14 March 2021

Brendan Cuddy
European Medicines Agency
Domenico Scarlattilaan 6
1083 HS Amsterdam/Netherlands

RE: Implementation Timing of Annex 1 Revision

Dear Mr. Cuddy,

We appreciate the opportunity to assist the EMA and PIC/S working groups by providing our recommendations regarding the implementation timing of the revised Annex 1. These recommendations represent our opinion and do not necessarily address all needs of all companies in the industries affected by the revised Annex. The companies covered by Annex 1 are diverse in the types of products they manufacture, the types of processes they use, and their size. As the revised Annex 1 is applied across the industries the changes will impact each of these groups differently based on their current situation. The recommendations are the result of discussions with, and input from, the respective industry associations.

Because our recommendations are being submitted prior to the release of an updated version of Annex 1, they are based on the revised Annex 1 Draft 12 version. It is important to note that while we have carefully considered the time and effort required to comply with this draft version, these recommendations are not intended to imply our agreement with the draft version as written, as reflected in the comments submitted in the 2020 targeted consultation.

The revised EU GMP Annex 1 draft 12 is a significant step forward in providing a comprehensive set of detailed requirements for the manufacturing of sterile products that has not been previously seen. This extensive revision of Annex 1 (moving from 15 pages to more than 50 pages) has provided the opportunity to align GMP requirements with QRM and current scientific knowledge. This alignment, together with the application of technology developments, if applied appropriately, provides and encourages a culture of continual improvement.

This much more detailed guidance includes current practices and current regulatory expectations, not previously explicitly documented. Also included are new requirements, as well as requirements that, while present in the current version of Annex 1, contain language that will lead to added actions being required. Based on these changes, upon publication of the final revised Annex 1 each company will need time to understand the full requirements, complete a gap analysis and identify the actual changes/solutions required along with the timing for their implementation.

The Contamination Control Strategy (CCS) requirement presented in section 2.5 and discussed throughout the revised Annex 1 draft greatly improves the document. While many of the individual

elements of the CCS are not new expectations, the requirement for a CCS is expected to be the driver for the creation of a documented approach to contamination control that provides a holistic perspective by considering the interaction of technical, organizational, and procedural contamination control measures. In the development of this CCS document, with its supporting risk assessments, it is expected that potential compliance and contamination control gaps related to the requirements set out in the revised Annex 1 will be identified in a formal gap assessment. Once identified and assessed, plans will need to be made for the required changes/solutions as well as for the timing of their implementation.

Some requirements that are new or have clarified interpretations are anticipated to present challenges in their implementation, to both individual companies and the suppliers/contractors that support them. In these cases longer timelines will be needed for completion to allow for the required activities such as identification of the potential solutions, technical evaluations, execution of studies to support the planned change, re-engineering of existing manufacturing processes/facilities, actual modification of facility/equipment, purchase/receipt/installation of equipment, qualification/validation of changes, procedure changes (creation/revision), development and delivery of training to ensure procedural control measures are followed, and the submission for regulatory approvals. In addition, for some of the requirements the technology is not yet available or reliable and new technology will need to be developed (e.g., 100% integrity testing of filled flexible bag containers in an automated line). In these cases, it will be dependent on when the new technology becomes available which may require significant time to develop.

Compounding these factors is the COVID-19 crisis that is currently impacting the Pharma industry as a whole, not just vaccine and treatment manufacturers. One of the impacts is that projects are being delayed as a result of resource re-deployed (in support of vaccine manufacturing and production of products in short supply), employee availability (due to restrictions), supply change disruptions, limited availability of professional services, etc. Combined with the new requirements in the revised Annex 1 the result is inevitably, changes to meet the full intent of the revision will take more time.

Based on these considerations, the industry association coordination group would appreciate a phased approach to the implementation of the revised Annex 1 to full compliance. An approach that includes a 12-month rather that 6-month general implementation period for items that require minor to moderate changes and an understanding that specific changes may require longer periods of time to implement, for example changes:

- that require specialized equipment,
- that require significant engineering or facility redesign work,
- to the manufacturing process,
- that require extensive studies to support, or
- with a significant impact on the manufacturing capacity that could lead to supply disruptions
- that require regulatory approval

With a clear expectation that the justification for individual items requiring longer implementation times, including any risk mitigation steps required, be documented and supported through the CCS with product quality and patient (human and animal) safety the top priority.

Based on the justification discussed above we recommend a 1-year implementation period as a minimum. The recommendations provided below take into consideration that this 1-year implementation of the revised Annex 1 is provided.

While each facility will have differing needs, the following is recommended as an approach to implementation timing on specific new requirements of the revised Annex 1 with the supporting justification. These are changes that will take significantly longer periods of time to implement based on the activities that must be completed to support the change. For these it is anticipated that implementation will require at a minimum 3 years. See Appendix 1.

In addition, we felt it was important to provide additional illustrations of other requirements that have been identified by the associations members as being challenging to implement and may result in implementation times longer than those normally provided, presented in Appendix 2. For these it is expected that an implementation timing of >1 year and less than 3 years is required.

Based on our evaluation of the implementation timing required for these items we recommend that for new requirements that cannot be implemented within the set implementation time, each facility is expected to have a clear justification, detailed project plan, and defined timeline in place. And that text be attached to the annex which conveys this expectation.

If you have any questions or would like additional input on this topic, please do not hesitate to contact me and the Associations' Coordination team will be happy to assist. We are also available to provide additional detail with examples of implementation activities and timelines for specific items if requested.

Yours sincerely, on behalf of A3P, AnimalhealthEurope, AESGP, ECA, EFPIA, EIPG, EQPA, ISPE, Medicines for Europe, PDA, PHSS, and Vaccines Europe.

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APPENDIX 1

For the following list of 5 requirements, the implementation timing is expected to be at a minimum 3 years.

As each facility will have differing needs (based on the process, equipment, and facility limitations) and a longer implementation time may be needed for a new requirement that cannot be implemented within the set implementation time, each facility is expected to have a clear justification, detailed project plan, and defined timeline in place.

	Draft Annex 1 Text	***Justification***
4.23	"Integrity testing of the barrier systems, and leak testing of the glove system and the isolator should be performed using a methodology demonstrated to be suitable for the task and criticality. The testing should be performed at defined periods, at a minimum at the beginning and end of each batch, and should include a visual inspection following any intervention that may affect the integrity of the system. For single unit batch sizes, integrity may be verified based on other criteria, such as the beginning and end of each manufacturing session. RABS gloves used in Grade A zone should be sterilized before installation and sterilized (or effectively decontaminated by a validated method which achieves the same objective) prior to each manufacturing campaign. The frequency of glove replacement should be defined within the CCS."	• *The requirement indicates that the leak testing of gloves and the barrier system should be performed at defined periods* ***at a minimum at the beginning and end of each lot.*** • *Rapid mechanical test would need to be developed and validated that would allow leak testing to be performed after sanitization while the isolators or RABS are in operations. While isolators are closed units, RABS are not sealed making the development of a test more challenging.* • *As this has both procedural and potential elements that will require engineering changes time will be needed to implement.*
5.5	"Direct and indirect contact parts should be sterilized. Direct contact parts are those that the product passes through, such as filling needles or pumps. Indirect product contact parts are equipment parts that come into contact with sterilized critical items and components"	• *As currently written, this will require a significant change in regard to isolators as currently indirect contact parts are often cleaned in place according to a validated procedure (e.g. removal of grease and silicone- oil, which might negatively impact the Vapor Phase Hydrogen Peroxide(VHP) cycle effectiveness) and then sanitized to reduce any bioburden present followed by a VHP cycle use to decontaminate the isolator and equipment surfaces which is capable of achieving a 6 log reduction on those surfaces, and renders surfaces incapable of microbiologically contaminating sterile products.* • *As it is understood that the decontamination with VHP would no longer be considered sufficient, procedural and in some cases equipment modifications will be needed along with revalidation. For some current designs where items such as stopper bowls are large and not able to be set in place manually, by hand, significant redesign will be needed.* • *Time will be needed to evaluate, re-engineer, implement, validate, train on, and gain regulatory approvals for the change.*

		• *As this requirement does not delineate between aseptic and terminally sterilized product. For terminally sterilized product significant design changes and installation of new equipment to perform the required sterilization will be required.*
8.21	"Containers should be closed by appropriately validated methods. Containers closed by fusion, e.g. Blow-fill-seal (BFS), Form-Fill-Seal (FFS), Small and Large Volume Parenteral (SVP & LVP) bags, glass or plastic ampoules, should be subject to 100% integrity testing."	• *For the 100% leak testing requirement, this may not be possible for many years as current technologies are not available for specific container types. (An example would be flexible containers that are sterilized in overpouches)* • *In these cases, technology will need to be developed as it does not exist today.*
8.82, 8.88	"Due to the potential additional risks of a sterile filtration process, as compared with other sterilization processes, a second filtration through a sterile sterilizing grade filter, immediately prior to filling, should be considered as part of an overall CCS." "The integrity of the sterilized filter assembly should be verified by integrity testing before use, to check for damage and loss of integrity caused by the filter preparation prior to use. A sterilizing grade filter that is used to sterilize a fluid should be subject to a non-destructive integrity test post-use prior to removal of the filter from its housing. Test results should correlate to the microbial retention capability of the filter established during validation. Examples of tests that are used include bubble point, diffusive flow, water intrusion or pressure hold test."	• *While 8.88 may not be viewed as a change by some from the previous Annex 1 version, from a text standpoint it is in that the new text specifically indicates an in-situ pre use post sterilization integrity test.* • *As this is required regardless of formulation type or the assessment of risk, the modifications required to achieve this will be challenging from technical standpoint for many companies, requiring engineering design work, validation, and regulatory approvals.* • *In addition, the recommendation for second (redundant) sterilizing filter placement noted in 8.82, for which an in-situ pre use post sterilization integrity test applies, will significantly complicate the engineering and procedural efforts. Design changes will be required along with validation and regulatory approvals to keep the filter as close as possible to the filling needles.*
6.22 8.112 8.113 8.115	6.22 "Any leaks from these systems that would present a risk to the product should be detectable (i.e. an indication system for leakage)" 8.112 "Lyophilizers that are manually loaded or unloaded should normally be sterilized before each load. For lyophilizers loaded by automated closed systems or located within systems that exclude operator intervention, the frequency of sterilization should be justified and documented as part of the CCS." 8.113 "The integrity of the lyophilizer system should be maintained following sterilization and during use. The filter used to maintain lyophilizer integrity should be sterilized before each use of the system and its and its integrity testing results should be part of the batch certification." 8.115 "Points to consider for the design of loading (and unloading, where the lyophilised material is not in a sealed container (e.g. open tray dried materials), include but are not limited to:"	• *These recommendations will require significant facility, equipment, and process changes as well as regulatory approvals.* • *If the expectation is that lyophilizers need to have detection systems for silicon oil leak, then development of the detection system and the associated design changes will be needed.* • *For the lyophilization process for sterile API there is currently no technology available for the automated loading and unloading of lyophilizers.* • *The requirement to sterilize the lyophilized before each use for manual operation is a significant change.* • *In order not to impact product supply (as this requirement will have a significant impact on production time due to the added activities required between lots and down time related to the additional mechanical stress on the lyophilizers) this change will require careful planning and time to implement.*

	“ii. The transfer of partially closed containers to a lyophilizer should be undertaken under Grade A conditions at all times and handled in a manner designed to minimize direct operator intervention. Technologies such as conveyor systems, portable transfer systems (e.g. clean air transfer carts, portable unidirectional airflow workstations) should be used to ensure that the cleanliness of the system used to transfer the partially closed containers is maintained). Alternatively, where supported by validation, containers closed in the Grade A zone and not reopened whilst in the Grade B may be used to protect partially stoppered vials (e.g. sealed sterilized trays)."	

APPENDIX 2

Listed are additional illustrations of other requirements that have been identified by the associations members as being challenging to implement and may result in longer implementation. For these requirements, the implementation timing is expected to be >1 year and less than 3 years.

As each facility will have differing needs (based on the process, equipment, and facility limitations) and a longer implementation time may be needed for a new requirement that cannot be implemented within the set implementation time, each facility is expected to have a clear justification, detailed project plan, and defined timeline in place.

	Draft Annex 1 Text	*Justification*
4.13	Both sets of doors for pass-throughs and airlocks (for material and personnel) should not be opened simultaneously. For airlocks leading to a Grade A zone and Grade B areas, an interlocking system should be used.	• *This requirement will require selection, receipt, and Installation of appropriate interlocking system along with the required modification and testing of the control system (e.g., Building Management System).*
4.15	"Airflow patterns within cleanrooms and zones should be visualized to demonstrate that there is no ingress from lower grade to higher grade areas and that air does not travel from less clean areas (such as the floor) or over operators or equipment that may transfer contaminant to the higher grade areas. Where air movement is shown to be a risk to the clean area or critical zone, corrective actions, such as design improvement, should be implemented. Airflow pattern studies should be performed both at rest and in operation (e.g. simulating operator interventions). Video recordings of the airflow patterns should be retained. The outcome of the air visualisation studies should be considered when establishing the facility's environmental monitoring program."	• *The new requirement does not indicate which area classification the visualizations at rest / in operations and the aligning EM program with the visualization (smoke studies) applies.* • *Visualization studies in areas with non-uniform airflow would have little relevance in clean rooms if classified to meet air cleanliness based on in operation particle loading from occupancy (worst case) and equipment where closed processing occurs. It can have relevance for open operations such as compounding or buffer preparation to understand if air currents can potentially create contamination.* • *If this is for all area classification (grades, A, B, C, and D) it will take time to implement, not only to complete the work but to establish what is an acceptable flow of air in areas outside of the Grade A area (Grade B, C, D) where unidirectional flow is not required.*
4.34	The requalification of cleanrooms and clean air equipment should be carried out periodically following defined procedures. The requirement for requalification of cleanroom areas is as follows:	• *Not all non-compliance events may have impact to the performance of the filters or airflow in the cleanroom and a formal integrity test of terminal filters or an airflow measurement for each event may not be required to confidently re-establish cleanroom conditions. It is assumed that a risk-based assessment of each event is needed to determine the extent of requalification testing to be conducted*

	Table 3: Minimum test requirements for the requalification of cleanrooms | Grade | Determination of the concentration of airborne viable and non-viable particles | Integrity Test of Terminal Filters | Airflow volume measurement | Verification of air pressure difference between rooms | Air Velocity test | | --- | --- | --- | --- | --- | --- | | A | Yes | Yes | Yes | Yes | Yes | | B | Yes | Yes | Yes | Yes | * | | C | Yes | Yes | Yes | Yes | * | | D | Yes | Yes | Yes | Yes | * | * performed according to a risk assessment documented as part of the CCS. However, required for filling zones (e.g. when filling terminally sterilised products) and background to Grade A RABS. For Grade A & B areas, the maximum time interval for requalification is 6 months. For Grade C & D areas, the maximum time interval for requalification is 12 months. Appropriate requalification consisting of at least the above tests should also be carried out following completion of remedial action implemented to rectify an out-of-compliance equipment or facility condition or after changes to equipment, facility or processes. The significance of a change should be determined through the change management process. Examples of changes to be considered include but are not limited to the following: i. Change in the operational use of the cleanroom, or of the operational setting parameters of 510 the HVAC system. ii. Interruption of air movement which affects the operation of the installation. iii. Special maintenance which affects the operation of the installation (e.g. change of final filters)	*based the event specifics. Consistent with the evaluation of changes allowed elsewhere in this section.* • *If this is not the case and the tests specified in 4.34 are required for each event, along with the addition of the 6 month and 12 month requalification requirements, time will be needed to develop and implement a strategy for these activities to reduce the anticipated significant increase in manufacturing downtime.*
4.35	"Other characteristics, such as temperature and relative humidity, should be controlled within ranges that align with product/processing requirements and support maintenance of defined cleanliness standards (e.g. Grade A or B)."	• *It is interpreted that the evaluation and determination of control needed, in regard to other characteristics, is to be included in the CCS.* • *If this is not to be determined by the CCS but required in all cases. HVAC upgrades will be needed to control humidity. In addition, modifications to the Building Management system to support the change will be required.*
5.9	"Particle counters, including sampling tubing, should be qualified. The tubing length should be no greater than 1 meter with a minimum number of bends and bend radius should be greater than 15 cm."	• *Built-in particle counters at filling lines often have a longer tube than 1 m that has been qualified.* • *This requirement will require significant engineering changes to the particulate monitoring systems and modifications to production lines.*

6.11	"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."	• *This requirement may involve procedural and design changes that would require training and qualification.*
6.19	"Gases used in aseptic processes should be filtered through a sterilizing filter (with a nominal pore size of a maximum of 0.22 µm) at the point of use. Where the filter is used on a batch basis (e.g. for filtration of gas used for overlay of aseptically filled products) or as product vessel vent filter, then the filter should be integrity tested and the results included as part of the batch certification process. Any transfer pipework or tubing that is located after the final sterilizing filter should be sterilized. **When gases are used in the process, microbial monitoring of the gas should be performed periodically at the point of use."**	• *This requirement will require method development and procedural changes to allow aseptic (sterile) microbial sampling to be performed at the point of use for gases used in the process.*
8.29	"All filled containers of parenteral products should be inspected individually for extraneous contamination or other defects. Defect classification and criticality should be determined during qualification and based on risk and historical knowledge. Factors to consider include, but are not limited to, the potential impact of the defect to the patient and the route of administration. Different defect types should be categorized and batch performance analysed. Batches with unusual levels of defects, when compared with routine defect numbers for the process (based on historical and trend data), should lead to an investigation. A defect library should be generated and maintained which captures all known classes of defects. The defect library should be used for the training of production and quality assurance personnel. Critical defects should not be identified during any subsequent sampling and inspection of acceptable containers. Any critical defect identified should trigger an investigation as it indicates a possible failure of the original inspection process."	• *Extended time needed for difficult to inspect container types (plastic bottles, amber glass, etc.).* • *These products are difficult, and in some cases imposible, to inspect for particulate matter unless destructive test are used.* • *Technology must be developed and qualified. Potentially a modification of the packaging area would be required to accommodate the equipment.*
8.45	"Where possible, materials, equipment and components should be sterilized by validated methods appropriate to the specific material. Suitable protection after sterilization should be provided to prevent recontamination. If sterilized items are not used immediately after sterilization, these should be stored using appropriately sealed packaging. A maximum hold time should also be established. Where justified, components that have been packaged with multiple sterile packaging layers need not be stored in a cleanroom if the integrity and configuration of the sterile pack allows the items to be readily disinfected during transfer by operators into the Grade A zone, (e.g. by the use of multiple sterile coverings that can be removed at each transfer from lower to higher grade). Where protection is achieved by containment in sealed packaging, this packaging process should be undertaken prior to sterilization. "	• *The use of Closure Processing Equipment's (CPE) for cleaning and sterilisation of Primary Packaging Material, loaded into bags, is commonly used within industry.* • *The main benefit with the Closure Processing Equipment's is that the cleaning and the sterilisation processes is one integrated closed process. Following the cleaning and sterilisation process the Primary Packaging Material is unloaded into sterile bags and sealed in a grade A environment.* • *The existing Closure Processing Equipment's must be re-engineered to allow bagging and sealing before sterilisation.*

8.49	"Each heat sterilization cycle should be recorded either electronically or by hardcopy, on equipment with suitable accuracy and precision. **Monitoring and recording systems should be independent of the controlling system (e.g. by the use of duplex/double probes)."**	• *While this is mentioned in previous Annex one in the moist heat section, this now becomes a mandatory requirement and has extended scope.* • *This will require the retrofitting of equipment. As on some equipment there is not independent recording and controlling systems.*
8.59	"There should be adequate assurance of air removal prior to and during sterilization when the sterilization process includes air purging (e.g. porous autoclave loads, lyophilizer chambers). For autoclaves, this should include an air removal test cycle (normally performed on a daily basis) or an air detector system. Loads to be sterilized should be designed to support effective air removal and be free draining to prevent the build-up of condensate."	• *This is a new requirement* • *This is a parameter normally evaluated during qualification.* • *The daily requirement will require air detectors which are not fitted to all autoclaves and lyophilizers and would require engineering change for retrofit and qualification/ testing in shutdowns.*
8.103	"For shuttle type equipment used for aseptic filling, the area between parison cutting and mould sealing should be covered by a flow of filtered air to provide Grade A conditions at the critical zone. The equipment should be installed in at least a Grade C environment, provided that Grade A/B clothing is used. The filling environment should meet Grade A for viable and non-viable limits at rest and the viable limit only when in operation."	• *From an engineering standpoint It is not certain that Grade A air for the shuttle BFS transport area can be attained nor is it necessary.* • *Whatever actions are taken to make improvements in this area will require significant engineering work including re-engineering which will take significant time.*
9.41	Where manual operation (e.g. aseptic compounding or filling) occurs, each type of container, container closure and equipment train should be initially validated **with each operator participating in at least 3 consecutive successful APS and revalidated with one APS approximately every 6 months for each shift.** The APS batch size should mimic that used in the routine aseptic manufacturing process."	• *It is difficult to interpret this requirement without understanding the context and scope of "manual operations", especially in regards to ATMP and some vaccine manufacture.* • *A requirement for each operator involved with a manual aseptic operation (regardless of whether the operation includes manual filling) on each shift to participate in at least 3 consecutive successful APS with revalidation for each operator for each shift at a frequency of every 6 months for each type of container, closure, and equipment train will significantly increase the time and facilities required for operator qualification and APS studies for specialized products, such as some vaccines and ATMPs.* • *Time will be required to modify procedures, add resources, and schedule operator re-qualifications.*
10.6	"Note: Where the manufacturing process results in sub-batches (e.g. for terminally sterilized products) then sterility samples from each sub-batch should be taken and a sterility test for each sub batch performed. Consideration should also be given to performing separate testing for other finished product tests."	• *Performing a sterility test for <u>each sterilizer load</u> (sub-batch) will significantly increases the testing burden when compared to performing <u>one sterility test per batch</u> of product as a batch of product is often sterilized in multiple (sometimes >10) loads with samples being pulled from each load and combined for the sterility test.* • *This is estimated to significantly increase the testing volume by many multipliers.* • *Additional sterility testing laboratories, sterility test equipment (procurement and validation), and the hiring and training of new*

		laboratory analysist will be required. This will take time to implement.
10.6	"The sterility test should be performed under aseptic conditions. Samples taken for sterility testing should be representative of the whole of the batch but should in particular include samples taken from parts of the batch considered to be most at risk of contamination, for example: i. For products which have been filled aseptically, samples should include containers filled at the beginning, middle and end of the batch **and after any significant intervention (e.g. interventions where the integrity of a barrier is breached (open door)) or an operator intervention into critical zones."**	• *Based on the examples provided this will result in a significant increase in the number of units pulled for sterility testing as some lines are built to have doors that are opened for specific interventions and almost all lines require operator intervention into the critical zone (expected/normally occurring interventions are qualified as part of the media fills, with interventions into the critical zone that could impact sterility requiring the clearing of containers).* • *In some cases, equipment modifications will be needed to allow tacking of these units so they can be collected after sealing of the units have occurred.* • *As no differentiation is given, based on the wording, multiple sterility test would be required per lot for many products produced. As a result, this is estimated to significantly increase the sterility testing volume.* • *Additional sterility testing laboratories, sterility test equipment (procurement and validation), and the hiring and training of new laboratory analysist will be required. This will take time to implement.*