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EU GMP Annex 1: What The 'Final' Draft Reveals

INTRODUCTION

In early 2018 in Volume 22 of the *Journal of GxP Compliance*, a review of the first proposed revisions to EU GMP Annex 1 was published (written by this author) (1). It was anticipated that, following a short period of public consultation, the final version would be issued and the first significant revision to the sterile products guidance would be completed and incorporated into the EU GMP framework.

However, things did not turn out quite like this. The proposed revision to the Annex (2), though signaling a shift in regulatory thinking in terms of sterile products manufacture (such as an acceptance of barrier technology and cursory acknowledgement of rapid microbiological methods), was met with a level of criticism as well as support. These two points of view were reflected in over 6,000 comments sent to the European Medicines Agency (EMA) (up until a closing date in March 2018) (3). Then nothing…until now, with a new draft being issued on February 18, 2020, curiously labelled version 12 (presuming the December 2107 draft was version 01, this means 11 redrafts which have not been made available to the public).

The new draft is generally similar to the December 2017 version, although there are some notable differences and the draft is, overall, easier to read and the use of scientific terminology is more consistent. This time the review process is more focused, with specific sections called out for review, and comments are only being sought from invited professional bodies or professional bodies who have written in expressing a desire to be involved with the review (which then required approval by the EMA). According to EMA (4):

> *"Due to widespread interest from industry following the first targeted consultation, and because of substantial modifications introduced in several sections, it was agreed to engage with stakeholders a second targeted consultation on the updated draft guidance (version 12) focused on the sections and/or significantly modified paragraphs that raised most concerns by stakeholders.*
>
> *The second targeted consultation aims at collecting experience from the sectors on certain manufacturing steps. The European Commission therefore expect to receive contribution from the European associations representing the sectors."*

The narrower focus of areas of the Annex 1 draft for public comment and the narrowing of voices to which the Agency will be listening to suggests there is a keenness to have the consultation process, final review, and final ratification completed in a reasonably short timescale, probably with the final version of the Annex issued during the course of 2020.

This paper reviews the new draft. In doing so the focus is on those aspects that are different to the 2017 draft, rather than spending much time comparing the 2020 draft with the current Annex 1 (which is dated 2009). Readers wishing to do this can refer to the 2018 *Journal of GxP Compliance* review. The reader should note that this paper contains some personal commentary at different points, either in praise of some of the updates or raising concerns about things that have not been changed which should have or with reference to some of the new things that have been added. Of course, the reader may not agree but the change is highlighted some that due consideration can be given.

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WHAT IS EU GMP ANNEX 1?

Before starting the review, and for the benefit of the more casual reader, there are two major, global guidance documents for sterile products manufacture: the FDA guidance, last revised in 2004 (5), and Annex 1 of EU GMP. Annex 1 of EudraLex "The Rules Governing Medicinal Products in the European Union" forms part of Volume 4 of the European guidelines (6) (there is also a WHO guidance, which generally mirrors Annex 1 and which is undergoing a similar 2020 consultation exercise) (7). The purpose of the current Annex, and its continuation as a new, finalized version expected later in 2020, 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 scope of Annex 1 relates to pharmaceutical companies who manufacture products within the European Union and those companies who import products into the European Union (including a post-Brexit United Kingdom).

Annex 1 of EU GMP 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). The lack of an update through the intervening years was especially notable in the context of updates to cleanroom technology and the appearance of new types of rapid microbiological methods.

CORE PRINCIPLES

Having stated in the introduction that the purpose of this article was not to spend time discussing points of continuity between the new draft and previous draft, the first draft did contain for areas of importance that will mark out the new Annex as a different type of document from the current in-place version. These remain consistent between the two drafts. Furthermore, there have been some changes in terms of emphasis with these core principles.

The principles are:

1. The global acceptance and implementation of ICH Q9 (Quality Risk Management) (8) 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 to reflect this.
5. There is the requirement for a formal, holistic contamination control strategy (which is now abbreviated to 'CCS' in the new draft). 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 (9). The requirements of the contamination control strategy have been widened (43 mentions, up from 19 in the 2017 draft), however, with the new draft, extending to the need to fully-understand and review design, procedural, technical and organizational controls. With the term 'contamination' it remains that contamination is used too broadly, and it would be useful if, for example, there was a specific microbiological concern that the nature of the contamination is referred to directly.

While the above have not changed, the references to Quality Risk Management are more extensive, with requirement to use QRM to review existing products and processes; new products and processes (where risk assessment needs to link to Quality by Design); and to address problems with procedures and processes, with the expectation that QRM becomes a key part of deviation management. There is no specific section on QRM in the draft. This is because the principles of QRM are intended to be ever-present in every section, as the draft states: "QRM applies to this document in its entirety and will not be referred to in specific paragraphs. Where specific limits or frequencies are written, these should be considered as a minimum requirement. They are stated due to regulatory historical experience of issues that have previously been identified and have impacted the safety of patients."

These elements reflect a significant shift in regulatory thinking towards a more risk-centric approach, accepting of new technology, and with seeing contamination control as a wide-range, interrelated and continuous concept (10).

RE-ORGANIZATION AND RETITLING

The new draft Annex has a slightly different title to the current version (and earlier draft). The current title of "Annex 1: Manufacture of Sterile Medicinal Products" is now tweaked to read "Annex 1: Manufacture of Sterile Products". The dropping of the word 'medicinal' broadens the scope to any sterile product, including active substances, sterile excipients, primary packaging materials and finished dosage forms. To add to this, the scope extends to packed sizes from single to multiple units, processes (highly automated systems and manual processes) and technologies such as biotechnology, classical manufacturing of small molecules and closed systems.

The new draft is easier to follow, and it is divided into eleven parts, which are presented across 52 pages (which means that it is two pages longer than the 2017 version). These sections are:

1. Scope
2. Principle
3. Pharmaceutical Quality System (PQS)
4. Premises
5. Equipment
6. Utilities
7. Personnel
8. Production and specific technologies
9. Viable and non-viable environmental and process monitoring
10. Quality control (QC)
11. Glossary

With 'premises and equipment,' this more common term replaces the 2017's draft use of "equipment and facilities." The 2017 sections were:

1. Design of plant and process
2. Equipment and facilities
3. Personnel
4. Utilities
5. Raw material control
6. Product containers and closures
7. Vendor approval
8. Process risk management

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9. Process validation
10. Preventative maintenance
11. Cleaning and disinfection
12. Monitoring systems
13. Prevention-trending, investigations CAPA
14. Continuous improvement.

The draft also embraces modern manufacturing approaches, in terms of barrier technology, robotics, and rapid methods.

CLEANROOMS, CLEAN AIR AND CONTAMINATION CONTROL TECHNOLOGY

It remains that the key changes between draft version 12 and the current version are with cleanrooms and clean air systems (as with the 2017 draft) (11).

Cleanroom design and qualification
With the overall design of cleanrooms, the draft stresses the importance of 'quality-by-design', with particular reference made to lay-out and process flow, where the process steps are reflective of an intent to maintain contamination control. This design concept extends to the necessity of conducting all non-essential processes outside clean areas.

Compared with the previous draft of the Annex, reference continues to be made to Annex 15 of the EU GMP guide ("Qualification and Validation") in relation to ensuring that equipment has been suitably qualified. However, the reference to the ISO 14644 standard has been dropped (except for particle counts) and instead the text makes reference to the specific series of tests required when a cleanroom is qualified. These tests are (where relevant to the design):

- Installed filter leakage and integrity testing.
- Airflow measurement - Volume and velocity.
- Air pressure difference measurement (with the new draft the specification changes from 10 to 15 pascals to a minimum of 10 Pascals).
- Airflow direction and visualization.
- Microbial airborne and surface contamination.
- Temperature measurement.
- Relative humidity measurement.
- Recovery testing.
- Containment leak testing.

Notably here is the task of microbiological monitoring. This is something that has been discussed in relation to the update of the ISO 14698 biocontamination standards, about adding a microbiological monitoring aspect to the classification of cleanrooms (6). This now appears to become a required part of the issuing of cleanroom certificates.

With particle assessments, the Annex keeps the requirement to count airborne particulates equal to or greater than 0.5 and 5.0 µm (which continues to create a difference with the FDA aseptic processing guidance, which refers to particles of ≥0.5 µm only). However, for Grade A zone and Grade B at rest, classification only needs to be for particles equal to or greater than 0.5 µm (hence the argument about the statistical limitations of measuring larger size particles which formed part of the 2015 ISO 14644 Part 1 update seem to have been accepted). The measuring of larger size particles for Grade A and Grade B areas is referenced as something that can be considered. The cleanroom classification expectations apply to the 'at rest' and 'in operation' states (with the 'in operation' state there is a suggestion that for aseptic processing areas that the exercise is

undertaken during media fills, in order to represent worst-case). With 'at rest' or 'static', this is said to be without personnel in the room (a change from 2017's without personnel in the facility) and with equipment "standing by for operation."

With the text relating to particle counts, it is unfortunate that the draft Annex continues to draw a distinction between viable counts (or 'viable particulates') and non-viable particle counts. The counts detected by a conventional particle counter cannot be differentiated to determine whether they are viable or non-viable, they are simply registered as a particle. Hence reference to 'non-viable' is inaccurate.

For selecting particle locations, the draft Annex states that the ISO 14644 methodology is to be followed, along with the additional expectation that, for aseptic processing areas, sample locations are positioned so that all critical processing zones like the point of fill and stopper bowls are included and based on a documented risk assessment.

Whilst there are no changes to requalification intervals (Grades A and B six-monthly and Grade C and D annually) additional text has been added stipulating that re-qualifications should be undertaken following any remedial works needed on equipment or where the facility requires work or where new equipment is added to the cleanroom, as assessed through change control. Other reasons for undertaking a re-qualification include change of room use and to reassess areas following a loss of power.

Recovery testing (or clean-up) testing has greater detail added. The revised draft now provides guidance that this particle testing begins from the 'at rest' state and that the requirement for a cleanroom is to recovery from a high level of particles back to its at rest classification is within 15 to 20 minutes. Some indication of the level of particles for the test would have been useful, as this is an area that often causes confusion for cleanroom operators seeking to perform this test.

Across all cleanrooms, a new requirement has been added for viable environmental monitoring to be conducted when classifying cleanrooms, in addition to the standard list of physical checks (including particulate levels).

Outside of classified cleanrooms, reference is made to 'controlled but not classified areas'. Here the movement of material from controlled but not classified to Grade C needs to be based on risk management principles, with means that the level of cleaning and disinfection and the control of materials needs to be commensurate with the level of risk assessed.

Cleanroom occupancy

An emphasis throughout the Annex is placed on the numbers of operators permitted in cleanrooms and changing rooms. For aseptic processing areas, the media fill sets the maximum numbers, whereas for other cleanrooms the expectation is that this is assessed through a risk assessment.

New particle limit for Grade D cleanrooms

For the first time the draft Annex provides guidance for Grade D particles, albeit for 'at rest' rather than for 'in operation'. Here a value of 29,000 particles for the ≥0.5 µm size particle is provided as the limit. The current Annex simply lists Grade D particles as 'separately determined', with no further guidance supplied.

More flexibility over unidirectional airflow velocity

The draft Annex offers more scope with unidirectional airflow velocities (notably 'unidirectional' is now consistently used throughout the text and all references to the archaic and unachievable term 'laminar' expunged – laminarity is a precise term referring to an
airflow moving in a single direction and in parallel layers at constant velocity from the beginning to the end of a straight-

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line vector) (12). With air speed, while the range of 0.36 – 0.54 m/s remains the general requirement at working height, this is presented in less stringent terms. Hence there is scope for companies to operate clean air devices outside of this range should be designed, provided that this is scientifically justified and detailed in the contamination control strategy. This takes account of variations with line and process configuration between different facilities. Included in this justification is the location for measurement and verification as to the appropriateness of the air speed as supported by airflow visualization studies ('smoke studies'). A further change is the removal of any reference to measuring air velocity at a specific location (the 2017 draft referenced a height of 150-300 mm of the filter face); this has been replaced with 'working height', which is an improvement and the position is now left to the user's discretion.

With a change with the new draft, airflow visualization studies need to be conducted in both the 'at rest' and 'in operational' states (previously the reference was just to 'in operation'). The draft Annex requires that following an adjustment to air velocities for qualified devices that part of the acceptance of the adjusted volume includes an airflow visualization to be conducted. For isolators that are 'closed' the Annex states that the air direction need not necessarily be unidirectional. This change is welcomed, in comparison with the previous draft, since given that the air within an isolator will have passed through a HEPA filter, and the barrier of the isolator keeps the internal environment free from external contamination, turbulent airflow can be an acceptable alternative to unidirectional airflow if the isolator has been appropriately qualified (turbulent airflow would not, however, be suitable for a RABS device).

Barrier technology

The Annex does not go as far as mandating the use of barrier technology; however, there is a recommendation that manufacturers consider adopting "appropriate technologies", such as Restricted Access Barriers Systems (RABS) or isolators. This is captured in part 4.3, which reads: "Restricted Access Barrier Systems (RABS) and isolators are beneficial in assuring the required conditions and minimizing the microbial contamination associated with direct human interventions in the critical zone. Their use should be considered in the CCS. Any alternative approaches to the use of RABS or isolators should be justified."

With the use of RABS one change between drafts that does not make sense is with changing the background requirement from Grade B (2017 draft) to "at least Grade B" in the 2020 draft. What is "at least" supposed to signifying here? If Grade A is expected – which is nonsensical because Grade A conditions cannot be consistently maintained if personnel are present – then state Grade A; if Grade B is still appropriate (which this author believes it is), then state Grade B. Adding terms like "at least" do not provide the necessary tightness of language required for pharmaceutical organizations to follow.

The recommendation extends to consideration of robotic systems, which will reduce the need for human intervention. With the emphasis upon barrier technology the Annex requires that any alternative must be robustly risk assessed.

With isolator technology, the text sates that pass through of items should be minimized and ideally go through a rapid decontamination chamber. Gloves are recognized as the weakest point with an isolator system, so consequently there is the requirement for glove leak testing at a minimum interval of before and after each batch (the leak assessment also extends to the main isolator unit as well). Here the time point for glove integrity testing has been improved. The 2017 draft stated that glove testing should be undertaken "following any intervention that may affect the integrity," something that was not technically feasible should an intervention occur mid-way through aseptic filling and it is also something that could lead to a contamination risk. This has now been changed in the 2020 draft to "a minimum at the beginning and end of each batch." This is far more sensible update. Also, with gloves, there is reference to the importance of selecting the correct isolator gloves; those with good mechanical and chemical resistance. The period of time between the replacement of gloves now requires justifying in the contamination control strategy.

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For the preparation of isolators for filling, the new draft stresses the importance of cleaning prior to disinfection (since the presence of residues can inhibit the ability of disinfectants to traverse microbial cell walls, which is necessary for the killing of microorganisms). In keeping with cleaning, the 'clean hold time' also requires qualifying and outlining in the CCS. Greater detail is provided as to the decontamination method and verification of the technology, and the stated aim of the decontamination process – to leave the isolator environment free of all viable microorganisms – is now clearly stated. Furthermore, there is a requirement to verify that the disinfectant used, in relation to any remaining residues, does not have an adverse impact upon the product. If a period of time is required prior to starting filling, so that any remaining disinfectant gas or vapor remains, this represents another step that requires qualification.

The text for the background environment for isolators used for aseptic processing has been revised. The 2017 draft stated Grade D for the cleanroom grade; the 2020 version indicates either Grade C or Grade D, inferring that if Grade D is to be used then this needs to be justified through a risk assessment.

A further change, with the set-up of filling line contained within barrier technology, is that a sporicidial disinfection process is used following set-up, as mechanism to reduce any microbial contamination that may have been presented during the assembly process.

Environmental conditions

The current version of the Annex sets limits for temperature for Grade B areas. This limit is no longer stated, and instead there is the requirement to adopt a risk-based approach for setting temperature and humidity requirements for any cleanroom grade. While the draft Annex does not go into specifics, maintaining operator comfort is important for both the operator and reducing excessive skin cell shedding into the environment.

The current Annex requires all connections for aseptic processing (such as vessel to manifold) to be performed under Grade A. The draft acknowledges advancements with sterile processing technology, permitting aseptic connections that use intrinsic sterile connection devices, designed to minimize any potential contamination from the immediate environment, to be performed in lower classified environments provided that the connection device has been appropriately validated to show no ingress of microbial contamination.

The revised Annex has added information relating to environmental controls in relation to pressure. In addition to revising the limit for pressure (as indicated above), there is a requirement that all areas with differential pressure have warning alarms in place, where the warning signals a potential problem with air supply. The guidance states that the alarm should "not be overridden without assessment and a procedure should be available to outline the steps to be taken when a warning signal is given." The advice also extends to alarm delays, indicating that the justification and reason for the delay must be outlined within the contamination control strategy.

Aseptic processing

In addition to the controls around aseptic processing captured in the above discussion around cleanrooms, the Annex has a large focus on applying contamination control principles to aseptic processing. Perhaps the most significant change is in relation to equipment sterilization when used for aseptic processing. The 2017 draft stated that critical surfaces with direct impact need to be sterilized (such as a filling manifold or stopper bowl); however, with the 2020 revision this now requires direct and indirect contact parts to be sterilized. This could present challenges to facilities with both isolators and RABS devices.

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Also mentioned in this section is the requirement to have a viewing window in place for all aseptic processing activities. This is to facilitate quality oversight of operations and also to minimize the number of personnel entering a cleanroom.

Aseptic processing simulations

Other revisions to the Annex which impact on operations conducted within cleanrooms include additional information about media fills (aseptic process simulations), where more 'time based' criteria have been added (such as assessing filling machine hold times and sterilized equipment hold times as part of the exercise). The importance of simulating all events remains (given that events, especially interventions are more important for the success or failure of a media fill than simply run time). Greater detail is provided for assessing the success of autoclave operations, such as the requirement to inspect sterilized packaging for its integrity and dryness. Such changes are designed to strengthen controls around sterile products manufacture.

PERSONNEL AND EQUIPMENT TRANSFER

The text relating to personnel and equipment transfer is more detailed. Here the requirement is for all items entering cleanrooms (and then moving to cleanrooms of a different grade) is via airlocks. The later requirements for disinfection needs to be read in conjunction with the transfer process. Ideally the transfer of materials and personnel are separate, as indicated in the new draft (this means, in essence, personnel not taking items through changing rooms). If there is no other alternative, people should not go through the area at the same time that items are transported through.

For transfer into aseptic processing areas, there is added emphasis upon unidirectional airflow and sterilization or decontamination. Here part 4.11 reads: "The transfer of materials, equipment, and components into an aseptic processing area should be carried out via a unidirectional process. Where possible, items should be sterilized and passed into the area through double-ended sterilizers (e.g. through a double-door autoclave or depyrogenation oven/tunnel) sealed into the wall. Where sterilization on transfer of the items is not possible, a procedure which achieves the same objective of not introducing contaminant should be validated and implemented, (e.g. using an effective transfer disinfection, rapid transfer systems for isolators or, for gaseous or liquid materials, a bacteria-retentive filter)."

MICROBIOLOGICAL ENVIRONMENTAL MONITORING

In relation to viable monitoring expanded information is provided in relation to sample site selection, stating that this needs to be risk based and, where applicable, determined through a review of airflow visualization studies. This greater detail explains why the sentence "This guidance does not lay down detailed methods for determining the microbiological and particulate cleanliness of air, surfaces etc.", has been dropped from the 2020 draft (this appeared in the 2017 draft).

A change is made to the EU GMP Grade A limit; which changes from 1 CFU to 'no growth'. This change is both a reflection of the expectation that microorganisms are not typically recovered from Grade A environments (and that every recovery requires an investigation) and with the different types of techniques that could be applied as replacements to the classic culture-based methods, such as the use of rapid and automated microbiological methods are permitted provided the facility has demonstrated their equivalency or superiority. As with the previous draft the term 'alternative' is missing. It is customary to use the phrase 'rapid and alternative microbiological methods' since a superior method for showing microbial recovery need not be rapid (and in the context of the 2020 draft, it need not be automated). Hence the draft Annex is out of alignment here.
There are no other changes to microbiological limits. Here it is unfortunate that the Annex continues to refer to 'limits' for environmental monitoring rather than 'levels.' This is because levels indicates a point where action needs to be considered

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but the where the overall risk is assessed through an analysis of trends; whereas 'limits' infers that a threshold has been crossed and that the area to which is the count relates to is now at some bigger risk.

A further change with the tone of the Annex in relation to environmental monitoring is the requirement for continuous monitoring. This is mandatory for Grade A and recommended for Grade B. The previous version stated that continuous monitoring was always required for Grade B. The change is probably reflective of some companies having large Grade B areas outside of filling rooms and hence continuous monitoring would not provide value if it was to be performed in such areas. By continuous monitoring this means air samples (either settle plates or volumetric air samplers).

For microbial identification the draft Annex stipulates that all isolates from Grade A and B areas should be identified, and recommends that those isolated from Grade C and D areas are identified. The Annex does not appear to acknowledge that it is not always possible to obtain an accurate identification result although the intent is presumably for the microbiologist to try to obtain a genus or species level outcome.

Further with the monitoring concept, the Annex is clear that simply monitoring (and testing) is no substitute for a robust sterility assurance system. With this there is an emphasis that testing is too imprecise to detect a weakness with the sterility assurance system. As the draft states: "Exclusively monitoring or testing does not give assurance of sterility." Instead, design and control matter far more for patient safety.

PERSONNEL

There are two points relating to personnel that have altered slightly and which are important (given that personnel are the primary contributors of contamination within cleanrooms) (13). These points related to gowning and qualifying operators to work in aseptic processing areas; and also, with ensuring that the personnel employed within the pharmaceutical facility possess the appropriate levels of experience.

Gowning and Operator qualifications

With qualifying operators, the language of the 2020 draft has slightly altered and it now refers to 'qualified' and 'unqualified' operators (it is also possible for qualified operators to become disqualified if there are concerns around microbial contamination). Part of the qualification is a gown test and the movement through a well-designed cleanroom system that seeks to minimize contamination. The requirements for entering changing areas for access into Grade B and C areas have been strengthened. The draft now states that outdoor clothing (other than personal underwear) cannot be brought into changing rooms (whereas in the previous draft this was a 'recommendation'). Changes include the need for suits to be full sleeves for Grade C (this always the case for Grade B) and for cleanroom socks to be worn for both grades prior to entry as part of the process to minimize contamination entering the change areas. In terms of what is not permitted to be taken into clean areas, the Annex now calls out mobile devices (reflecting the ubiquity of smartphones and the like) unless these have been supplied by the organization and are shown to be suitable for cleanroom used and covered by a cleaning and disinfection process. With entry into Grade B changing areas, there needs to be a separate way in and a separate way out (the requirement to add this to Grade C areas has been dropped). This is in order to reduce cross-contamination.

With gowns, the 2020 revision requires that:

- Gowns must be suitable to prevent shedding and the environment in which operators work and the movements they may be undertaking needs to be taken into account.
- The gown worn needs to be of a suitable size.
- Gowns must not affect the product (this is a reference to the risk of fibers being released from gowns and ending up in the product).

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- That gowns are assessed for their suitability (e.g. no signs of damage) prior to be being worn and once donned, prior to entering the cleanroom. There is a comment that visual inspection may not be sufficient to assess gown integrity. However, no further advice is afforded, and this is something for which there is no obvious solution for, prior to entering a cleanroom.
- Gowns must be processed in dedicated laundry facilities and the process of cleaning, evaluating and sterilizing gowns must be qualified.

For cleanroom operators entering aseptic processing areas a gowning test is required (which is a combination of visual assessment and microbiological monitoring). The new draft expands the list of recommended locations on an operator's gown that require monitoring as part of the gowning qualification: hands, arms, chest and forehead. Each one of these locations presents a different microbial contamination risk, in terms of the types of organisms and the route of contamination transfer. In addition, microbiological limits are presented for gown plates for the first time (these are the afforded the same maximal values as finger plates).

Further with gowning, the new draft now requires the maximum time that a gown can be worn for to be defined.

The text reads sticker in terms of visiting aseptic processing areas. Those who are not qualified to work in an aseptic processing area should not enter Grade A or Grade B when in operation, unless there are exceptional circumstances. To cover such circumstances, a risk assessment is required along with procedural controls.

Suitably qualified personnel
All staff working in cleanrooms are expected to have knowledge of 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. As well as requiring that personnel are suitably qualified to work in cleanrooms, the new draft of the Annex states that each facility must have staff who are specifically experienced in microbiology, environmental monitoring regime and with conducting microbiological investigations.

With aseptic operations specifically, the revised draft places strong emphasis upon how operators are trained and to move, especially in relation to any interventions with Grade A. It is stressed that practices must not disrupt Grade A unidirectional airflow in terms of movement or with the placing of objects that might cause air disruption. To aid with operator training a recommendation is made that airflow visualization studies constitute part of the operator training program.

STERILITY ASSURANCE AND CONTAMINATION CONTROL STRATEGY

The sterility assurance concept is fundamental to the development of sterile products in relation to patient safety. Considerably more detail about developing a sterility assurance system is provided in the drafts compared with the current Annex (14). Central to sterility assurance and the contamination control strategy is the application of barrier technology (either isolators or RABS), since such technology can greatly assist with the minimization of microbial contamination that is connected with direct human intervention.

With the contamination control strategy, this is afforded strong emphasis within the new draft (seemingly to a greater degree than with the 2017 draft). The strategy is foremost present as something dynamic, in need of regular review and update as necessary. As the new draft states: "The CCS (Contamination Control Strategy) should be actively updated and should drive continuous improvement of the manufacturing and control methods."
Drawing on Hazard Analysis Critical Control Points (HACCP) concepts, the definition of the strategy discusses the importance of pinpointing the critical control points that will signal contamination build-up (both microbial and in relation

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to bacterial endotoxin). Once selected risk-based approaches must be used to attempt to reduce the contamination risk and then once risks can be reduced no further, then monitoring is put into effect. Furthermore, the onus is upon the facility user to review the effectiveness of the controls on a regular basis and especially in relation to any process changes.

STERILIZATION

With sterilization, there is a specific update for freeze-dried products in terms of freeze-dryers (or lyophilizers). This is for lyophilizers which are manually loaded or manually unloaded. Here the freeze-dryers should be sterilized before each load. The remaining references to sterilization remain unchanged between the drafts.

Filtration

The controversial issue of pre-use post sterilization integrity testing (PUPSIT) has been softened for small volume products, with a list of criteria to be taken through a risk assessment provided so that a risk-based alternative to this stage of filter integrity testing can be considered as an alternative. This risk-centric approach would include:

- In depth knowledge and control of the sterilization process, ensuring that the risk of damage to the filter is minimized.
- In depth knowledge and control of the supply chain. This would need to cover contract sterilization facilities; modes of transport; packaging of the sterilized filter, designed to prevent damage to the filter during transportation and storage.
- Detailed process knowledge including the specific product type, including microbial challenge and whether there exists any risk of impact on filter integrity values, such as the potential to alter integrity testing values and therefore prevent the detection of a non-integral filter during a post-use filter integrity test.
- Pre-filtration and processing steps, prior to the sterilizing filter, which would remove a microbial challenge and clarify the product prior to the sterile filtration.

The necessity of PUPSIT is not supported by all experts. There are some who challenge whether the PUPSIT risk is actually manifest; whereas others are of the view that a well-documented, risk-based assessment of the actual control strategy implementation to address potential filter and device assembly defects and filtration failures caused during manufacture by mishandling, is a better approach.

A further point with filtration is that the reference, in the 2017 draft, to the final sterile filtration needing to be performed as close as possible to the filling point has been removed. Presumably this is to reflect advances with single-use systems.

Disinfection

The section of the text relating to disinfection does not appear to have undergone any major update between drafts (the reference to disinfectant rotation and the periodic use of a sporicide remain, as examples). The section on disinfectants remains far more detailed in the new draft compared with the current Annex, with references to rotation with a sporicide and the need to qualify each disinfectant against different surface materials.

In terms of changes in relation to the 2020 draft, there are the added requirements that:

- The disinfection process is validated.
- Validation studies relate to the specific manner in which disinfectants are use (by this there will be differences between sprays, sprays followed by wiping, and pre-saturated wipes, for example).
- Validation needs to be extended to the in-use expiry periods of prepared solutions.

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- It remains that disinfectants used in Grade A and B areas needs to be sterile; to this point the text has been revised to state that disinfectants used in Grade C and D areas may need to be sterile (this generalization is not especially helpful).
- There is a requirement that disinfectants that are not purchased ready-made and which are thus made up in-house as assessed for microbial contamination (the time point is not specified, but presumably this means end-of-use to represent 'worst case'). For ready-made disinfectants, assessment can be undertaken by a review of certificates of analysis.
- Monitoring the effectiveness of disinfectants through environmental monitoring does appear in the earlier draft; however, reference to "spore-resistant strains" has been replaced with "organisms resistant to the disinfection regime currently in use", which is more scientifically accurate since a microorganism does not always need to enter into a spore state to be difficult to kill. By resistance this does not refer to 'acquired resistance' (for which there is little scientific support) but to the fact of innate resistance, where some microorganisms are more resistant (such as due to a factor of their cell wall, for example) to a given disinfectant.

With the section on disinfection, it is unfortunate that the reference to disinfectant residues remains since there are disinfectants on the market that leave no residues, or which are sufficiently low residue that any remaining residue is not of significance in terms of interference with cleaning agents or with other disinfectants.

Single-use systems

Another area without any further update is with the use of single-use systems and technologies (except that 'SUS' is now used to abbreviate the technology); where their use continues to be encouraged albeit with the caveat that the interaction between the product and product contact surface (notably adsorption, leachable and extractables) is carefully understood.

Utilities

The section on utilities contains a few changes between the two drafts, such as the adding of a reference to heating systems for the first time. There is also an added requirement for the trending of critical utility parameters. This is expressed as an important step so alarms can be reviewed to determine if they are specific causes or common causes, thereby enabling the appropriate engineering action to be taken.

Unfortunately, with cooling and vacuum systems the text remains that infers
that periodic cleaning and disinfection of vacuum and cooling systems is required. However, this is design dependent and a closed cooling system located outside of a cleanroom may not need to be periodically cleaned and disinfected. Instead, requiring a risk-based approach would be more sensible.

With alarm-based monitoring particular emphasis is placed on Water-for-Injections systems where is stated technology for monitoring Total Organic Carbon and conductivity is put in place, at locations determined by risk. This is because this type of process analytical technology that permits continuous monitoring is seen as superior to the type of discrete monitoring that might be conducted by a chemistry department.

As part of design controls the Annex requires that water remains in a state of turbulent flow through distribution systems (this minimizes the risk of microbial adhesion and hence biofilm development) and that a sanitization method is used. As an example, holding water at 70^{o}C or above is provided (although there are other forms water control, such as chemical treatments).

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Further with water systems the reference to "water treatment plant and distribution systems" is a little limited in terms of definition. Many prefer the term "water treatment generation, storage and distribution." In part 6.7 of the draft there is reference to the "sloping of piping to provide complete drainage and the avoidance of dead legs;" however, the degree of slop is not specified, and it would be helpful if this was so. Furthermore, while dead legs should be minimized, they cannot be completely avoided.

Another control measure is filtration. In section 6.11 the new text states: "Where WFI storage tanks are equipped with hydrophobic bacteria retentive vent filters, the filters should be sterilized, and the integrity of the filter tested before installation and after removal following use." While the use of filters is commonplace, it is not typical for them to be sterilized in advance or to be subject to integrity testing for both pre- and post-use. This is not to say that some form of integrity testing is not useful; however, the sterilization requirement for an uncontrolled plant room comes across as excessive.

Where microbial counts occur, especially in response to an upward trend, a normal recourse is to disinfect the system (by heat or by chemicals). In relation to this, the draft Annex states: "To minimize the risk of biofilm formation, sterilization or disinfection or regeneration of water systems should be carried out according to a predetermined schedule and when microbial counts exceed action limits." The reference to 'sterilization' is inappropriate to a water system and this cannot be adequately delivered or assessed; not is it necessary. Further, the inference that full system sanitization is required for each action level excursion is unnecessary (the term 'limit' in the draft is better expressed as 'level'), at least without determining root cause and where the contamination is found to be in association with a specific outlet and due to an issue like local tubing management.

GENERAL UPDATES

With the new draft there have been some general updates to the text, especially where the terminology has been tightened up and it is less contradictory (this was one of the main criticisms of the 2017 draft). Gone are confusing references to "Grade A/B", "Grade A conditions", "Grade A air", or to "critical areas". Now exact cleanroom grades are specified. In terms of what has not been addressed is the background grade for isolators; this is left to the user to decide. Some guidance as to Grade C or D would have been helpful. Furthermore, it remains that the monitoring requirements for classification and 'routine' monitoring are contained in different sections and separated by a twenty or so pages.

Also dropped is the ungainly reference to 'clean areas', which is now replaced with the more accepted "cleanroom". Any reference to "preparation of unlicensed sterile medicinal products" has also been removed.

SUMMARY

The latest draft Annex (version 12) is an improvement upon the 2017 draft, at least in terms of consistency and with clearer definitions and expectations. The text will, however, not satisfy all parties and the window is open for additional comments to be made. How different the final draft will be is a matter of conjecture. With this review, points which stand-out to this author as still requiring further work have been highlighted.

This further development with the path towards a finalized Annex also raises questions for the FDA sterile products guidance, which already predates the current EU GMP Annex 1 (by three years). There is a sense that FDA are waiting for the Annex 1 process to be completed, before the Agency embarks on updating its own guidance document (the possibility of a unified standard does not appear likely at the present time).

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In summary, the key takeaways from the latest draft are:

- The expectation for each facility to have in place a formal, holistic contamination control strategy, focused on minimizing contamination control with respect to sterile manufacturing.
- Additional requirements for cleanroom classification (beyond ISO requirements).
- A major focus on risk-based approaches.
- Recommendations for the wider use of barrier technology.
- A strong focus on personnel controls, such as gowning, and training.

Such broad requirements are unlikely to alter greatly and sterile product manufacturers should invest time in examining the expected changes to ensure they are compliant, ready for a future regulatory inspection.

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