Quantifying and Assessing Cleaning & Disinfection Residues

HiTechHealth

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Introduction

The purpose of this presentation is to review the impact of cleaning and disinfectant residues on an ATMP cGMP manufacturing facility and discuss how to assess and manage these residues. The term "disinfectant residue" can have different connotations. For some, it may be evidence of potential product contamination, or evidence that cleaning and disinfection was being performed, and for others it could be a sign of lack of control. With the most recent revision to Annex 1 there has been as renewed focus on control and removal of disinfection residues. This poster discusses how to minimize disinfectant residues by design and investigates the methodology associated to quantifying residues beyond visual assessment that may often be subjective.

The emphasis placed on residues and residue management is driven by numerous audit findings, new guidelines such as the most recent revision to EU GMP EudraLex Volume 4 - Annex 1 (August 2022) [1], and best practice recommendations such as those shared in PDA Journal of Pharmaceutical Science and Technology [2].

EU GMP EudraLex Volume 4 - Annex 1 (August 2022) section 5.4 states:

"The cleaning process should be validated to be able to:

- Remove any residue or debris that would detrimentally impact the effectiveness of the disinfecting agent used
- Minimize chemical, microbial and particulate contamination of the product during the process and prior to disinfection"

Residues should be managed, removed or reduced to an acceptable level if: a) An impact to the performance of disinfectants subsequently applied is expected

b) Cross-reactions of different chemistries, or adverse material interactions are possible

c) Safety risks to the personnel can occur

Residues may also present a source of physical contamination within the cleanroom environment, potentially leading to the release of non-viable airborne particulates that can cross-contaminate pharmaceutical finished goods.

This poster describes the residue management approach used within HiTech Health (HTH) cleanrooms as to measure residues on different types of surfaces, using a semiquantitative conductivity method.

Methodology

Residues present on different types of surfaces were measured with a semi-quantitative conductivity method to compare the conductivity values between "clean" surfaces (surfaces notionally free of residues) and surfaces that have been subjected to the cleaning and disinfection regime in place at HTH.

A 45% polyester and 55% cellulose wipe was placed in a beaker containing 75 mL of Klercide Water for Injection (KWI). This wipe was used to remove residues from an area of 0.5 m² from the cleanroom surface. The wipe was then placed back into the beaker to measure the conductivity. Conductivity was measured by placing the conductivity probe into the KWI containing the wipe and stirring for approximately 60 seconds.

Baseline conductivity of the water and wipe material is measured for each sample prior to using the wipe across a surface. A second conductivity reading is taken when the used wipe is returned to the beaker of KWI. To determine the residue level recovered from the surface, the baseline conductivity reading of the KWI and unused wipe were subtracted from the conductivity reading of the KWI and used wipe. The values measured in representative "clean" and "in-use" surfaces were compared. [4]



Figure 1 - Conductivity of a 300 x 300 mm 45% polyester and 55% cellulose wipe in KWI. Typical values should be ideally below $< 10 \pm 2 \mu \text{S/cm}$. The example shows 4.38 µS/cm for the chosen wipe and water quality selected.

Visual Assessment of Residues versus Conductivity

Collection of data by conductivity allows a more appropriate quantification compared with the current standard of visual assessment, which is subjective and dependent on human perception, light, and reflection. Furthermore, it allows monitoring of the residue build-up over time with successive applications of the applied disinfectants or detergents. The effectiveness of any residue removal process via rinsing can also be assessed which allows end users of disinfectants to implement one or multiple rinsing steps at the ideal frequency.

Figure 2 below highlights the significant difference between visual scoring and data derived from conductivity measurements. The conductivity measurements prove that a higher amount of residue was present on the surface, than the visual scoring (1 to 5, with '1' being visually residue-free and 5 being significant visible residue) indicated. [3]

The conductivity method is an excellent tool. It allows for measurement and assessment of residue profiles of different disinfectants in a simple manner, on-site, and in real-time. In general, a low conductivity value correlates to a low level of ionizable residues left on a cleanroom surface, and achieving this state reduces the risk to user safety and product quality. High residue disinfectant products in turn, can be tracked regarding their level of build-up with the option to implement more frequent rinsing steps to lower the risks from these residues.

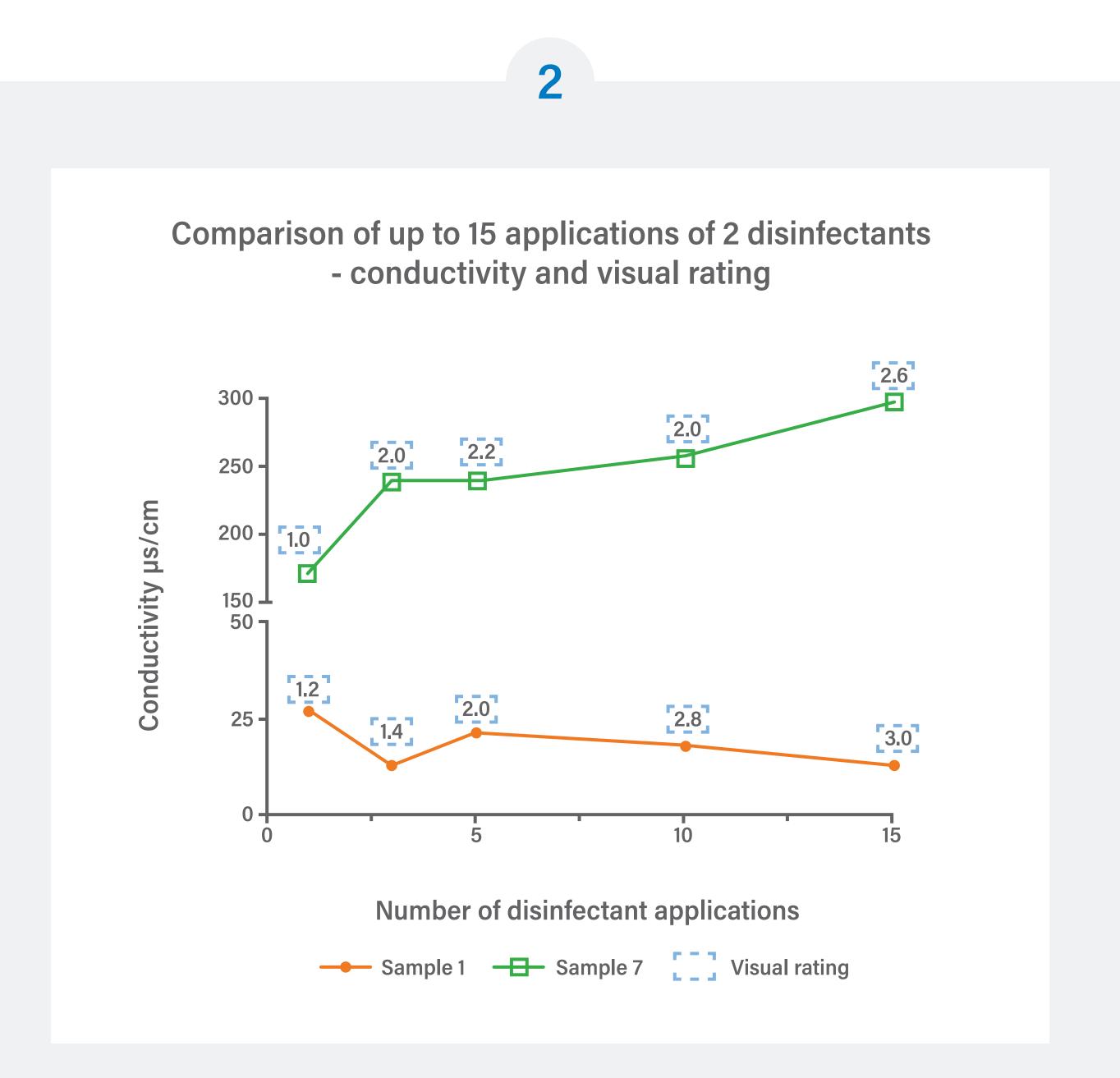


Figure 2 - Comparison of visual scoring versus conductivity measurement over 15 applications of two Quat-based disinfectants.

Measurement of Residues with Conductivity on HiTech Health "Clean" and "In Use" Surfaces

There are currently no regulatory guidelines or specifications for residue limits on non-product contact surfaces. All measurements were recorded for information only and to evaluate if residue level remains low in comparison with a "clean" surface baseline, to assess if additional actions of rinsing are required to lower residue level, if necessary.

All values displayed in Figure 3 for the 'clean' surface baseline were lower than the values observed for the pre-defined cleanroom representative surfaces following the application of cleaning and disinfection agents, with the exception of stainless-steel Grade 304 sample. For this material, two cleanroom locations had lower measurements than the 'clean baseline, however the difference in values were determined to be minimal.

In general, the floor samples showed the highest values measured, in comparison with the 2 stainless steel types and the wall surfaces. This is likely due to the floor surface profile (not smooth), which is a common characteristic of these type of materials that are used for flooring as a safety feature to provide grip when operators walk through the surface in cleanroom garment boots and/or overshoes and avoid slips, trips, and falls. Due to this feature, residue removal could be slightly less efficient as residues would naturally aggregate on the textured profile of the material. However, the values measured are still very low. In addition, considering that floors are the least critical surface in relation to process activities within the cleanroom, the residue values are acceptable.

The most critical surface sampled of the BSC in a Grade B laboratory (G08) showed one of the lowest values measured, even lower than the 'clean' sample baseline. This confirms that residue removal practices are effective as outlined by current cleaning and disinfection regime.

All measurements were below <60 µS/cm, which is acceptable as to maintain low residue profiles in cleanroom surfaces and confirms that current residue removal practices can be considered efficient and fit for purpose, and therefore no further actions to enhance residue removal are required.

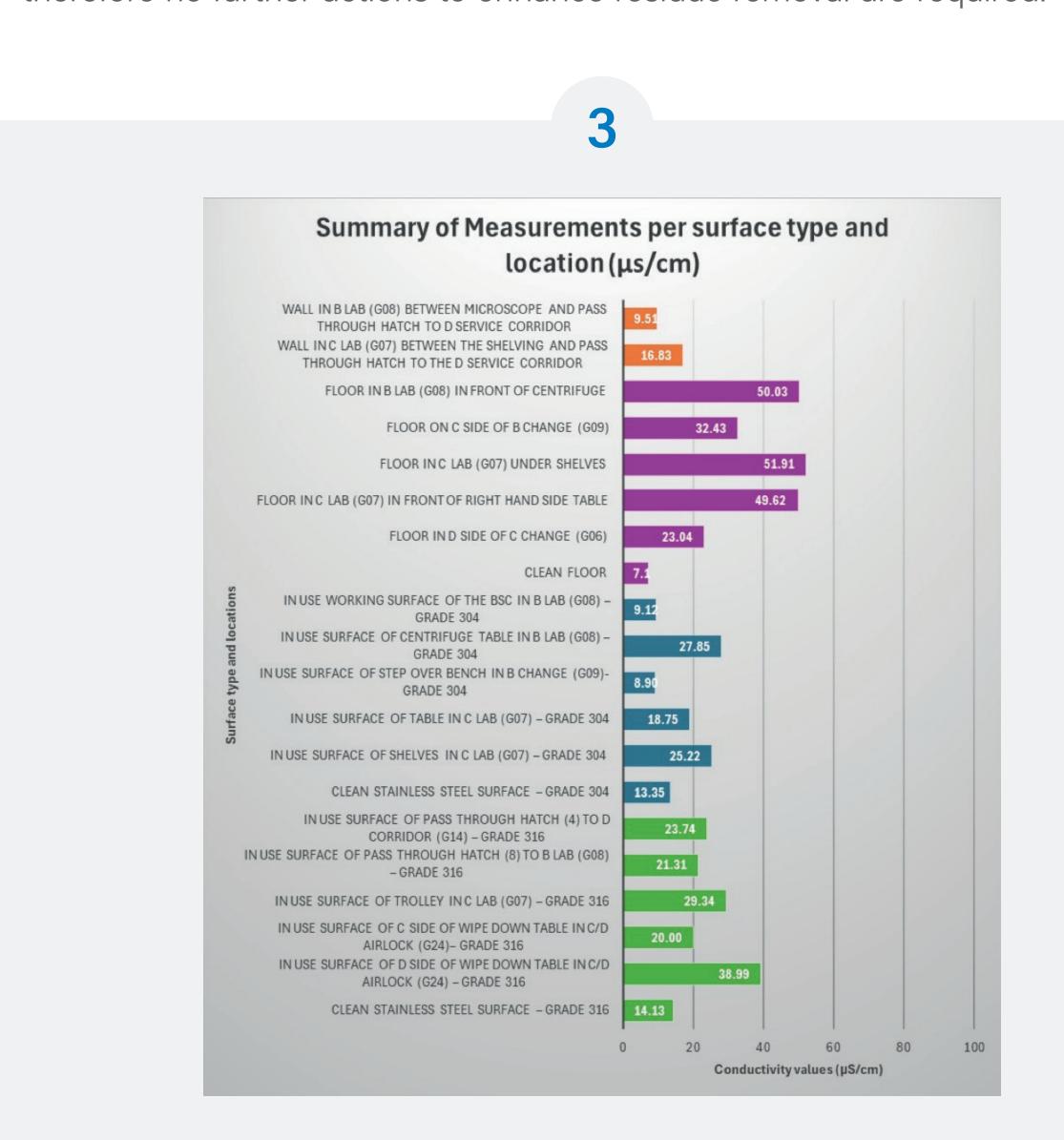


Figure 3 – Summary of Measurements per surface type and location

Conclusion

Despite the regulatory focus on removal of disinfectant residues, there are currently no regulatory guidelines or specifications for residue limits on non-product contact surfaces. Conductivity is a simple and pragmatic tool for residue quantification to aid design and control of cleaning and disinfection regimes in cleanrooms of the pharmaceutical industry.

To control residues effectively, consideration should be given to the residue profile of the products that are intended to be used within the cleaning and disinfection regime. Depending on the residue profile of products used and how much residue is left on the surface after each product application, the use of residue management techniques using appropriate rinsing agents should be considered. Alternatively, the use of low residue profile products can significantly reduce the frequency of rinsing steps necessary to control residues.



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1. The Rules Governing Medicinal Products in the European Union Volume 4 EU Guidelines for Good Manufacturing Practice for Human and Veterinary Use. Annex 1 Manufacture of Sterile Medicinal Products (August 2022) 2. Derek Willison-Parry et al., Disinfectant Efficacy: Understanding the Expectations and How to Design Effective Studies That Include Leveraging Multisite Data to Drive an Efficient Program, PDA Journal of Pharmaceutical Science and Technology, Vol. 74, No. 2, March-April 2020. 249-263 3. Use of Conductivity as a Tool for On-site Residue Management and Definition of Smart Cleanroom Regimes, EJPPS peer reviewed article, 4th January 2023 https://www.ejpps.online/post/vol27-4-use-of-conductivity-as-a-tool-for-on-site-residue-management-and-definition-of-smart 4. ECO HTH 001 HiTech Health Protocol for Residue Control Assessment