BECKMAN COULTER
Life Sciences

Cleanroom Routine Environmental Monitoring – FDA Guidance on 21CFR part 11 Data Integrity

Abstract

A recent report suggests that circa 79% of 483 warning letters issued by the FDA to the biopharmaceutical industry sited deficiencies in their data integrity[1]. Despite guidance from the FDA, cleanroom environmental monitoring remains an intensely manual process, with many opportunities for human error to create gaps and errors in the data. In their 21CFR part 11 guidance, the FDA have given recommendations on what good data integrity looks like and this presentation explains their advice in the context of current cleanroom environmental practices and shows how the FDA guidance can be applied to improve data integrity.

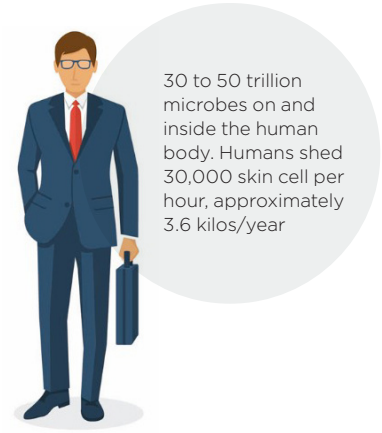


Figure 1. Human skin and microbes

Cleanroom Routine Environmental Monitoring

Of course the FDA mandates the air quality conditions for bio/pharmaceutical production in cleanrooms. In fact the real danger is the microbes on the human body. Humans shed around 30,000 skin cells per hour[2], all of which are potential carriers of microbes. Unfortunately we do not currently have technology to detect airborne microbes real-time. So air particle counters are used as a surrogate.

Discussions between the author and Environmental Monitoring Managers at facilities across the world suggest highlights an increasing trend where the burden of carrying out environmental monitoring is moving away from the QC microbiology team over to the production staff, for two reasons: a) microbiology staff are relatively expensive to employ to carry out such routine tasks and b) it reduces the number of people inside the cleanrooms, thus reducing the potential for product contamination. However, the production team do not have the same level of knowledge about routine environmental monitoring and this is creating challenges itself.

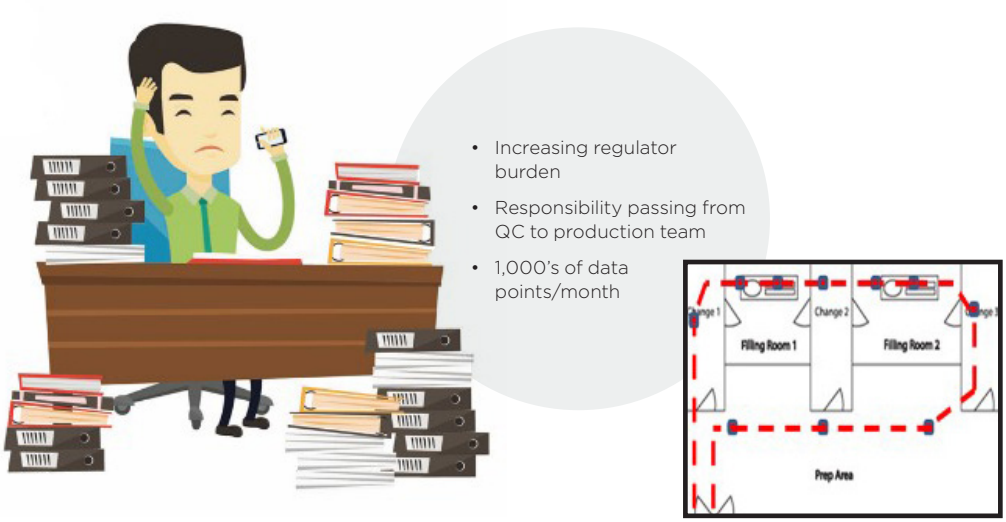
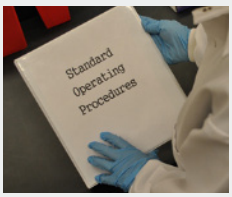


Figure 2. Risks to environmental monitoring data integrity

In larger biopharmaceutical manufacturing plants, there can be teams 10 technicians or more whose job it is every month to take thousands of routine environmental monitoring samples. At each location, they have to manually type the location name into the counter before they start sampling. Counters have to be manually configured following written SOPs. At the end of each day, the paper print outs from each sample location have to be photocopied because the printers in the particle counters are thermal and the print-outs fade over time. Then the results from every location have to be manually transferred into electronic format one by one.

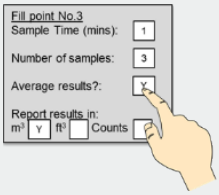


Touch-Point 1

- Ensure correct SOP
- Read and understand SOP

Touch-Point 2

- Manually Type each and every sample location name



Touch-Point 3

Manually Configure counter:

- Sample time,
- Number of samples
- Results averaging
- Correct multiplier for m^3

Touch-Point 4

- Take paper print-out and photocopy

Touch-Point 5

- Manually transcribe results

Figure 3. Manual Routine Environmental Monitoring SOPs

Following environmental data errors, a typical response is to mandate re-training for the team. However, the industry and the FDA is gradually coming to the conclusion that this does not solve the problem it merely treats the symptoms for a short while until human error starts to creep in again and that the correct way forward is to reduce manual steps in the SOP in order to reduce the human errors and make the whole process more robust.

FDA Guidance on Data Integrity

In their guidance on the implementation of their 21CFR part 11 data integrity rule[3], the FDA use the acronym ALCOA, where they define good data integrity practice as creating records that are Attributable to the technician carrying out the testing, are Legible, are created Contemporaneously, Original and Accurate.

In this case Attributable means that the records should somehow be traceable to the technician who did the test. They should also include a label stating where the sample was taken and the date and time it was taken.

The record of course is required to be legible, which implies that hand-written records are not acceptable. The FDA goes on to suggest that electronic records should be stored in a format that is open and can be read on many computing formats so that it will be accessible and readable for years to come. The FDA recommends typical formats such as PDF, XML or SGML[3].

In this instance the word contemporaneously implies that the electronic records should be created immediately the sample is measured, implying that manual transcription of paper records is not good practice and that collating paper records and then manually transcribing them into electronic format at a later time/date is not good practice.

Naturally the electronic records should be accurate. This implies that the process for capturing those electronic records should be robust, implying manual calculations and manual data entry where opportunities for human error exist should be avoided.

Now let's take a look at current environmental practices in the light of the FDA ALCOA guidance. There are many manual steps in the typical environmental process and usually the paper record does not contain an electronic signature, so it is not attributable to the technician. Sample locations are manually typed in for each location, inviting human error and miss-typing, preventing the sample being easily attributed to the sample location. Usually the final electronic record is legible, but it certainly is not created in a contemporaneous manner, instead the original paper record is created by a thermal printer and fades over time, so the final record is not the original and, as it is manually created, the final record cannot be guaranteed to be accurate.

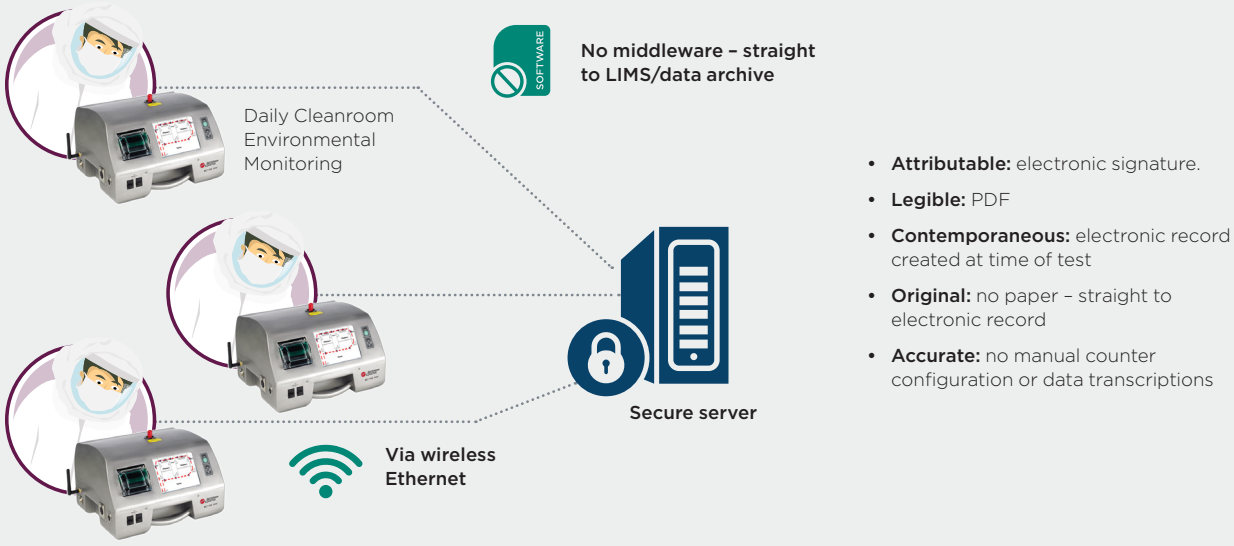


Figure 4. Beckman Coulter MET ONE automated routine environmental monitoring SOPs help with data integrity

Fortunately a more compliant solution exists. Air particle counters from MET ONE can have the sampling SOP and locations pre-programmed and automated to remove the manual sample location entry and counter configuration steps. Instead of producing paper records that have to be manually transcribed at a later stage, the counter instantly generates an electronic record that contains the user's electronic signature and the sample location name. This electronic record is in one of the recommended formats from the FDA, PDF, and can be transmitted via wired or wireless Ethernet to a secure server where the user keeps the final records. This removes all manual configuration steps, manual location typing and manual data transcription, thus reducing the opportunities for human error and improving data integrity.

Conclusion

In many cases, cleanroom routine environmental monitoring programs still carry a high risk of human error with SOPs being implemented manually and thousands of data records being manually transcribed into electronic format. No matter how often staff are trained, the opportunity for error is such programs remains very real, with the associated implications for data integrity. The technology exists and is commercially available to mitigate this problem and make these programs more robust, reducing the impact on data integrity and also supporting the industry's move towards environmental monitoring by production staff in the cleanroom.

References

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3. U.S. Department of Health and Human Services Food and Drug Administration Guidance for Industry, Part 11, Electronic Records; Electronic Signatures — Scope and Application, August 2003 U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER) Office of Regulatory affairs (ORA) Division of Drug Information, HFD-240 Center for Drug Evaluation and Research Food and Drug Administration 5600 Fishers Lane Rockville, MD 20857 USA

About the author

Tony held the Convenorship of the ISO Working Group revising ISO 14698-1 & -2 for microbial control in cleanrooms and was the UK subject matter expert to the ISO Working Group who revised ISO 14644-1 & -2 for cleanroom classification and monitoring at the heart of the aseptic manufacturing chapters of both the European GMP and the USA CGMP documents.

Tony holds a Bachelor's Degree in Electrical & Electronic Engineering and is employed by Beckman Coulter Life Sciences as a Senior Marketing Manager. Experienced in water system TOC, conductivity and ozone analysis and cleanroom monitoring systems as well as particle characterisation, Tony has spent the last fifteen years in applied metrology for 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 on the ISPE Guide to Ozone Sanitization of Pharmaceutical Water Systems and was also chief editor of the PHSS Best Practice Guide for Cleanroom Monitoring.

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, Malaysia, China, USA, Scandinavia, Ireland, Hungary, Switzerland, Indonesia, Belgium, Greece, Switzerland, Turkey, Egypt, Denmark, Poland, Italy and most recently Singapore and South Korea.

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