Annex 1 Anticipated Update & Our Interpretation

Chris Kyle January 2020

Introduction

We have to remember that this is for Pharmaceutical Manufacturers of Sterile Product – a lot of the content is not applicable to our industry (our cleanrooms), although we have to take into account what our customers expect from us and also the sales opportunities these changes bring us.

Revisions

This is the first comprehensive update to the document, previous updates have been specific changes only.

The previous document was 16 pages and it is now likely to be over 50 pages, which demonstrates the level of change.

The new version will comprise of 269 clauses, this is compared to 127 in the previous version. Only 40 clauses remain unchanged.

The consultation document resulted in 6200 comments being received from 140 different contributors

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Changes

There is more reference to RISK and RECOMMEND/RECOMMENDATION – this is in line with a lot of regulatory documents now which use Quality Risk Management as a tool as there is **not one rule for all**.

The document has been assess and the most relevant areas to our industry, be this is our own cleanrooms or requirements for our customers are :

Section 2 Principles - Contamination Control Strategy
Section 4 Personnel - Gowning
Section 5 Premises - Cleanroom Design / Classification
- Cleaning & Disinfectant

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Update as of 21 February 2020

It was communicated that an updated CONSULTATION document was being issued to a select organisations for review. The consultation period is to end on 20 May 2020

Update as of 21 February 2020

The title has now been changed from Manufacture of Sterile Medicinal Products to Manufacture of Sterile Products

Frequent reference to CCS (Contamination Control Strategy) document

Phases such as ‘WITH AN AIM TO MINIMISING’ have been added – this is in line with the risk assessment approach

Contamination Control Strategy

The requirement is to provide a detailed list of elements that we will need to have records for :

- Vendor approval – including key component suppliers, sterilisation of components and single use systems, and services
- Outsourced services – sufficient evidence should be provided to the contract giver to ensure the process is operating correctly
- Process Validation
- Cleaning & Disinfection

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Contamination Control Strategy

We have created a document that will form the basis of an audit which will be conducted at each Plant and results issued at the end of April 2020, example below shows the section for Vendor Approval :

Vendor approval

- Supplier categorisation based upon risk assessment
- Key suppliers audited
- Completed Quality Questionnaire for all suppliers
- Ongoing monitoring of quality

Exists – appropriate	Exists - needs updating	Does not exist	Actions with Due Dates

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Our Interpretation

Section	Line No.	Statement	Our Interpretation
2	59-62	Contamination control and steps taken to minimise the risk include the requirement to assess, control and monitor certain aspects, these include the following, so for customers this may mean more emphasis on us as a supplier as well as our own assessments - this includes the following :	
	83-84	Vendor approval – key component suppliers, sterilisation of components and single use systems, and services	This will be covered in the Contamination Control Strategy document and audit/checklist that will be rolled out to all plants
	86-87	Outsourced services – sufficient evidence should be provided to the contract giver to ensure the process is operating correctly	
	91	Process Validation	We need to ensure that we validation our processes (or risk assessment if applicable) from start to end, including qualifying all machines
	97	Cleaning & Disinfection	You cannot disinfect a dirty area, this is the reason the sections for cleaning and disinfectant have been merged. Sections below will give more details

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Gowning (Personnel)

- There is a **recommendation** for dedicated **socks** to be worn prior to entry into changing rooms for Grade B and Grade C This has now been changed and is no longer a recommendation, is has been changed to SHOULD BE WORN

- Added **requirement** for **sterile eyewear** and garment change at least every work session

- Added **requirement** to check the **integrity** after washing and prior to sterilisation (this would be during the cleanroom folding operation for us and bag integrity checks) This has been changed to AFTER WASHING AND BEFORE PACKING and INTEGRITY changed to FOR DAMAGE

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Gowning (Personnel)

- Added **requirement for visual inspection** of garments for cleanliness & integrity (as well as sterilisation check) when unpacking for use – this it at the customer and also in our cleanroom use GOWN INTEGRITY CHECK has been added on exit by the user

- Added DAMAGE TO GARMENTS MAY NOT BE INDENTIFIED BY VISUAL INSPECTION ALONE, SO THE QUALIFICATION SHOULD CONSIDER ANY NECESSARY GARMENT TESTING REQUIREMENTS – this may lead to more questions from customers

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Gowning (Personnel)

- Change to **footwear** such (as overboots) in Grade A/B (ISO 4), these **must** be sterilised (no longer sufficient to just disinfect)
- Separate laundry facilities for such clothing are desirable. Inappropriate treatment of clothing will damage fibres and may increase the risk of shedding of particles. This has been changed to CLEAN AREA CLOTHING SHOULD BE CLEANED IN A DEDICATED LAUNDRY FACILITY USING A QUALIFIED PROCESS
- Addition of – GRADE A/B Dedicated garments are to be worn under a sterilised suit

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Our Interpretation

Section	Line No.	Statement	Our Interpretation
4	181 -186	Only the minimum number of personnel required should be present in cleanrooms. The maximum number of operators in critical areas should be determined based on QRM principles, documented in the contamination control strategy, and validated during activities such as initial qualification and aseptic process simulations, so as not to compromise sterility assurance. This is particularly important during aseptic processing. Inspections and controls should be conducted outside the clean areas as far as possible.	Risk Assessment/Validation on worse case for number of operators
	210 - 214	There should be systems in place for disqualification of personnel from entry into cleanrooms, based on aspects including ongoing assessment and/or the identification of an adverse trend from the personnel monitoring program. Once disqualified, retraining and requalification is required before permitting the operator to have any further involvement in aseptic practices.	Procedures should include all reasons for disqualification, be this failing of number of finger-dabs, aseptic gowning, medical reasons

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Our Interpretation

Section	Line No.	Statement	Our Interpretation
	241-243	Handwashing, changing & Managing Garments - added requirement for visual inspection of garments for cleanliness & integrity (as well as sterilisation check, ie colour indication) when unpacking for use.	This is at the 'use' of our garments, be this at the customer or using in our own cleanrooms, checks needs to be made
	244 - 245	Reusable garments should be replaced based at a set frequency determined by qualification or if damage is identified.	This would be primarily be for sterile production areas and garments used
	266 - 267	Gowning Requirements for Classified Areas– in addition to the sterile eyewear & socks, change to footwear in Grade A to B (ISO 4/5), these must be sterilised (no longer sufficient to just disinfect).	This is for ISO 4/5 (Grade A/B). Grade C/D stays at 'appropriately disinfected or sterilised shoes or overshoes'

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Our Interpretation

Section	Line No.	Statement	Our Interpretation
	276 - 278	Outdoor Clothing & Facility Clothing - there is a recommendation for dedicated socks to be worn prior to entry into changing rooms for Grade B and Grade C.	This is a RECOMMENDATION only
	281-282	Grade A/B – added requirement for sterile eyewear and garment change at least every work session.	
	286 - 287	Clean area clothing should be cleaned, handled and worn in such a way that it does not gather additional contaminants which can later be shed.	Cleaning of garments, including packing should take place in Cleanrooms

Our Interpretation

Section	Line No.	Statement	Our Interpretation
	288 - 289	Separate laundry facilities for such clothing are desirable. Inappropriate treatment of clothing will damage fibres and may increase the risk of shedding of particles.	Implies outsourcing to textile specialist versus inhouse operations
	290 - 291	Washing & Sterilisation of Cleanroom Garments – added requirement to check the integrity after washing and prior to sterilisation	This should be part of the process during folding and there should be some packaging Integrity testing, seal checks, vacuum testing etc – question is do we need to document that this is carried out ?
	299 - 300	The ambient temperature and humidity should be set to prevent shedding due to operators becoming too cold (leading to excessive movement).	The question is what temperature should this be – people are different – we should be following the cleanroom specifications and the monitoring of staff

Cleanroom Design / Classification

The requirement to define 'in operation' and 'at rest' conditions.

Portable particle counters should be with short tube lengths - units with long tube lengths are not acceptable for classification purposes (although the length is not specified) This has now been clarified : THE TUBING LENGTH SHOULD BE NO GREATER THAN 1 METER WITH A MINIUM NUMBER OF BENDS AND BEND RADIUS SHOULD BE GREATER THAN 15CM.

Our Interpretation

Section	Line No.	Statement	Our Interpretation
5	363 - 367	Typically, airlocks used for personnel movement are separate to those used for material movement. They should be flushed effectively with filtered air. The final stage of the airlock should, in the at-rest state, be the same grade as the area into which it leads. The use of separate changing rooms for entering and leaving clean areas is generally desirable.	
	390 - 392	The movement of material from clean not classified (CNC) to grade C should be based on QRM principles, with cleaning and disinfection commensurate with the risk.	Risk assessment could be undertaken, but this is primarily for our pharmaceutical customers
	519-520	The requirement to define 'in operation' and 'at rest' conditions	This is a change as previously it could have been one or the other for Validation. The monitoring frequency and number of points is defined in the ISO Standard.
	629-631	Portable particle counters should have short tube lengths - units with long tube lengths are not acceptable for classification purposes	There are no lengths specified so the rule should be ‘as short as reasonably possible’

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Cleaning and Disinfection

Cleaning & Disinfectant in previous versions they were treated separately these have now been brought together as you cannot have one without the other..

In rotation, it now references that a sporicidal agent should be used.

Reference is also made to disinfectant qualification, for both cleanrooms and for transfer disinfection (introducing items into cleanrooms). Disinfectant efficacy testing should be carried out by the facility independently.

Disinfectant effectiveness – clause enhanced on demonstration of effectiveness of the shelf life and its use (type of surfaces, method of application) of the disinfectants, as well as the effectiveness of the disinfectant programme

“Disinfectants and detergents used in Grades A and B should be sterile prior to use”

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Our Interpretation

Section	Line No.	Statement	Our Interpretation
5	569-578	The updated now brings together Cleaning & Disinfectant whereas in previous versions they were treated separately. The routine is you need to clean first to remove the physical soiling, before you disinfect – the microorganisms will 'hide' under the soiling if not, so cleaning and disinfection should always be one regime.	This is part of the CCS Audit Checklist to ensure that plants are complying to this
		As well as the reference to using two different disinfectants in rotation, it now references that a sporicidal agent should be used. Reference is also made to disinfectant qualification, for both cleanrooms and for transfer disinfection (introducing items into cleanrooms). Disinfectant efficacy testing should be carried out by the facility independently. All sites should have validated the cleaning regime the frequency is revalidation is not set. The sites must be able to proof that the cleaning regime is working, environmental monitoring results/trends are a good indication.	There are tests that can be completed, in addition to our normal environmental monitoring and is to check on the 'killing of ALL inhouse fauna & flora", this is a very intensive action and maybe a 'one off' exercise – it is very time consuming and expensive as external laboratories are required, but it something that a pharmaceutical customer may ask to be completed

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Our Interpretation

Section	Line No.	Statement	Our Interpretation
	569-578	Disinfectant effectiveness – clause enhanced on demonstration of effectiveness of the shelf life and its use (type of surfaces, method of application) of the disinfectants, as well as the effectiveness of the disinfectant programme.	This is primarily for pharmaceutical customers to action, but we should have a justification for NOT doing this – ie we are not regulated to GMP