size setting	± 10 %	The error in the detectable minimum particle size and other sizes specified by the manufacturer shall be equal to or less than ± 10 % using method described in 4.2.
50% Counting efficiency	± 20 %	The counting efficiency shall be (50 ± 20) % for calibration particles with a size close to the minimum detectable size.
100% Counting efficiency	± 10 %	The counting efficiency shall be (100 ± 10) % for calibration particles with a size of 1.5 times to 2 times larger than the minimum detectable particle size.
Size resolution	± 15 %	The size resolution shall be equal to or less than 15 % for calibration particles of a size specified by the manufacturer.
False count rate	Specified by LWS	The false count rate is the measured particle concentration (in particles per cubic meter) for the minimum detectable size when sampling particle free air. The data should be statistically processed using the Poisson distribution with a 95 % upper

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		confidence limit.
Maximum particle number concentration	Specified by LWS	The coincidence loss at the maximum particle number concentration of a particle counter shall be equal to or less than 10%.
Sampling flow rate	± 5 %	The standard uncertainty of volumetric flow shall be equal to or less than ± 5. Note: If the LSAPC does not have a flow rate control system this does not apply, however the manufacturer shall specify the allowable flow rate limit.
Sampling time	± 1 %	The standard uncertainty in the duration of sampling time shall be equal to or less than ± 1 % of the preset value.
Response rate	± 0.5 %	The response rate obtained according to the test method given in 4.9 shall be equal to or less than 0.5 %.
Calibration interval	≦1 year	The recommended calibration interval is one year or less.
Test report	N/A	The following minimum information shall be recorded: •Date of calibration •Calibration particle sizes •Flow rate •Size resolution (with the particle size used) •Counting efficiency (50% & 100%) •False count rate •Voltage limit or channel of internal pulse height analyzer (PHA)

Fig.4 Critical Test Parameters of ISO 21501-4

By calibrating particle counters following ISO 21501-4 the end result is a higher accuracy calibration. If the particle counter is passing an ISO 21501 calibration you can be assured that the sensor is operating correctly and the particle count data is accurate.

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What is Data Integrity and the FDA's approach?

Data Integrity risks are inherently proportional to the complexities of the processes and computerised systems where the data is sourced from. Particle Counter data plays a critical role in the product lifecycle. By selecting the right equipment and services you can mitigate these risks and have more reliable data from a validated source. The data from your particle counter must be reliable and accurate and from that source without manipulation.

FDA warning letters within the last year have cited several companies for lack of data integrity in their processes and for flaunting data integrity based on a lack of proper traceability and security measures

In April 2016 the FDA released a draft guidance document "Data Integrity and Compliance with CGMP Guidance for Industry". Under the question of "What is "Data Integrity"? the following answer was provided by the FDA;

For the purposes of this guidance, data integrity refers to the completeness, consistency, and accuracy of data. Complete, consistent, and accurate data should be attributable, legible, contemporaneously recorded, original or a true copy, and accurate (ALCOA).

A new acronym, ALCOA, had been released to the masses, although ALCOA has been around for many years it has now taken on a phoenix like resurgence and every man and his dog is talking about it. But data integrity is nothing new. Data Integrity has been the expectation in PIC's Guide to GMP, Chapter 4 and Annex 11, ISO 13485: Sections 4.2.3, 4.2.4, as well as the Australian Code to GMP human blood, blood components, human tissues and human cellular therapy products: Sections 400-415.

As you see Data Integrity is not new, however I would like to explain what you should look for when investing in a monitoring system or portable monitoring instruments such as particle counters, which sample and record critical environmental data used to make informed decisions about cleanroom status, product safety and batch releases during a products lifecycle.

So what does ALCOA actually mean?

ALCOA is basically a set of guidelines which assist in verifying if your data is Attributable, Legible, Contemporaneous, Original and Accurate. Since particle counter data is deemed critical data then it is important to understand that the data source is accurate, reliable and the system or instrument can be validated to verify data records and who made them.

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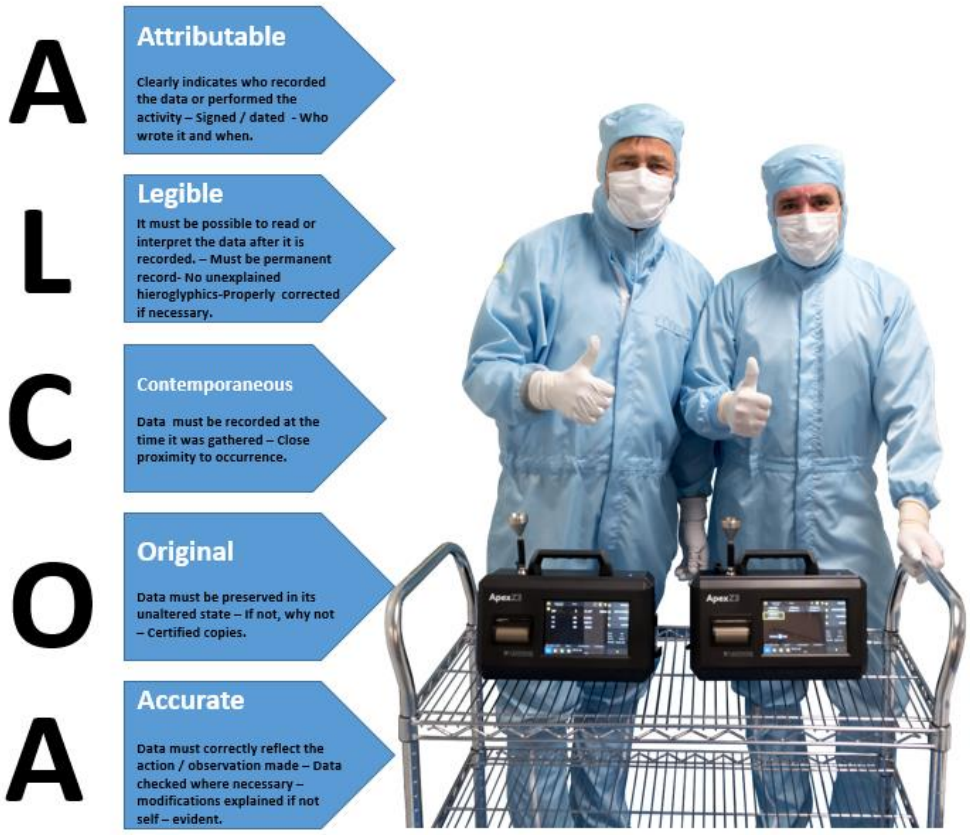

Fig.5 The FDA's ALCOA Acronym for Data Integrity

The big picture and putting it all together…

Particle Counters are critical in today's Cleanrooms. Mitigating data integrity issues on particle count data comes by really understanding how particle counters operate and the critical parameters that need to be tested and maintained.

Knowledge of Particle Counter technology at this level helps you the end user understand the importance of properly maintaining the instrument so the data supplied by the particle counter is reliable and accurate. There are many parameters to consider which effect particle counter accuracy. Lasers are sensitive to heavy handling and major vibrations as the laser alignment could be affected. Contamination of the sensor is also a major problem and a sensor with built in sensor health checks is the best option in mitigating data integrity issues.

Proper training and internal SOPs should be developed and maintained to support good housekeeping.

Regular maintenance and calibration programs are highly recommended along with more regular tests to verify the sensor is functioning normally. Using zero count filters and monitoring sensor health is a big step in the right direction to further mitigating data issues. Annual calibration is good practice to confirm the instrument has been in tolerance but more frequent calibrations should be considered if the

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instruments data is critical to your process. For example most remote particle counter users calibrate their sensors more frequent as the data is used to support batch releases. Therefore it is critical that the calibration data indicates that as founds are within tolerance. ISO 21501-4 plays a major role in particle counter calibration to ensure repeatability and accuracy. Validation of the particle counter on-site also adds a level of confidence that the particle counter operates correctly.

About the Author

Jason Kelly is Director of Systems at Lighthouse Worldwide Solutions and has spent over 20 years working in the Pharmaceutical Industry managing many major Environmental Monitoring projects and developing testing protocols for IQ/OQ. He has also set up ISO 17025 Particle Counter facilities and has many years technical experience with particle counter calibrations to ISO 21501 standards. He can be contacted on jasonk@golighthouse.com or LinkedIn and welcomes any feedback or questions in relation to Particle Counting and Monitoring Systems.

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