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## New Guidance for Sterile Products Manufacture is Coming: Review of EU GMP Annex 1

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By **Tim Sandle** Jan 23, 2018 8:00 am PST

### Introduction

There are two major, global guidance documents for sterile products manufacture: the FDA guidance, last revised in 2004 (1), and Annex 1 of EU GMP (2). It is Annex 1 that has recently undergone a substantial revision, albeit in draft form; now containing 269 total clauses (compared with 127 in the most recent version). The importance of the new Annex 1 draft is that it not only signals changes in approach from European regulators around the safeguards needed for sterile products manufacture, it further signals a new global direction given that the FDA took part in the document review through the PIC/S convention.

Annex 1 of EudraLex “The Rules Governing Medicinal Products in the European Union” forms part of Volume 4 of the European guidelines (2). The purpose of the current Annex, and its continuation as a new, finalized version expected later in 2018, is to emphasize that the manufacture of sterile products is subject to special requirements. These requirements are necessary in order to minimize risks of microbiological, particulate and pyrogen contamination of sterile products; and also, to provide guidance as to how sterile products are best protected. This guidance embraces personnel training, equipment qualification, cleanroom design and environmental monitoring.

The trigger points for the revision to the Annex included emergence of new technologies, inadequate root cause analysis and ineffective CAPA, poor implementation of ICHQ9, and also in relation to various points of ambiguity in the interpretation of the Annex 1 requirements.

Annex 1 of EU GMP was first issued in 1989 and it has undergone no major revision since 2007 and no change whatsoever since 2009 (in 2009 there was a minor point of clarification about the required air supply grading for oversealing - Grade A air supply) (2). The lack of an update through the intervening years has been notable in the context of updates to cleanroom technology and the appearance of new types of rapid microbiological methods. In 2014 it was announced, during the conference season rounds, that the Annex was set to go into review.

The release of the draft has been a lengthy process; a signal that the draft was imminent was first sent via a January 2015 issued ‘Concept Paper’ (3). There are also several points drawn from a European Medicines Agency sterile products guideline issued in 2016 (4) (which still remains in draft form, at the time of writing).

The concept paper was preceded by several ‘coming soon’ messages. The draft was finally issued, via the European Medicines Agency, during the third week of December 2017 (5). The reasons for the protracted release process has no doubt been due to national differences over the revisions to certain technical aspects of the document.

There are four broad areas of change to the draft, in terms of tone and emphasis. These are reflected at various intervals in the document (often through repeated occurrences). These areas are:

1. The global acceptance and implementation of ICH Q9 (Quality Risk Management) and Q10 (Pharmaceutical Quality System), is not reflected in the current Annex. The new draft contains many references to Quality Risk Management (QRM) in particular, emphasizing that QRM should be used as a proactive tool. There are now 92 instances of the word “risk” in the new draft, an increase from 20 in the previous version.
2. There have been advances in sterile manufacturing technology, especially with RABS and isolators. There have also been advances with rapid microbiological methods, which the draft Annex acknowledges.

3. There was some ambiguity with the current version and these needed correction or clarification
4. Annex 1 is often beyond sterile manufacturing, including aspects of non-sterile manufacturing. The scope of the new draft has been modified and broadened to reflect this.

There is also the new requirement for a formal, holistic contamination control strategy. The expectation now appears to be for a formal document which reflects the site-wide strategy for minimizing contamination control with respect to sterile manufacturing.

The purpose of this article is to review the primary changes, in relation to these broad themes, and to better understand the new paradigm for sterile drug products manufacture. This will be helpful for those wishing to comment on the draft and to those seeking to prepare for the using of the final document (anticipated to be later in 2018), since many of the key concepts are unlikely to change.

### **The Change Process**

The update of the Annex has taken the course of some three to four years, following the declared intention by the European Medicines Agency to begin the update process in late 2014. The resulting product has expanded considerably in length, increasing from around 15 pages to 50. In addition there are now 269 different clauses (up from around 100 in the current version, and many of these expanded upon). Moreover, some 100 clauses contain no link with an existing clause. It is also notable that 14 clauses from the previous revision that are not present in any form in the update and that just 40 clauses are effectively unchanged from the original version.

Included among the new sections are single use technologies; aseptic operator qualification; the application of Quality Risk Management to various topics; disinfectant qualification for cleanroom surfaces; process water systems, including the manufacture of Water-for-Injections; other utilities and closed manufacturing systems. Many of these are addressed, together with other updates, in this article.

### **Introductory Sections**

The draft Annex opens with a contents list and it is divided into eleven parts, making it easier to navigate compared with the previous version (which lacked any such document guide). This is then followed by a section titled 'Scope' (whereas the current Annex enters straight into a declaration of 'principle', which discusses sterile products in general). With the new Scope section, the new draft contains a wider definition of sterile products (sterile active substance through to finished dosage form); variations are noted in terms of batch sizes, packaging materials and the types of technologies used to produce sterile products.

References is made here to Quality Risk Management (QRM) for microbial contamination control. That QRM needs to be a proactive exercise is emphasized here and this point is repeated several times throughout the document; reference to QRM aligns the Annex with ICH Q9 "Quality Risk Management" (6). In terms of language the phrasing is not always elegant or consistent: there are several references to actions as "preventative"; here, unless the guidance is specifically talking about CAPA, in which case then it would be customary to use the word "preventive".

The Scope section further notes that that the contents may be applicable to certain types of non-sterile processing. This is in relation to microbial, particulate and pyrogen controls, where the principles can be applied to the design of controlled environments, gowning, and personnel practices. This is probably a reflection of many non-sterile products manufacturers using the Annex 1 guidance to set some internal standards for microbial control.

Following Scope, there is a section titled Principles. This section addresses a number of important areas. The first addresses qualification and validation. Here reference is made to equipment used in cleanrooms; facilities (cleanrooms, utilities); and process design. The draft states that users must follow other EU GMP Annexes, particularly Annex 11 ('Computerised Systems') and Annex 15 ('Qualification and Validation'). This connects up Annex 1 to other parts of EU GMP, in a formal way, for the first time.

Reference is made to personnel, indicating early on that people are critical to processes. The point made is about the importance of employing personnel with the appropriate skills, training and attitudes, focused on "protection of sterile product". This applies to manufacturing, packaging and distribution in the form of skills, training and attitudes. The latter two areas called out: packaging and distribution are often excluded from contamination control awareness courses in companies so attention may need to be paid here. The skills required are, according to job function: process, engineering and microbiological. Of

interest is the reference to 'attitude' which infers greater emphasis on human behaviors and with employees being content and motivated to produce a high-quality product.

### **Contamination Control Strategy**

A substantial part of the opening section is given over to each facility having a detailed, facility-specific contamination control strategy. To be effective this needs to be an approach that can assess seemingly isolated contamination events holistically and which is capable of putting appropriate corrective and preventive actions (CAPA) in place (7). This is intended to signal a new paradigm in terms of contamination control, shifting the risk review process to one that assesses the impact of a contamination event in a far wider context.

The main elements of such a control strategy are:

1. Design of both the plant and process.
2. Equipment and facilities.
3. Personnel.
4. Utilities.
5. Raw Materials Control – including in-process controls.
6. Product containers and closures.
7. Vendor approval – such as key component suppliers, sterilization of components and single use systems, and services.
8. For outsourced services, such as sterilization, sufficient evidence should be provided to the contract giver to ensure the process is operating correctly.
9. Process risk assessment.
10. Process validation.
11. Preventative maintenance – maintaining equipment and premises (planned and unplanned maintenance) to a standard that will not add significant risk of contamination.
12. Cleaning and disinfection.
13. Monitoring systems - including an assessment of the feasibility of the introduction of scientifically sound, modern methods that optimize the detection of environmental contamination.
14. Prevention – Trending, investigations, corrective and preventive actions (CAPA), root cause determination and the need for more robust investigational tools.
15. Continuous improvement based on information from the above systems.

With each of these different elements it is notable that they are not confined to biocontamination, since reference is also made to subvisible particles (the classic appearance tests) and the overall appearance of the pharmaceutical product.

The draft makes reference to ISO and other standards which should be reviewed when putting the control strategy together (although not directly called out, as many commentators had hoped, this would infer attention is paid to ISO 14698 Parts 1 and 2) (8). Also, to be considered in the strategy are 'modern methods' (read rapid microbiological methods) and the process of continuous improvement. This signals to manufacturers that they need to continually surveying industry trends for the best available technologies to ensure contamination control.

The draft also emphasizes that the contamination control strategy, to be effective, must be regularly reviewed in terms of its appropriateness and also in terms of how well CAPA are being applied. This includes not only considering the effectiveness of investigation outcomes but also regular reviews of trend data.

### **Pharmaceutical Quality System**

The first main section of the draft refers to the Pharmaceutical Quality System, a quality system that each manufacturer should have in place. While general matters are covered in Chapter 1 of EU GMP, the draft Annex makes reference to specific aspects for sterile products manufacture. These include:

- The proactive use of risk management.
- Regular review of risk assessments.
- Rationales in place to address different categories of risk arising from risk assessments.
- Employing staff with sufficient expertise to undertake risk assessments.
- Use of effective root cause and CAPA.
- Those tasked with releasing products must be fully conversant with risks and quality issues.

The first two bullet points signal the continuing reference to risk management and risk assessment throughout the document.

In keeping with earlier comments, the process of risk assessment is not simply confined to manufacturing, it needs to extend to packaging (primary and secondary) and to the distribution of the finished medicinal product, thereby embracing the requirements of Good Distribution Practice.

## **Personnel**

There is a large section within the draft dedicated to personnel. Within this personnel section, the content has considerably increased in the draft document. The section opens with a comment about restricting the numbers of personnel permitted to enter cleanrooms. The recommendation is that personnel numbers, especially in sterile manufacturing areas, is minimized based on risk assessment. This acknowledges that the biggest risk of microbial contamination in cleanrooms derives from people, principally through shedding and by touching critical surfaces (9).

With controlling access to cleanrooms there is reference made to the importance of on-going checks, such as those undertaken by the Quality Unit, being completed outside of the cleanroom. This infers the use of inspection windows or use of a closed-circuit camera system. A further restriction applies to Microbiology staff who handle microbial cultures, suggesting some level of internal control to prevent staff working on the identification bench carrying out environmental monitoring related tasks since the new addition indicates that such staff should not normally enter aseptic processing areas.

As expected, training plays a significant part in the personnel section. This extends to everyone entering the cleanroom, including cleaning and maintenance staff. The minimum basis for a training program is set out as to include: hygiene, cleanroom practices, contamination control, aseptic techniques, and potential safety implications to the patient of a loss of product sterility and in the basic elements of microbiology. For access into the higher-grade cleanrooms (Grades A and B), personnel are expected to have completed aseptic process qualifications (such as through a media fill). An exception is made for maintenance staff under exceptional circumstances, although procedures need to be in place to describe how this will be controlled.

Core to training for any person entering a cleanroom is a gowning assessment; this should also include samples of personnel, such as contact plates of their suits and finger plates (10). This monitoring should also be conducted following each critical activity. Here there is additional reference to some of these samples being taken independently, such as by Quality Unit personnel. With gowning, a reference to fully enclosed eyewear has been added – effectively this means the wearing of goggles. This is something the U.K. MHRA have been pushing for over the course of several years.

Other new additions include having a system for reporting ill-health plus periodic health checks; requiring the enter phase into a building to have handwashing facilities; and for staff entering Grade B or C cleanrooms to have undergone an initial change to remove outdoor clothing and to don cleanroom 'scrubs' prior to accessing the final stage changing room.

Environmental control appears under the personnel section. A notable change is with the removal of the reference to a set temperature range for Grade B cleanrooms, with the longstanding  $18 \pm 3^{\circ}\text{C}$  temperature range dropped. Reference to humidity has been added, with phrase: "ambient temperature and humidity should be met to prevent shedding due to operators becoming too cold (leading to excessive movement) or too hot" now appearing. Essentially, this a call for further risk assessment. Such a risk assessment should also include factors such as how long an operator should spend working in a Grade B cleanroom (here the answer will need to take account of the temperature and humidity).

## **Cleanroom Design**

There are various references to the design and operation of cleanrooms in the Annex. One notable change is with the draft Annex now having the potential intent to mandate HEPA (or higher) grade filtration in all classified areas (including Grade D). Hitherto, a Grade D area could be, at least in theory, without the need for HEPA filtration. The text, as it stands in the draft, is a little ambiguous and may be altered following the consultation period.

Added to section 3 is the requirement for each manufacturer to define 'in operation' and 'at rest' conditions for all cleanrooms or suites of cleanrooms. This is because facilities differ, although "at rest" is typically the room complete with all "HVAC systems, utilities functioning and with manufacturing equipment installed as specified but without personnel in the facility and the manufacturing equipment is static" and "in operation" taken to be "the condition where the installation is functioning in the defined operating mode with the specified number of personnel working." It is also suggested that clean up procedures, rest periods and any other variable conditions be nominated in the definition.

Unfortunately, with the draft there remains some ambiguity around 'Grade A'. This is a carry-over from the 2009 update, where the Annex refers to "Grade A conditions" for aseptic processing and to "Grade A air supply" for oversealing. The requirements for "Grade A air supply" have a point of discussion ever since they appeared, with the consensus being for assessing Grade A 'at rest'. To complicate matters further a new reference appears to "Grade A environment". Although there is now a glossary at the end of the Annex, there remains insufficient clarity between these three terms.

A further change is with the maintenance of laminar conditions which must be demonstrated in open applications compared with in isolators/glove boxes where "lower conditions are allowable." The continuation of the word "laminar", interspaced with uses of the more conventional "unidirectional", are a further cause of ambiguity in the draft version.

On the subject of unidirectional air there is an extension, with clause 5.12, from this being a requirement of Grade A environments to include Grade B in relation to the cleanroom used to house a RABS (notably not an isolator). This could prove challenging to some facilities. A continuing measure of unidirectional air is the monitoring of air velocity; here warning systems will need to be in place to alert as to any reduction in air velocity or pressure.

With the cleanroom used to contain an isolator, where this is a positive pressure isolator, the Annex addresses a long-standing discussion over the appropriate background environment (as to whether Grade C or Grade D is appropriate) by settling on Grade D.

Further to design, transfer hatches without airflow have been called out as being of concern. The Annex stipulates that hatches, together with airlocks, should be flushed effectively with filtered air, for both personnel and material transfer.

### **Barrier Technologies**

Containment devices receive a number of references within the Annex, in terms of RABS (which are described as passive, open or closed) and isolators. While there is no direct requirement for medicines manufacturers to use such devices, the Annex infers by the statement "RABS, isolators or closed systems, should be considered in order to reduce the need for interventions into the grade A environment and minimize the risk of contamination" that barrier technology should be being adopted. With all forms of RABS, the Annex requires that studies should be performed to demonstrate the absence of air ingress.

With isolators, there is reference to the importance of selecting the correct isolator gloves; those with good mechanical and chemical resistance, and for testing gloves for leakage prior to each production batch (glove integrity testing). With both RABS and isolators there is the requirement that all items transferred in be decontaminated by a disinfection or sterilisation process, and that these processes be validated.

### **Cleanroom Classification**

With cleanroom classification, classification according to ISO 14644-1 is mandated and this has added to section 4. In addition, limits for non-viable particles in Grade A through D environments are set-out in section 5 ISO class equivalents are helpfully included alongside EU GMP grades; with a Grade D – ISO class 8 equivalency stated for the first time).

In keeping with the revisions to ISO 14644, the requirement to monitor for particles of a cut-off size of  $\geq 5.0 \mu\text{m}$  has been removed. Importantly, the exclusion of  $\geq 5.0 \mu\text{m}$  applies to classification only; the continued monitoring of these particles remains a requirement for monitoring of aseptic processing and other cleanroom activities as set out in section 9. Confusingly, the monitoring requirements for classification and 'routine' monitoring are contained in different sections and separated by 25 pages.

Further with classification, the draft Annex discusses additional requirements for cleanroom classification (beyond ISO requirements) in critical areas. This is in terms of adding extra locations based on risk and examples such as stopper bowls inside filling machines are referenced.

Portable counters with short tube lengths are nominated as appropriate equipment for classification; this implies that central units with long tube lengths are not acceptable for classification purposes. While tubing lengths are not specified, this requirement may require investment in new equipment for some manufacturers.

## **Filters**

Sterile filtration is a critical step for aseptically filled products, where products are passed through a 0.22 µm filter, with pressure and time controlled. A key measure is an assessment of the product bioburden prior to filtration. Surprisingly the Annex makes no reference to the European CPMP guidance for 10 CFU/100mL (11), and instead makes a comment about a requirement to link bioburden limits to filter efficiency, which seems out of step with most approaches (12).

The Annex also clarifies the need for conducting pre-use post-sterilization integrity testing (filter integrity test performed immediately before use). This is an issue that has begun to be raised by European Medicines Agency inspectors ahead of the draft Annex appearing.

## **Sterilization**

The sections on sterilization have been expanded, with different sterilization processes given subsections. A general comment about sterilizer qualification is made concerning temperature assessment. This is that temperature probes need to be checked against a second independent temperature probe located at the same position.

For moist heat sterilization, the important validation parameters are spelt out, namely: equilibration time, exposure time, correlation of pressure and temperature and maximum temperature. Other sterilization technologies discussed are dry heat sterilization, sterilization by irradiation, and sterilization using ethylene oxide. Of these, ethylene oxide is presented as a technology to be selected only when no other method is suitable. This relates to concerns with the potential for residuals of the gassing agent to remain.

## **Aseptic Processing**

Central to sterile products manufacture, for products that cannot be terminally sterilized, are the controls required around aseptic processing. Here the days of not using full barrier technology for aseptic processing, quite rightly, appear to be numbered. Tube draft runs: "RABS, isolators or closed systems, should be considered in order to reduce the need for interventions into the grade A environment and minimize the risk of contamination." Although what RABS (restricted access barrier system) is and what it is not could be made clearer among the references in the Annex to closed, open, active and passive RABS.

With aseptic processing there is new clarification that, within Grade A, monitoring must be performed for all of setup and critical operations. There is a further comment that sample frequency and size must be such that all excursions are captured. With sample sizes there is clarification on sample size requirements, indicating that sample sizes do not necessarily need to meet full classification volumes.

The control of operation time is discussed in several places, perhaps with the view that times outside what is ordinarily seen can lead to an increased contamination risk. Time is referred to with:

- Pre-fill time should be assessed as part of media fills.
- A time limit required for aseptic assembly
- Maximum exposure time of sterilized containers and closures prior to closure. This infers oversealing times need to be set. This has an impact with regards to ensuring crimping is conducted expediently (see the discussion about oversealing below).
- For items sterilized "in house" (such as by autoclaving), these need to be stored in Grade A or B, using appropriately sealed packaging and a maximum hold period must be established.

With the previous point (in relation to cleanroom classification), concerning the need to continuing monitoring for particles of the cut-off size  $\geq 5.0$  µm, some information on how to interpret particle count excursions is detailed. This may prove useful when investigating counts, particularly as a prompt as to what impacts and mitigations might be considered.

Single-use systems and technologies are mentioned and their use is generally encouraged. There are some concerns with single-use technology that need to be addressed, according to the text. These are the interaction between the product and product contact surface (notably adsorption, leachable and extractables).

The Annex sets out the main elements for Grade A processing, which allows manufacturers to risk assess the essential elements. These have been put into check-list form by this author, and they are:

- Maintaining the critical processing zone.
- The aseptic assembly of filling equipment.
- Aseptic connections (these should be sterilized by steam-in-place whenever feasible).
- Special focus on aseptic compounding and mixing.
- The risks around the replenishment of sterile product, containers and closures.
- Concerns around the removal and cooling of items from heat sterilizers.
- Staging and conveying of sterile primary packaging components.
- Aseptic filling, sealing, transfer of open or partially stoppered vials, including interventions.
- Loading and unloading of a lyophilizer

These elements could be cross-referred back to the contamination control strategy and implied risk assessment.

### **In-Operation Particle Counting**

Requirement to monitor clean rooms routinely 'in operation' has been expanded to require justification of monitoring locations through risk assessment. Auditors will expect to see formal risk assessment for the selection of all monitoring locations, including justification of critical locations. Use of classification and previous monitoring data, where available, should form part of the assessment. The recommendation states that monitoring locations should NOT be based on ISO 14644.

Requirement for continuous monitoring for Grade B areas – The new Annex clearly requires “a similar system” to Grade A continuous monitoring in Grade B areas, however, there is some confusion as to what this actually entails. It probably means that the Grade B monitoring system should operate at a frequency and sample size to detect changes in contamination levels and system deterioration, including the triggering of alarms. In addition, it can also be inferred that:

- The sample frequency may be less than for Grade A systems
- The more effective the segregation between Grade A and B zones, the less important the Grade B sampling becomes.
- The capture of interventions and transient events is not paramount in Grade B monitoring.

### **Cleaning and Disinfection**

The references to disinfection have been expanded. The need to rotate between two different disinfectants remains, although the fact that one of these should be a sporicidal agent is a new one. Reference is also made to disinfectant qualification, for both cleanrooms and for transfer disinfection (the act of introducing items into cleanrooms or between cleanrooms of different grades). Not only is disinfectant efficacy testing described as important the Annex infers that this is a type of testing that needs to be carried out by facility independently. One reason for this is because the different types of surfaces found in different facilities, together with regional variations with the microbial flora. With the discussions about disinfectants in section 5, references are made to the need to assess the bioburden of non-sterile disinfectants and to assign expiry dates.

### **Freeze-Drying (lyophilization) and Grade A Containment**

Environmental requirements for partially stoppered freeze-drying vials detailed – As a standalone requirement, this section is clear; partially stoppered vials must be maintained in Grade A conditions until fully stoppered, even during transfer to freeze drying. However, when considered against section 34 (which allows transport in sealed containers through Grade B environments), there is some confusion.

For vials prior to oversealing the draft requires “Grade A conditions” are maintained. Here there is a distinction from the Grade A air supply required while oversealing. In light of the earlier point about ambiguity with regards to Grade A, the change to “Grade A conditions” sees the use of the language used as per aseptic filling. Does this new form of words infer monitoring of vials held prior to oversealing? (13) This is a matter that will hopefully be clarified through the consultation period.

Section 118 of the draft introduces a definition of integral container closure, indicating this is the stoppered and capped vial. The emphasis upon the capped vial is new; this possibly has some impact with regards to ensuring crimping is conducted

expediently, and with the environmental requirements discussed above. For the oversealing process, there is some new information provided for handling of vials rejected due to missing/displaced stoppers.

With oversealing, there is no mention of viable monitoring. However, the new guidance indicates that smoke studies should be performed, albeit that unidirectional (laminar) flow does not need to be demonstrated. There is a further comment that air velocities are to be justified by the manufacturer.

### **Media Filling Trials**

Section 69 provides specific and prescriptive requirement for the acceptable failure limits in media fill studies, based on filling run size. The formally specified statistical approach of >99.9% at 95% confidence interval is no longer applicable to determine acceptable failure limits. Instead the expectation is zero, irrespective of the media fill size. This will create tighter limits for those manufacturers who have yet to adopt more stringent, especially for large batch sizes.

A further point with media fill failures is that, following investigation and root cause analysis, the previous 'suggestion' for running one media fill has changed to a near requirement to run three media fills. Some may question this as being above and beyond should, say, the reason for the media fill failure be traced to a simple operator error. Others may regard three runs as the core principle of revalidation, in order to rule out chance.

### **Visual Inspection and Containers**

Sterile, medicinal pharmaceutical products need to be sterile, apyrogenic and particle free. This latter point relates to visual inspection, a subject that has not been covered in any great detail by the Annex before. Each facility is required to have a list of critical deficiencies – such as particle, hairs and turbidity – and to subject operators to regular assessment. The assessment should be under practical conditions, with control of inspection time, line speed, and component size. To capture operator fatigue the test should be executed at the end of the shift.

There are several references made to container integrity. The first is that containers sealed under vacuum should be tested for maintenance of vacuum after an appropriate, pre-determined period and during shelf life (which relates to a stability studies). The second is that container closure integrity testing needs to consider the impact of transportation, a further reference to Good Distribution Practices. The third point is that microbial ingress studies (or alternative methods) should be utilized to determine the acceptable stopper height displacement.

### **Water Systems and Other Utilities**

During 2017 the European Pharmacopeia moved into closer alignment with the United States Pharmacopeia in permitting Water-for-Injection (WFI) to be prepared, from purified water, using alternative methods to distillation (in essence, reverse osmosis). Annex 1 acknowledges this, although several warnings and caveats are provided for manufacturers intending to alter the method of producing WFI. Much of this centers on minimizing the risk of biofilm formation and hence on downstream endotoxin control. This appears to be based on an earlier position paper from the European Medicines Agency (14). The importance of WFI systems being hot water systems remains with the stipulation that WFI needs to be circulated at temperatures >70oC.

One part of the water monitoring section has somewhat ambiguous wording. This is a requirement that a sample is taken from the worst-case location of a process water system each time the system is used for manufacturing. As this reads this requirement is unrealistic, although this is probably a reflection of the phraseology used. Given that some systems may be used multiple times per day it is instead assumed that the Annex means sampling at a sufficiently high frequency as so to assess a contamination problem, but not at each time of use. Few Microbiology laboratories could cope with the workload.

A reference to trending data is made, something which the draft Annex applies to all utilities in the statement: "Results for critical parameters of the high-risk utility should be subject to regular trend analysis to ensure that system capabilities remain appropriate." This could create issues for facilities where the monitoring of cleanroom controls like pressure differentials remain based on audible alarms and without the means for electronic data capture.

With other utilities, compressed gasses are called out as being potential sources of microbial contamination. As with other parts of the pharmaceutical manufacturing process that require filtration, the integrity of the filters used to supply compressed gasses received attention. There is an added requirement to include filter verification data in batch records with the sentence: "Confirmation of the integrity of the final sterilization gas filter need to be as part of the batch release process."



## Grade C and D Monitoring

Requirements for Grade C and D cleanroom routine monitoring is detailed in the draft Annex. Here there is a requirement to use risk management techniques to justify locations, number and frequency of samples for routine monitoring of Grade C and D areas, in relation to both particle count and viable count monitoring (15). Unlike for Grades A and B due aseptic products manufacture, monitoring need not be continuous, monitoring episodes should be more frequent than requalification. Importantly, the risk assessment should justify the frequency.

With the lower grade cleanrooms the way that such cleanrooms interface with other areas is called out in terms of airlocks and transfer hatches. There is also a reference made, for the first time, to 'controlled but not classified areas'. Here the movement of material from controlled but not classified to Grade C needs to be based on QRM principles, with cleaning and disinfection commensurate with the level of risk assessed.

## Rapid Microbiological Methods

Rapid methods are mentioned for the first time in the draft (in section 9 for environmental monitoring and section 10 for end-product testing, such as sterility testing). While it is disappointing that further detail is not presented, the references to rapid microbiological methods at least paves the way for considering alternatives like real-time spectrophotometric counters. The Annex emphasizes that these methods should be considered only after validation and "as long as they are demonstrated to be at least equivalent to the established methodology"

## Records and Data Integrity

A surprising omission from the Annex is any reference to records or data integrity. This could be inferred by the cross-references to other chapters and Annexes in the draft. Nonetheless, given the significance that regulators have placed upon data integrity and especially given the vagaries around how data integrity principles can best be applied to microbiology laboratories (16), some mention at least might have been expected.

## Summary

The draft of Annex 1 signals a large number of changes for sterile products manufacturers to consider. This article has attempted to summarize, and to provide commentary where appropriate, on the most significant changes. It is not possible, or even necessarily productive, for a single article to go through each of the clauses point by point. It is important to re-emphasize that the document is a draft and that its contents might change after comments from the public and professional bodies have been received. However, for those who prefer to plan ahead it is unlikely that many of the core principles will alter and thus many of the points called out in this article are most likely to appear in the finished document.

Consultation on the Annex 1 draft closes on 20th March 2018. Any parties interested in providing input to the consultation process need to provide feedback directly to European Commission to: [Sante-Pharmaceuticals-B4@ec.europa.eu](mailto:Sante-Pharmaceuticals-B4@ec.europa.eu), with the title: "Targeted Public Consultation – Revision of annex 1 of EU GMP Guide".

## References

1. FDA. Guidance for Industry Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice, U.S. Department of Health and Human Services, Food and Drug Administration, Bethesda, MD, U.S., 2004
2. 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, European Commission, Brussels, Belgium, 2009: <https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-4/2008...>
3. EMA. Concept paper on the revision of annex 1 of the guidelines on good manufacturing practice – manufacture of sterile medicinal products, EMA/INS/GMP/735037/2014, issued jointly by the European Medicines Agency and the Pharmaceutical Inspection Convention: [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guidelin...](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guidelin...)
4. EMA. Guideline on the sterilisation of the medicinal product, active substance, excipient and primary container – draft, EMA/CHMP/CVMP/QWP/BWP/850374/2015, European Medicines Agency, London, U.K. (issued April 2016)
5. Annex 1 – Consultation Document, European Medicines Agency, December 2017: <https://picscheme.org/layout/document.php?id=1268>

6. ICH Q9 Quality Risk Management. ICH Harmonised Tripartite Guideline, Step 4, Geneva, Switzerland. 2005
7. Sandle, T. 2015 Development of a biocontamination control strategy, *Cleanroom Technology*, 23 (11), 25 - 30
8. ISO 14698-1:2003 Preview Cleanrooms and associated controlled environments -- Biocontamination control. Part 1: General principles and methods; Part 2: Evaluation and interpretation of biocontamination data, International Standards Organisation, Geneva
9. Sandle, T. (2014) People in Cleanrooms: Understanding and Monitoring the Personnel Factor, *Journal of GXP Compliance*, 18 (4): 1-5
10. Sandle, T. (2017) The people factor: investigating the gown, *European Pharmaceutical Review*, 22 (4): 23-26
11. European Agency for the Evaluation of Medicinal Products Committee for Proprietary Medicinal Products (CPMP) Note for Guidance on Manufacturing of the Finished Dosage Form, CPMP/QWP/486/95
12. Sandle, T. (2012). Making the grade in filters, *Cleanroom Technology*, December 2012, 20 (12): 19-20
13. Anon. White paper: PIC/S GMP Guide – Annex 1 Revisions & Interpretations, PharmOut, 2016
14. EMA. Questions and answers on production of water for injections by non-distillation methods – reverse osmosis and biofilms and control strategies, EMA/INS/GMP/443117/2017, European Medicines Agency, London, U.K.
15. Sandle, T. (2014) Applying spectrophotometric monitoring to risk assessments in biopharmaceutical cleanrooms, *Clean Air and Containment Review*, Issue 20, pp22-25
16. Sandle, T. (2016) Data Integrity Considerations for the Pharmaceutical Microbiology Laboratory, *Journal of GXP Compliance*, 20 (6): 1-12

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