Achieving Compliant Batch Release – Sterile Parenteral Quality Control

Tony Harrison, Compliance and Applications Specialist | Beckman Coulter, Inc., United Kingdom

Abstract

Demonstrating compliant final product release for a sterile parenteral batch requires the use of Quality Control (QC) instrumentation that share certain common key elements. Of course each QC instrument must complete the requirements laid down in the pharmacopoeias or GMP, but in addition each instrument should be optimized to underpin compliance, help reduce human error and maintain data integrity for the test results. This paper describes those common QC instrumentation elements and gives examples of best practice for instruments used for compliant QC batch release.

Introduction

As part of the final batch release record for sterile parenteral solutions there should be records to prove:

a) The manufacturing environment (cleanroom) was in control and compliant

b) The parenteral itself is compliant to the rules regarding contaminating particles

c) The water used to manufacture the parenteral was in control and compliant

All instrumentation should be optimized to support data integrity for the analysis results and guidance for this is laid down in the FDA's 21CFR part 11[1] ruling.

Cleanroom Compliance

Guidance on cleanroom compliance for sterile parenteral manufacturing can be found in the various guidelines to good manufacturing practice. The World Health Organisation[2], European GMP[3] and Pharmaceutical Inspection Co-operation Scheme (PIC/S)[4] all agree that the air in a cleanroom must be controlled and monitored for particles ≥0.5microns and ≥5microns. The FDA's cGMP[5] document is different in that it only requires monitoring of particles ≥0.5microns. In any case, producers of sterile parenteral product must be cognisant of where each batch being produced is destined to be sold to ensure that they are being compliant to the relevant regulation(s).

The cleanroom monitoring process has traditionally been a manual process where airborne particle counters are moved around the cleanroom in a daily routine of sampling, relying on the counter operator to ensure that the test carried out at each location is correct to demonstrate the cleanroom was compliant at the time of testing. Additionally, the integrity of the final record was dependant on the operator collating all paper records from the day's routine environmental monitoring and accurately transcribing these records into either an Excel spreadsheet, or into a secure data repository. Usually, manual calculations are also required as it is common practice to sample quite small samples at each location and then multiply the results by a factor to report the number of particles per cubic meter (m^3), as is required by all of the rulebooks.

Figure 1. Routine cleanroom environmental monitoring practices are complex and fraught with opportunities for error

As can be imagined, all of this manual process can be fraught with opportunities for errors. In a modern air particle counter optimized for pharmaceutical cleanroom use, it is an expectation that the cleanroom facility routine environmental monitoring regime Standard Operating Procedure can be pre-configured inside the counter, removing the need for the operator to manually configure the sample location name, counter run time and alarms for each and every location. In addition, counters optimized for this process also automatically calculate the results per m^3 and then export the results via secure file transfer, such as File Transfer Protocol (FTP), in electronic format directly to a remote file repository without any manual data manipulation required by the user/operator. Such a counter provides secure, 21CFR part 11 records to demonstrate that the cleanroom was in compliance during the manufacturing process.

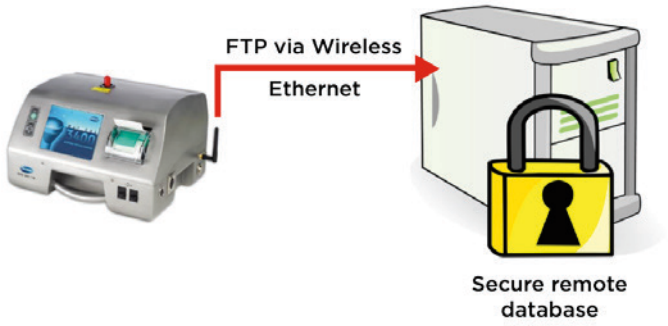

Figure 2. Beckman Coulter MET ONE 3400 particle counter exports cleanroom Routine Environmental Monitoring electronic records securely via FTP

Final Product Particulate Contamination Compliance

The United States Pharmacopoeia chapter on therapeutic proteins, USP<787>[6], suggests that sources of particles found in parenteral products can be grouped into three sources: intrinsic, extrinsic and inherent. Intrinsic particulate contamination is usually contamination from the vial or filling process due to inefficient cleaning, whereas extrinsic particulate contamination is usually introduced to the vial from the environment where the filling takes place. Inherent particles are particularly prevalent in biopharmaceutical products, where the therapeutic proteins clump together, either through adverse environmental conditions, such as bright light, temperatures or simply naturally over extended time periods.

Although largely harmonized, the rules for parenteral particulate testing do vary from country to country and from product to product. The volume of the sample to be analysed and the format that the results are reported varies from product to product, e.g. the sampling requirements for small volume parenteral product, such as vaccines, is different for that of a large volume parenteral such as an intravenous drip bag. Results must be calculated and expressed in the correct format, e.g. counts per container, or counts per mL.

Whilst general-purpose liquid particle counting instrumentation can be used for the testing of particles in parenteral products, counters that have been optimized for the application are preferable due to the wide range of complexity in the testing. Particle counters that have been optimized for this testing will have the various compendial tests built-in and will calculate a pass/fail result automatically. As QC teams tend to use their product name to describe the sample under test, optimized particle counters will allow the user to select the required test for each sample by selecting the product by name from a drop-down menu.

Counters that allow the operator interface to reside on a local p.c., but store the results database automatically on a secure remote server are preferred to ensure secure, 21CFR part 11 records to demonstrate that the batch was in compliance.

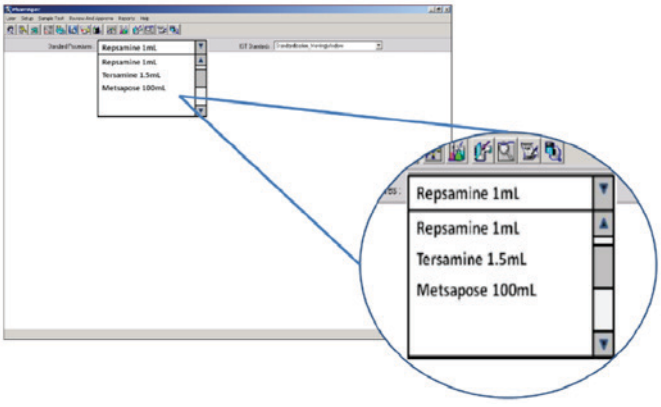

Figure 3. Beckman Coulter HIAC 9703+ allows user to select final product quality testing by brand name/product name

Water Purity Compliance

Water is the largest raw material used in a parenteral manufacturing facility. Water quality parameters are clearly defined in all the major pharmacopoeias and are generally harmonized globally.

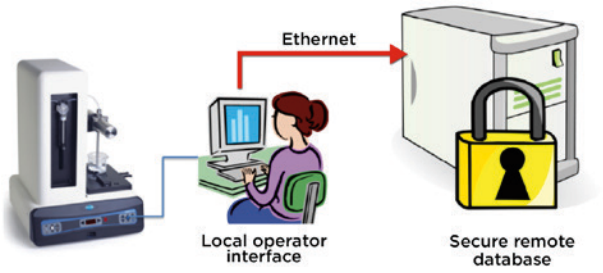

Figure 4. Beckman Coulter HIAC 9703+ stores final product quality test result records on a remote, secure server

One major quality parameter is Total Organic Carbon (TOC). Most modern pharmaceutical-grade water systems have extremely low TOC content, frequently in the low ppb region, compared to the amount of Total Inorganic Carbon (TIC) present, typically in the low ppm region, usually caused by the increased concentration of dissolved CO_2 caused through the commonly used reverse-osmosis water production process. General purpose TOC analysers that measure TIC and Total Carbon (TC) and derive the TOC level from these two measurements often struggle to accurately calculate TOC in the presence of the interfering TIC.

TC ppm (measured) – TIC ppm (measured) = TOC ppb (calculated)

Small errors in the sensor measurements for TC and TIC can lead to large variances in the calculated TOC result, sometimes producing negative TOC results where the measured and reported TIC value is slightly higher than the reported TC value.

Guidelines on instrumentation validation can be found in the International Conference on Harmonization guideline, ICH Q2[7]. This document explicitly guides the reader to conduct an investigation on the specificity of an analytical technique to ensure that it can discriminate between compounds of closely related structures. Such guidelines can help a user validate if an analysis method designed to measure TC and TIC and calculate TOC is suitable for the water quality on their site.

As with the other instruments discussed in this paper, the ability to export results via a secure electronic transfer, such as File Transfer Protocol (FTP), to a remote 21CFR part 11 secure data repository finalizes the optimization requirements for a TOC analyser used to provide batch release data in the pharmaceutical QC application.

Conclusion

Pharmaceutical QC testing is complex and at the same time absolutely critical to a successful, compliant batch release. When selecting instrumentation, the QC team leader is well advised to look for instrumentation that has been optimized for pharmaceutical QC use, taking into account automated, pre-configured SOPs, built-in compendial tests and secure electronic transfer, such as File Transfer Protocol (FTP), for 21CFR part 11 electronic record retention.

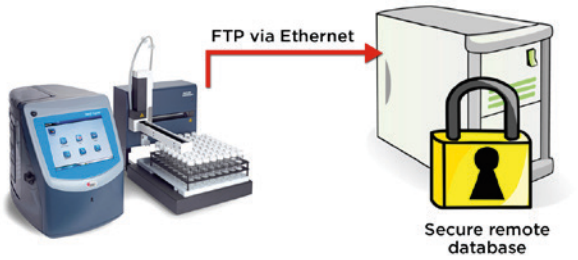

Figure 5. Beckman Coulter QbD1200 particle counter exports WFI test records in electronic format securely via FTP

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Author Biography

Tony Harrison

Compliance and Applications Specialist for Beckman Coulter Life Sciences

Tony has spent the last twelve years in applied metrology in the pharmaceutical and healthcare manufacturing industries. Prior to that, he worked for companies providing process control automation solutions for manufacturing industries.

Tony was joint-editor of the ISPE Guide to Ozone Sanitization of Pharmaceutical Water Systems[8] and was also chief editor of the PHSS Best Practice Guide for Cleanroom Monitoring[9].

Tony is a well-known international speaker and has provided educational seminars on TOC, liquid particle counting, ozone sanitization for water systems and cleanroom monitoring in UK, France, Italy, India, Germany, Malaysia, China, USA, Scandinavia, Ireland, Hungary, Switzerland, Indonesia, Belgium, Greece, Switzerland, Turkey, Egypt and Denmark.

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