TECHNICAL PAPER

How to Perform a PQ On a Particle Monitoring System

by Jason Kelly

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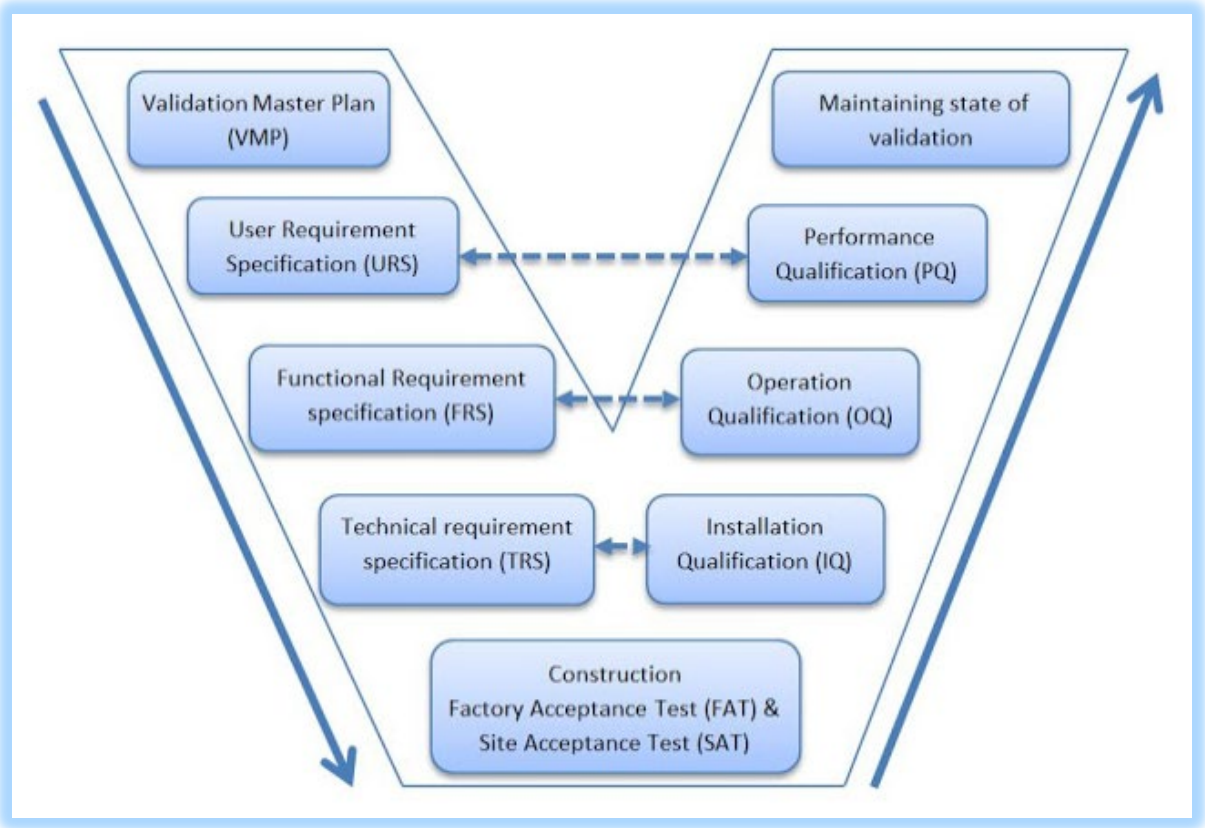
What is a PQ?

A PQ is a performance qualification which is conducted prior to a system becoming operational. The PQ tests the system to ensure it meets its operational objectives in a real world operational environment. It is the final step in equipment and systems qualification. A PQ should never be a re-execution of the vendor supplied Operational Qualification (OQ). The OQ should have tested all the operational critical attributes of the system and these tests should be traced back to the SYSTEMS User Requirement Specification (URS).

An effective Particle Monitoring System PQ should force the system into operational errors and verify the system outputs are efficient in handling and notifying operators and managers of these errors. Customer developed Standard Operational Procedures (SOP's) should also be tested against the error to validate their effectiveness. Alarm limits at this stage should be set based on the data from the PQ.

The diagram below highlights the lifecycle of a typical Particle Monitoring System project. The validation master plan should also include a risk assessment and the URS should be designed based on this risk assessment. Operational and Performance testing should be traceable to prove the URS requirements are been addressed and tested. Once the system is completely validated a change control process should be enforced to ensure proper management of the validated system.



GAMP V Model for System lifecycle from URS to PQ

How does Lighthouse plan and execute a PQ?

A Performance Qualification demonstrates that equipment or system installed and operational is what it is purported to be and does what it is supposed to do based on the URS. A poor URS will result in a poorly executed PQ. When manufacturers take time to plan qualification projects, they sometimes ignore important considerations. Companies often fail to take a science- or risk-based approach, based on product and process knowledge, to define the extent of qualification and for most part they redo the OQ protocol and call it good. This is a major mistake and a missed opportunity to get to know how the system operates and the capability of the system in a real working environment. During the IQ/OQ which is normally conducted by the vendor (in most cases) with the Customer as a witness (depending on customer staff availability (they are busy elsewhere either working on the production floor or engaged with other projects) which is detrimental to a successful IQ/OQ execution). The IQ/OQ with the Particle Monitoring System supplier should be seen as an opportunity for the customer end users and managers to fully understand the system. It's kind of like taking a car for a test drive. Customer end user participation in the IQ/OQ is an absolute must. Valuable knowledge picked up during the IQ/OQ will help the customer develop a robust PQ.

Furthermore a good risk analysis identifies the critical and noncritical work to be done and helps companies focus on the appropriate elements of the qualification project. Validation should address the critical areas, and commissioning should address the noncritical. Because it identifies the factors that have a direct effect on product or process quality, risk assessment can also reduce the number of systems requiring qualification and robust commissioning.

Pharmaceutical Customer working with Lighthouse validation engineers conducting a PQ of a remote particle counter with internal pump in a Grade B cleanroom

In order to perform a science and knowledge based PQ Lighthouse encourages and recommends a risk assessment to be performed and documented with the process critical attributes to be tested. This risk

assessment should be completed with the customer and their subject matter experts to identify the factors that have a direct effect on product or process quality. The risk assessment can also reduce the number of systems requiring qualification and robust commissioning. During the qualification-planning process, manufacturers sometimes do not consult all of the employees who will be responsible for using, maintaining, or approving the equipment. This oversight leads to inadequate plans that delay the completion of qualification projects or result in failure to meet requirements. “A successfully executed qualification is difficult to obtain without a good core knowledge of the equipment and its operation.

Case Study: Pharmaceutical Sterile Injectable Manufacturing Process

Most injectable medications are filled inside a filling machine in an ISO 5 (Grade A) environment that requiring continuous particle monitoring during the manufacturing process. With the experience and data obtained from the OQ and a refined risk assessment the PQ performance should be based with the filling machine running and with operators in place.

Example of a Filling line for sterile injectable product fill

What are the critical factors in a particle monitoring system?

What does a particle monitoring system do? If we break a particle monitoring system down the main objective is to gather real-time environmental data of the process environment during product manufacturing. If the environment conditions change (if particle concentrations are too high indicating that the environment is no longer safe to continue the fill process) operators and managers need some form of notification typically by a local alarm audio/light system, by email/SMS or locally by the particle monitoring sensors or a combination of all notifications.

Let's assume the initial risk assessment at the early stages of the project identified the locations for the sample probes. The IQ and OQ verified the sample probes were in the right locations and the samples were taking from the locations and all alarms were triggered successfully. If the original risk assessment identifying the locations was robust enough and science/knowledge based then the OQ would have verified the sampling and alarming from the locations were validated. The PQ should again redo the alarming conditions and these alert and action alarms are critical to the process. However the difference with the PQ is the alarming conditions are going to be triggered by the process or simulated. The addition layer on the PQ which did not exist on the OQ is what occurs during the PQ when these alarms are in fact triggered.

Critical Factor in a particle monitoring system to be tested during PQ

1. Appropriate alert and action alarm setting
2. PQ Validation of alarm limits
3. Sample location gathering meaningful data
4. Report generation on real time events either process driven or simulated
5. Adherence to SOPs that come into effect during the alarm events
6. Operator interventions
7. Routine service SOP's
8. Backup and Recovery
9. Change Control Process

1. <u>Appropriate alert and action alarm setting</u>

This critical process attribute is probably one of the most significant PQ tests. In real time monitoring alarm limits should be based on (1) Particle Counter flow rate and (2) Particle Counter update rate. In EUGMP Annex1 cGMP states that the sample volume should not be that used in Cleanroom Certification following ISO 14644-1 and the update rate is based on the sample period time of the particle counter which is typically every minute. If you apply ISO 14644-1 particle count/volume count thresholds to real time monitoring and setting your thresholds in line with current tables for Certification/Classification based on EU or ISO 14644-1 standards then you are at risk of setting your alarming system up with a unworkable sensitivity.

What is an unworkable sensitivity? Let's look at an example for a filling line in an ISO 5(Grade A) environment. EU Annex 1 (2018) GMP and ISO 14644-1:2015 standards have similar particle count thresholds in their tables for a sample volume of $1m^3$ for 0.5µm and 5.0µm particles. (ISO 14644-1:2015 removed 5.0µ reporting for ISO 5 class and replaced it with a macro-particle descriptor "M" which can be adapted to continue counting and reporting 5µm and the results would be indicated as ISO 5 (20≥5.0) in at rest and operational conditions).
Therefore following EU GMP or ISO 14644-1 the alarm limits for an ACTION ALARM based on a $1m^3$ sample would be the following;

ISO 14644-1:2015 - Sample Volume = $1m^3$
0.5µm Action Alarm = 3,520
5.0µm Action Alarm = 20 (M descriptor)

EUGMP - Sample Volume = $1m^3$
0.5µm Action Alarm = 3,520
5.0µm Action Alarm = 20

With these alarm thresholds for action alarms and remember these thresholds were derived from Cleanroom Certification which is a mathematical formula for cleanroom pass or fail results based on cleanroom size, particles to be sampled and the size of the cleanroom. Applying this formula to real-time monitoring during your manufacturing process run is not appropriate and will introduce an unworkable sensitivity. With this alarm set-point especially around 5µm size range and the low range even if you correlate the $1m^3$ to the typical 1cfm (cubic foot per minute) flowrate of the particle counter the limits at 5µm are too tight to achieve in a real process environment.

2. PQ Validation of alarm limits

Taking the 5.0µm threshold of 20 particles per $1m^3$ and correlating to 1cfm will yield a threshold of 20 divided by 35.31 which equates to 0.57 and this value is rounded up to 1. Therefore with a sample volume of 1cfm the 5.0µm action alarm is 1. We can agree this is a really tight action alarm limit. Way too tight for comfort. Particle counting technology is susceptible to electronic noise, vibration, and dark noise (solar radiation). The recommendation is to adjust the alarm sensitivity to look for trending instead of unmanageable one off events. Introducing X out of Y events using Statistical Process Control (SPC's) is the best approach and the most sensible one for real time monitoring.

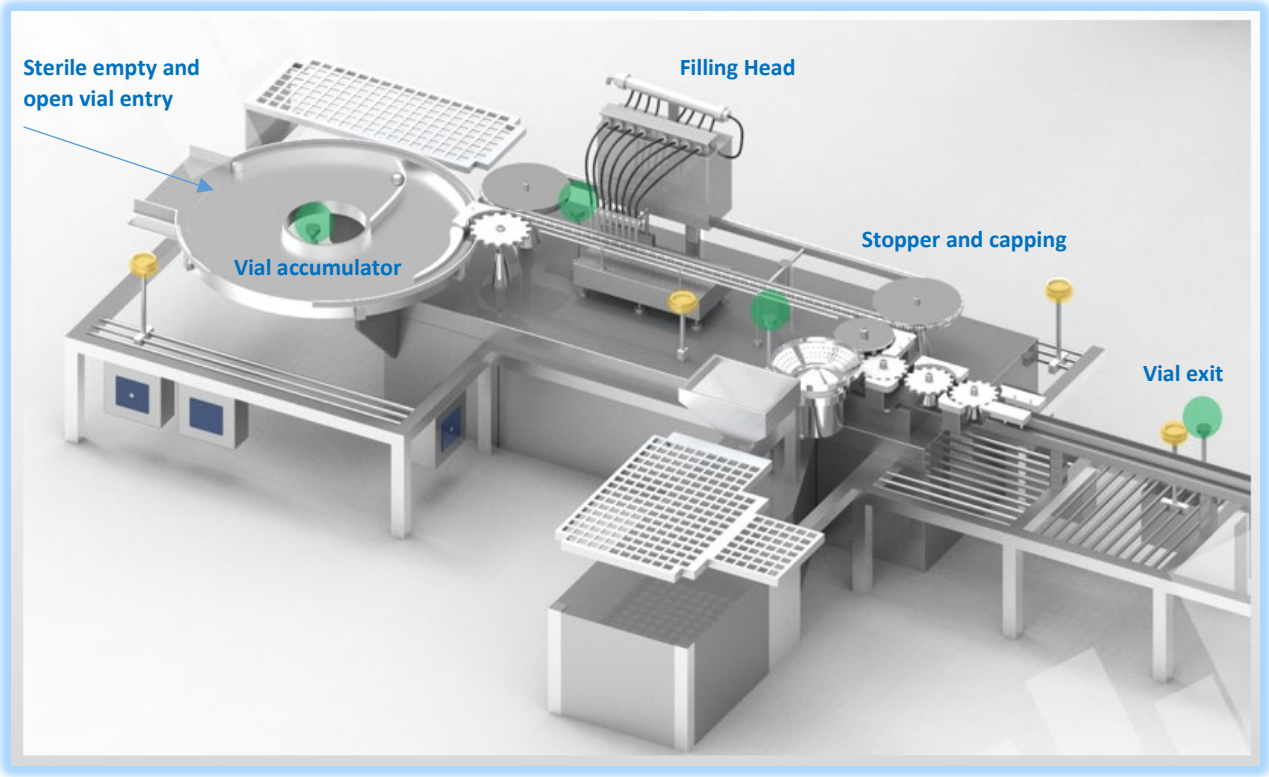
Cleanroom PQ Validation of Remote Particle Counter

A risk assessment process should be adopted to produce a science based approach to setting the SPC's based on the probability of X out of Y events (1) turning into a detrimental trend that will effect product quality and (2) probability of level of X out of Y events having viable particles in the environment. If the filling line and the air barriers are working correctly and operators are not present then the probability of viable particles in the X out of Y events is low. This can be backed up in the PQ with active air sample and settle plate data. The air sampling should be downstream of the process i.e. below the ISP. This can be further evaluated when you purposely introduce operator intervention into the process. Yes you will see a spike in particle counts however with proper monitoring during the PQ you can evaluate the impact of that intervention

down to the microbe level using air sampling monitoring data. With this level of testing you can determine if your X out of Y events can be set at 2 out of 3 counts > than 5.0µm or if your filling line and background environments as well as your operator gowning are Uber clean then you can push the X out of Y events further out to 5 out of 7 for example. If you do not see the effected environment cleanup back to the baseline threshold within a few samples then you have a real event which could be a HEPA filter failure. Therefore a root cause study is merited.

3. Sample location gathering meaningful data

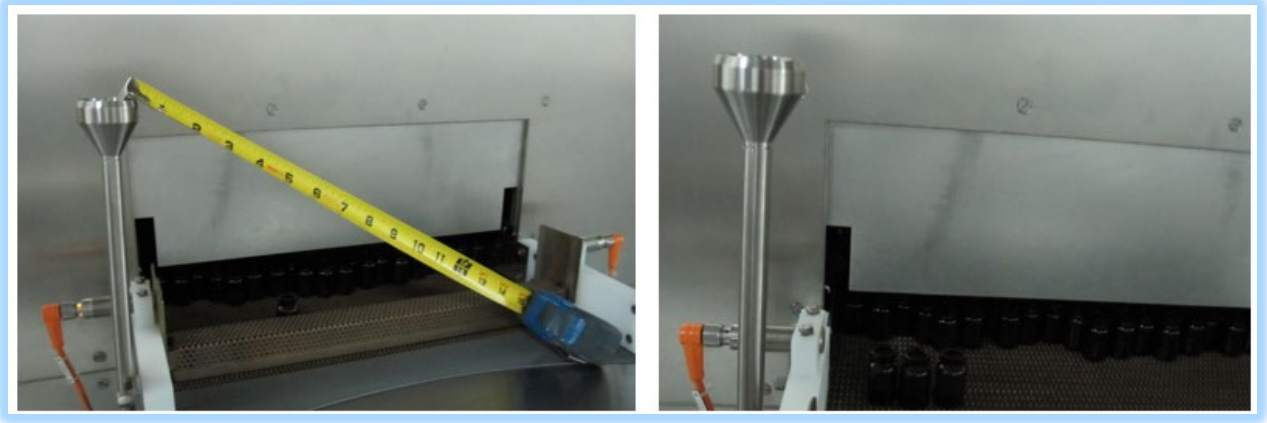
The SPC control depends on the location of the particle counter sample probe and the location should be near critical zones. On a filling line there are many critical zones but placement of the ISP must not interfere with the process or influence air flow over the process in a negative way. Particle sensor ISP placement is critical and has a major influence on the level of meaningful data gathered and on the use of X out of Y event SPC controls for trending. Isokinetic Sample Probe (ISP) height is a major factor.



Example of a filling line with viable (orange) and non-viable particle counter (green) sampling locations based on a risk assessment with a scientific approach to capture events in critical locations.

The objective of the particle counter should not be overlooked. The particle counter should be set up to alert and flag events that could have a detrimental impact on product quality and safety. The probe height must be above the process and not down at the process level.

The data gathered should verify that clean sterile air from the HEPA filters is passing over the process and acting as a barrier keeping particles from the moving parts of the filling machine from entering the product. The ISP should not be positioned too low otherwise it can potentially pick up process particles which are non-viable. If the ISP is too low the system could potentially be in alarm all the time. If the ISP is too high it is not indicating sterile air is passing over the process. Trial and error can eventually locate the "sweet spot". Here at Lighthouse we have >30 years' experience understanding filling lines and correct ISP placement.



Example of ISP positioned within 12" of the process where sterile open vials exit a sterilization oven onto the fill line.

4. Report generation on real time events either process driven or simulated

Simulation during the PQ where particle excursion alarms are purposely generated can greatly help to understand the system and process dynamics. Understanding what type of reports need to be generated for different situations is a key factor. Should data analytics be covered? Can we find the root cause of a given excursion with confidence and without bringing the whole micro team into the cleanroom? Are we seen the same particle signature when a certain operator is in the cleanroom? Is that operator a repeat offender for aseptic gown-up issues? Is the X out of Y SPC strategy working effectively and are we confident if we have 5 out of 7 high alarms that the probability of contamination of the product is low? Do we need to change our alarms before we go Live?

5. Adherence to SOPs that come into effect during the alarm events

This is an important part of the PQ. Many auditors want to know what you do when an excursion occurs. How you react to an event rather than the actual event is more important to them. Has an SOP been followed once the event has been notified via the particle monitoring system alarm notification? Is this event a trend or a once off spike? Are your SOP's been followed? How effective are your SOP's. What decisions are been made? How are the decisions made? Are operator training records up to date have they been properly trained on the SOP's? Strong SOP's can be developed after the OQ based on the knowledge gained from the particle monitoring system. The PQ should test the effectiveness of these SOP's

6. Operator interventions

On a filling line during fill process runs the greatest risk to the product is the operator. Simulation or real time media testing runs should be conducted to see how effective the operator interventions are during the fill process. Operator interventions should only be required if absolutely necessary for example in the case of a broken vial. The intervention should be validated and particle count data as well as microbial data gathered and evaluated to understand the impact of the intervention. Comments should be tagged to particle data in the EMS software of any interventions.

What is the operator intervention impact on product quality and safety?

7. Routine service SOP's

This is one area which is overlooked frequently. Particle counters like any other process instrument require regular calibration (at least annually based on manufacturer and GMP requirements). An SOP on service should have features like adding information to the system audit trail that the particle counter has been put into service status through the EMS software. The instrument should be carefully taken out of its location and sent out for service. A spare unit should be replaced and tested and the location should be validated so the data from the particle counter is recorded in the EMS and is actually from that location. Luckily with Lighthouse location ID's embedded in our smart bracket technology we offer a true plug and play validated system that assures the data is always from that particular location.

Lighthouse ApexR5 with Smart Bracket

8. Backup and Recovery

A critical process that needs to be exercised during the PQ. System backup and recovery has a major importance attached to it. As Particle Monitoring data is GMP data there should be a couple of layers for data backup. Data buffers built into particle counters enable a few days' worth of data to be stored. This data can be automatically uploaded to a secure (21CFR11 compliant) database or manually to 21CFR11 software that can read the data securely.

System recovery levels of redundancy if they exist should be tested. For example is the EMS software or external vacuum used to pull samples through remote particle counters on a redundant system? Are these on the facility UPS grid? What do you do in the event of an EMS server failure? Is there an automatic redundant EMS server running in the background waiting to take over? Is the system set up on a virtual server?

What is the business impact? How long does this recovery take? Is it automatic and will the data be purged from the backup server to the secure data server? Many questions need to be addressed to make sure your backup and recovery process allows for business continuity. Does the EMS or particle counter vendor have remote technical or on-site technical services available? Are they 24/7? Are we in compliance with GMP Annex 11? Do we have spare instruments and parts to minimize downtime? Is the system a plug and play setup? How much manual technical support do we need? Do we have a Service Level Agreement in place? What is the escalation process? Before going live you will want to address all of these critical questions and validate the process.

9. Change Control Process

Once the system is validated and goes live it is important to have an established and well documented change control process. With the amount of energy, labor and costs involved in getting your EMS to a validated state and in a live environment you should have your bases covered so the system does not require any changes for several years'….. right? In reality many projects are rushed based on the business impact or have only tiny shutdown windows. However if you do put the right energy and labor and address the PQ correctly and all the stages before the PQ, right back to the initial risk assessment your URS, SAT and IQ/OQ will be robust enough so you can conduct a really thorough PQ. If changes are required following your

qualities change control processes then updated SOP's and training around change control are mission critical. The last thing you want is an auditor looking at your EMS audit trail and noticing alarm limits were changed 6 months ago and there was no change control documentation to support the change. You should manage any changes through an internal risk assessment. Are these changes necessary? What will the impact be and what level of revalidation do we require? Who requires re-training, and should the SOP be updated? Having a strong Change Control process will mitigate against overlooked issues around the system changes.

In Summary

A robust PQ is an essential step to ensure your particle monitoring system is fully operational before going live into a production environment. A PQ should cover the critical process attributes and each should be tested to ensure they work as expected and operators and managers should be trained up and strong SOPs developed as a result.

Understanding particle counting technology and your EMS software is also a major recommendation. If you have a car and do not know how to drive it correctly then you will ultimately crash. This crash can have a major impact on your business. The PQ is your final step to nailing down the delivery of your particle monitoring system. It is the last chance to iron out any issues, train your staff and polish off your SOPs. Do not rush it and do not redo a vendor OQ.

If you do put the right resources, time and energy into your PQ you can be assured when you go live your system will be robust and your chance of downtime will be greatly reduced.

Lighthouse Worldwide Solutions offers expertize in Project Management and Validation

With our team of subject matter experts in viable and non-viable monitoring we can offer our Customers experienced advice in line with cGMP. From Project Management, Validation protocol development and execution we have learned over the many years we have been in business what works and how to get your EMS operational and with the right back up and services in place.

We have thousands of Monitoring Systems worldwide and we focus on designing and implementing EMS and Monitoring Systems to meet and exceed regulatory audits. We want our customers to focus on making life saving products and have an EMS working for them and not against them.

About the Author

Jason Kelly is Vice President of Services at Lighthouse Worldwide Solutions. He has spent over 25 years working in the Pharmaceutical and Semi-Conductor Cleanroom Industry managing and delivering major Environmental Monitoring projects and developing testing protocols for IQ/OQ and PQ. He has also set up multiple ISO 17025 Particle Counter facilities worldwide and has many years technical experience with particle counter calibrations to ISO 21501 standards. Jason also has published many technical articles on Environmental Monitoring in Cleanrooms and Particle and Air sampling technologies and travels frequently as a guest subject matter presenter around the world.