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Science and Technology Feature

The proposed changes to Annex 1: considerations for the cleaning and disinfection processes

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Introduction

The long-anticipated revision to Annex 1 (from the EudraLex Guidelines to Good Manufacturing Practices[1] requirement for sterile drug manufacturing) is now closed for public consultation. Nearly 3 years after the initial announcement and more than 10 years since the previous revision was published, it is reasonable to suggest that an update is certainly due, and this new document delivers a considerable increase in the depth and breadth of Annex 1.

Whilst many debates will continue around the timing of its publication, implications, perceived meaning and level of implementation expected from the final version post consultation; this article explores the author's view of the potential impacts specifically affecting cleaning and disinfection regimes.

The following review will focus on a few key areas of the Annex understood to significantly affect the use of disinfectants within the sterile manufacturing areas once implemented. As a holistic, risk-based approach to contamination control is fundamental to the Annex, this is a critical aspect for consideration when reviewing the proposed updates.

Cleaning and disinfection

The first aspect for consideration is cleaning and disinfection. It has long been widely accepted that cleaning and disinfection are two distinct processes within the cleanroom environment.

Cleaning

The objective of cleaning is to remove physical soiling, which could present a contamination risk. This is usually achieved via systems such as vacuums, detergent cleans, wet cleans with water for injection, isopropyl alcohol, or even dry cleans with wipes and mops. Removal of soiling may reduce bioburden or protective contaminants that improve subsequent disinfection efficacy. Typically, cleaning is applied to achieve removal of visual soiling in line with risk requirements of standard operating practice frequencies.

Disinfection on the other hand is designed to kill microorganisms. Disinfectants can be divided into distinct groups, generally termed sporicidal and broad-spectrum disinfectants with various chemistries having different effects against each organism; however, they share a common goal, that being to render the specific target group of microorganisms with the inability to proliferate.

The segregation of these two processes is, for the first time, reinforced in the Annex.

Disinfection

One key area of the Annex which is critical within the pharmaceutical industry is the disinfection section, which has replaced the previous santisation section; and is now further expanded.

The requirement for rotation of disinfectants is further clarified, with the statement that more than one type of product should be employed including the periodic use of a sporicidal agent. This leads to the conclusion that one sporicide and a broad-spectrum disinfectant is sufficient for cleanroom contamination control.

As part of the validation requirements for disinfectants, there is an increased emphasis on contact times, surface and manner in which products are applied, suggesting that these will be key areas for both qualification, validation studies and reviews of validation data held moving forwards.

It also places a requirement to ensure that efficacy is demonstrated throughout the in-use shelf life, which will place an increased burden on those

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making product up from concentrate as opposed to using ready to use products because the data sets required to support the product in the final format will be more detailed.

The Annex revision continues to reference the development of microbial resistance; however, the development of acquired rather than innate resistance is still unproven at in-use concentrations. The requirement for disinfectants to be effective against the flora is a logical approach. For example, bacterial spores will not be killed by alcohols and therefore a sporicidal agent is required for efficacy against bacterial endospores.

The new Annex also maintains many of the original statements, for example, monitoring disinfectants and detergents for microbial growth, product must be sterile when used in Grade A and B environments, dilutions should be stored in previously cleaned containers, only stored for defined periods, etc. Annex 1 revision has removed the exception for sterile, demonstrating the need for a holistic approach across the processes to show the effect on facilities, equipment and processes.

Another key aspect of cleaning and disinfection is the in-practice demonstration of efficacy via environmental monitoring, as this should include monitoring pre- and post-disinfection. Furthermore, the Annex specifies that microbes within Grade A and B environments should be identified to species level, and the impact of this identification on the state of control should be assessed. This makes it easier to ensure the correct product(s) is(are) being used and identify which corrective action should be followed, as required.

Residues

As a disinfectant manufacturer, we have seen a prolonged and increased concern over residues left post-application from disinfectants. The visual aspect of residues has always been of concern and there are records of pharmaceutical companies being cited for the presence of residues in the cleanroom environment. As another critical topic in review, the Annex now calls out the need to control these residues as well as raising concerns over the potential latent effect of residues as highlighted in Section 6.5 A and B, which references residues potentially creating a barrier and/or posing a particulate risk to the product being manufactured.

The new Annex now includes a statement for cleaning processes in the equipment section, stating that cleaning processes should be validated so that they can remove any residues that would otherwise create a barrier between the sterilising agent and the equipment surfaces. As sterilising would indicate achieving complete kill, this instance of the use of the word 'sterilising' has been challenged as incorrect, the changes also highlight that residue removal should occur to prevent chemical and particulate contamination of the product during the process, all of which also links in with the requirement for cleaning stages.

There is a new specific statement on cleaning programmes, which should be effective at removing disinfectant residues. This ties in with low residue requirements and clearly states that it is no longer acceptable practice to allow residues to build up uncontrolled on surfaces.

It is a necessity that products used for decontamination of restricted access barriers systems (RABs)/isolators demonstrate they have no impact on manufactured product sterility testing, therefore residual impact must be assessed. This assessment is not limited to the sterility testing isolators, but also the impact on product manufactured and product contact surfaces should be considered.

Furthermore, there are significant enhancements to expectations for visual inspection discussed, which fits with a focus on residues and reflects a clear industry trend towards the need to remove residues to protect product quality.

Preparing products from concentrates

When preparing disinfectants on-site from concentrates, the following will need to be considered; the increased requirements around filtration including minimising the number of connections, cleaning, in-place integrity testing, assuring sterility, validation including parameters such as flow rate, minimum and maximum time in contact with the fluid, validation pre- and post-use, pressures in use, and bacterial retention testing (ability of the filter to retain bacteria and render the subsequent fluid sterile). Liquid sterilising filters should be discarded after processing of a single lot (unless validated).

There is also a requirement to link bioburden limits to filter (used for rendering disinfectants sterile) efficiency, which if interpreted literally, could leave levels which are very high and make monitoring difficult.

Additionally, if those who are making up disinfectants from concentrate are using water from their own system to do so, they may also need to consider the requirement in the Annex that a sample is taken from the worst-case location of a process' water system each time the system is used for manufacturing. This could be considered highly problematic, placing considerable burden on the operators and their resources. This may well be revised in the final version of the Annex, but at this point, is included.

Quality risk management

Annex 1 reinforces the need for quality risk management (QRM) and this was one of the key drivers for the change, and the concept of risk management is embedded in the new document like never before. There is specific emphasis placed on using the principles of QRM to support decisions made within the document.

The document also considers a few key points which will doubtless continue to raise questions within the industry. Of specific interest, a clear expectation for a formal, holistic contamination control strategy. The expectation appears to be for a formal dossier which reflects the site-wide strategy for minimising

contamination with respect to sterile manufacturing. This document should include specific sections which cleaning and disinfection will influence and contribute to, namely, equipment and facilities, personnel, vendor approval/outsourced services and most importantly from a contamination control perspective, a specific section on cleaning and disinfection.

Additional requirements for cleanroom classification (beyond International Organization for Standardization requirements) in critical areas has been raised and therefore consideration must be given as to how to maintain these.

Water quality system design and implementation, widely reported as one of the key reasons for delay in release of the Annex draft, is another focus point. There is an increased focus on water, biofilm control and filtration, all of which affect disinfection dilution, rinsing and clean-in-place processes.

The expectations around personnel include a requirement for setting a minimum and maximum (validated) number of personnel in a cleanroom and meeting regular training needs, including qualification and assessment.

The update contains substantial additional detail on virtually every topic considered by pharmaceutical company auditors. Hence, there are more than twice the number of clauses in this draft document with time for this to continue to develop.

Material transfer/transfer disinfection

From a cleaning and disinfection perspective, transfer disinfection is another key area tackled in the Annex. New requirements include a pre-qualified list of items, products and processes which are used to transfer these between different areas within the cleanroom. It also suggests that items for transfer excluded from the list of pre-qualified items should be included in a specific sanitisation and monitoring regime. This will provide transparency on disinfectant product performance against in-house flora and practical use. Transfer of items from Controlled Not Classified (CNC) areas to Grade C should be commensurate with the risk as per QRM, which may well support the use of a sporicidal agent depending on the level and type of incoming bioburden. This recognises the need for companies to understand and control the risk, especially in the early stages of production processes.

Pre-packaged items should be transferred via a validated method (e.g. disinfection of the exterior packaging), but there is a need to demonstrate effectiveness at not posing an unacceptable risk. This means reducing contamination to an acceptable level, which may well mean there will be a risk based on the trade-offs of chemistry versus activity, material compatibility and residues required.

A single-layer can be removed from multi-layered items at each interface, meaning that the benefits of multi-layered items can be seen in practice.

Any non-packaged items should be transferred disinfected using a validated process, stored as to prevent re-contamination and included as part of environmental monitoring, all increasing the requirement for chemistry to be validated for the transfer disinfection process.

As part of the initial design of RABS and isolators, one of the key factors highlighted is the disinfection and sterilisation regime (direct and indirect product contact parts, not sterilised by disinfectants), which means a requirement is present for material compatibility studies on all chemistries in-use with these systems.

Single-use technologies

Single-use technologies is a new section within the Annex, but some concerns have been raised which may require further investigation in terms of the trade-off from traditional cleaning-in-place and the move towards the use of single-use technology. These considerations include particulate contamination, performance and integrity of filters, pinhole leakage, increased processing, leachable, absorption, extractables, fragility and design.

Conclusion

The revised or new Annex 1 is, as promised, a comprehensive re-examination of the previous version, with a focus on application of QRM and Pharmaceutical Quality System to sterile manufacture.

There is some excellent new information on a wide range of technologies not adequately covered in the previous version; several ambiguities and inaccuracies from the 2008 version have been addressed.

Public consultation is now closed for comment, but as with all new publications – especially drafts – there are some points of contention. Public consultation may be able to address these. Regardless, it is expected to deliver changes which will affect cleaning and disinfection and the requirements around it for all involved in the pharmaceutical industry.

This paper has been amended from a previously published paper in *PDA Letters* (September 2018; issue 8).

References

1. European Commission. *EudraLex. The Rules Governing Medicinal Products in the European Union. Volume 4: EU Guidelines to Good Manufacturing Practice – Medicinal Products for Human and Veterinary Use. Annex 1 – Manufacture of Sterile Medicinal Products*. Brussels, Belgium: European Commission; 2008.