2018 PDA Europe Conference

Annex 1

Revision of the EU GMP Guideline

Annex 1 PDA Commenting Committee Report

Gabriele Gori, VP, Head of Quality Audit & Risk Management, GlaxoSmithKline Vaccines
Hal Baseman, Chief Operations Officer, ValSource

DISCLAIMER

This presentation is based on the document submitted by PDA to the European Commission, containing the Association's comments to the draft revision of the EU GMP Annex 1 (released on Dec.20, 2017).

The views expressed during this presentation reflects the consensus views of the PDA Task Force, which includes subject matter experts from various pharmaceutical and consulting companies and PDA, and do not necessarily reflect the views of particular individual members of the Task Force or the companies/organizations by which those members are employed.

Agenda

- PDA Annex 1 Commenting Process
- General Comments
- Terminology – suggested replacement
- Selection of comments
- Conclusion
- Acknowledgements

PDA Annex 1 draft commenting process

- Expert team made up of 16 sterile product manufacturing experts from 14 companies, representing Europe, Japan, the U.S., and PDA
- Considered comments and input from PDA membership in formulating expert team opinions, as well as existing published PDA positions (e.g. Points to Consider for Aseptic Processing, Part 1 (Jan 2015) and Part 2 (May 2016), PDA Technical Reports, etc.).
- Team debated positions and formulated comments and proposed recommendations for EMA/European Commission.

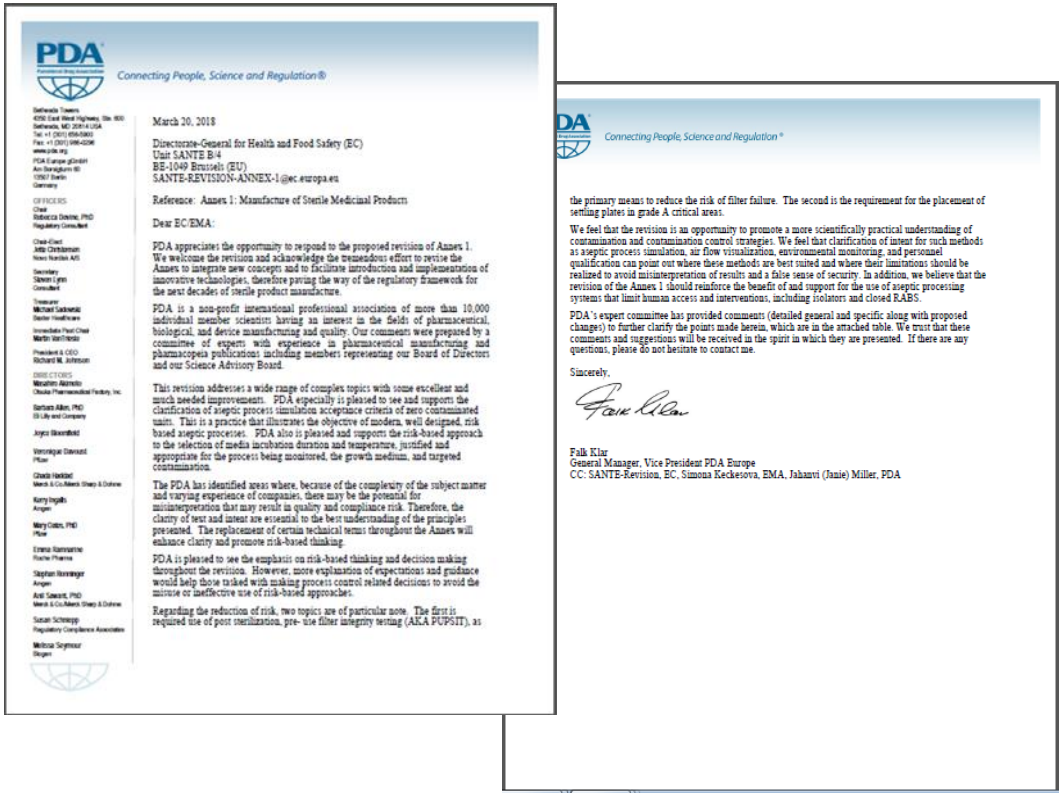
PDA Annex 1 draft commenting process

Elaborated approximately 90 specific comments and a dozen general comments, which have been reviewed and approved by the PDA Advisory Boards, Senior Staff and Board of Directors.

Where comments to the document were made, a rationale and proposal for new wording were offered.

Line number(s) of the relevant text	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
321-323	Comment: Section 5.3 states prescriptive guidance for air speed as well as an expectation for justification of sampling distance. Air velocity guidance may or may not be appropriate for unidirectional flow in all cases and at all points within the Grade A zone. ISO 14644-3 clearly indicates that the test for unidirectional air flow and referencing 0.4 – 0.6 m/s should be taken within 150-300 mm of the filter face. While using the ISO guidance for qualification or re-qualification may be suitable, implication that the guidance velocity values have any validity elsewhere in the Grade A zone is not accurate. The prescription of a standard velocity is not necessary, and should depend on line and process configuration. The requirement for individual determination of standard measuring distance is not necessary, if a standard distance is already available. Proposed change: Remove recommended velocity, but add guidance recommendation for measurement distance. "~~Unidirectional air flow systems should provide a homogeneous air speed in a range of 0.36 – 0.54 m/s (guidance value), the point at which the air speed measurement is taken should be clearly justified in the protocol. During initial qualification and requalification air speeds may be measured either close to the terminal air filter face or at the working height,~~ Airflow systems that are designed to be unidirectional should provide a homogeneous air velocity as measured within 150 – 300mm of the filter face that is adequate to prevent the ingress of particulate from the less-clean surrounding environment into the working area.

PDA Annex 1 draft commenting process



PDA

Connecting People, Science and Regulation®

March 20, 2018

Directorate-General for Health and Food Safety (EC)
Unit SANTE B/4
BE-1049 Brussels (EU)
SANTE-REVISION-ANNEX-1@ec.europa.eu

Reference: Annex 1: Manufacture of Sterile Medicinal Products

Dear EC/EMA:

PDA appreciates the opportunity to respond to the proposed revision of Annex 1. We welcome the revision and acknowledge the tremendous effort to revise the Annex to integrate new concepts and to facilitate introduction and implementation of innovative technologies, therefore paving the way of the regulatory framework for the next decades of sterile product manufacture.

PDA is a non-profit international professional association of more than 10,000 individual member scientists having an interest in the fields of pharmaceutical, biological, and device manufacturing and quality. Our comments were prepared by a committee of experts with experience in pharmaceutical manufacturing and pharmacopeia publications including members representing our Board of Directors and our Science Advisory Board.

This revision addresses a wide range of complex topics with some excellent and much needed improvements. PDA especially is pleased to see and supports the clarification of aseptic process simulation acceptance criteria of zero contaminated units. This is a practice that illustrates the objective of modern, well designed, risk based aseptic processes. PDA also is pleased and supports the risk-based approach to the selection of media incubation duration and temperature, justified and appropriate for the process being monitored, the growth medium, and targeted contamination.

The PDA has identified areas where, because of the complexity of the subject matter and varying experience of companies, there may be the potential for misinterpretation that may result in quality and compliance risk. Therefore, the clarity of text and intent are essential to the best understanding of the principles presented. The replacement of certain technical terms throughout the Annex will enhance clarity and promote risk-based thinking.

PDA is pleased to see the emphasis on risk-based thinking and decision making throughout the revision. However, more explanation of expectations and guidance would help those tasked with making process control related decisions to avoid the misuse or ineffective use of risk-based approaches.

Regarding the reduction of risk, two topics are of particular note. The first is required use of post sterilization, pre- use filter integrity testing (AKA PUPSIT), as

PDA

Connecting People, Science and Regulation®

the primary means to reduce the risk of filter failure. The second is the requirement for the placement of settling plates in grade A critical areas.

We feel that the revision is an opportunity to promote a more scientifically practical understanding of contamination and contamination control strategies. We feel that clarification of intent for such methods as aseptic process simulation, air flow visualization, environmental monitoring, and personnel qualification can point out where these methods are best suited and where their limitations should be realized to avoid misinterpretation of results and a false sense of security. In addition, we believe that the revision of the Annex 1 should reinforce the benefit of and support for the use of aseptic processing systems that limit human access and interventions, including isolators and closed RABS.

PDA's expert committee has provided comments (detailed general and specific along with proposed changes) to further clarify the points made herein, which are in the attached table. We trust that these comments and suggestions will be received in the spirit in which they are presented. If there are any questions, please do not hesitate to contact me.

Sincerely,

Falk Klar
General Manager, Vice President PDA Europe
CC: SANTE-Revision, EC, Simona Kecksova, EMA, Jahanvi (Janie) Miller, PDA

- ✓ Comments submitted to the European Commission on 20 March 2018 and made available in the PDA website: https://www.pda.org/docs/default-source/website-document-library/scientific-and-regulatory-affairs/regulatory-comments-resources/2018/pda-annex-1-comments-20march2018.pdf?sfvrsn=4

PDA Annex 1 General Comments

This revision addresses a wide range of complex topics with some excellent and much needed improvements.

- More comprehensive document
- Acceptance criteria of zero contaminated units for aseptic process simulation
- No measurements/limits for particles of 5µm and bigger in the classification of Grade A areas
- New definition of "At rest" conditions (manufacturing equipment is static)
- Emphasis on **risk-based thinking** and decision making throughout the revision (e.g. for the selection of media incubation duration and temperature, based on the process being simulated and the targeted contamination)

PDA Annex 1 General Comments

The revision is an opportunity to promote a more scientifically practical understanding of contamination and contamination control strategies. We would expect:

- More explanation of expectations and guidance on risk management: risk identification and risk mitigation or reduction
- Requirement for post sterilization, pre- use filter integrity testing (aka PUPSIT)
- Requirement for the placement of settling plates in grade A critical areas.
- Clarification of intent for such methods as aseptic process simulation, air flow visualization, environmental monitoring, and personnel qualification (requirement, recommendation, or suggestion?)
- Terminology: clarification / harmonization needed

In addition, more emphasis on the use of systems that limit human access and interventions, including isolators and closed RABS, was expected.

PDA Annex 1 : Terminology - suggested replacement

Replace:	**With :**
Laminar air flow	Unidirectional air flow
Non-viable particulates	Total particulates
Alert/Action limits	Alert/Action levels
Grade A/B/C/D…	ISO 5/6/7/8...
Contamination (concept)	Contamination control strategy (concept)
SAL or sterility assurance level	PNSU or probability of a non-sterile unit
Clean Not Classified (CNC)	None (No use of CNC)

PDA Annex 1 : selection of comments

Topic: Principles (2).

-Risk assessments should be used to justify alternative approaches to those specified in this Annex only if these alternative approaches meet or surpass the intent of this Annex

Comment:

-This statement appears to prohibit risk assessments that are perceived as justifying a lessening of standards. This may undermine the value of risk assessments, if certain outcomes are prejudged. Also, the phrase: “the intent of this Annex” is vague.

-Suggested: Risk assessments should be used to justify alternative approaches to those specified in this Annex provided that these alternative approaches ensure the same or greater level of contamination control of the ones described in this Annex

PDA Annex 1 : selection of comments

Topic: Sterile Filtration - PUPSIT (8.84)

-Section 8.84 requires an integrity test of the sterilized filter assembly prior to use, commonly referred to as the pre-use, post-sterilization integrity test or PUPSIT, in order to mitigate risk of filter failure posed by damage to the filter and assembly through sterilization and use.

Comment:

-The use of PUPSIT methods pose their own risk to the integrity of the aseptic line and process. We feel that the risk associated with integral filter and assembly failure during use can be adequately controlled. Further, we feel that there are other means to prevent and mitigate such failure.

PDA Annex 1 : selection of comments

Topic: Sterile Filtration - PUPSIT (8.84) - Continued

Comment / Proposed Change:

-The filter and filter assembly preparation, sterilization, and use for sterilization of the product should be qualified to ensure that the filter and assembly maintain their integrity throughout the entire process. **This should include a well-documented risk based assessment of and corresponding control strategy implementation** to address potential filter and assembly defects and filtration failures caused by manufacture, handling, storage, sterilization, and use of the filter and assembly prior to and during product filtration.

-Control strategies should include efforts to prevent such defects and failures, as well as test the filter and assembly at appropriate phases of the process, including testing prior to the filter sterilization, immediately after use, and where the risk assessment indicates the need, after the filter sterilization

-In addition, where serial filtration (one filtration is followed by a subsequent filtration) is a process requirement, pre-use testing of the sterilized filter assemblies should not be required, due to the complexities of the testing procedure

PDA Annex 1 : selection of comments

Topic: Media simulation as a mean to qualify operators (4.4).

-Only trained personnel who have passed the gowning assessment and have participated in a successful aseptic process simulation test, in both cases simulating or performing their normal duties, should be authorized to enter any grade A/B area […] whilst unsupervised

Comment:

-Testing through Aseptic Process Simulation is not sensitive enough to fully qualify personnel to work in the Grade A/B area. Participation in media fills does not provide additional assurance of adherence to proper clean room behavior. Instead we recommend an emphasis on training and monitoring, as noted in the corresponding PDA TR and Points to Consider.

PDA Annex 1 : selection of comments

Topic: Media Simulation duration – Freeze Dryer. Cycle (9.35)

-Section 9.35 (f) requires full duration cycle aseptic process simulations for lyophilized processes.

Comment:

-There is no value to mimic the full cycle duration time (can be 40-50 hrs). Instead it is important to include parts that would challenge the freeze dryer the most e.g. vacuum pulses to challenge the microbe ingress into the chamber and transport into the vials due to turbulence during the vacuum pulses. This must be assessed via a risk assessment

PDA Annex 1 : selection of comments

Topic: Media Simulation duration (9.38)

-Section 9.38 (g) sets a requirement for full duration media fills.

Comment:

-Full duration media fills may not be necessary and may lead to decisions based on invalid scientific information, the setting of production batch duration merely on results of APS, and a false sense of security in regards to the length and conditions of production runs.

-Contamination of an aseptic process is primarily a function of events rather than time:

- the duration of the process simulation should be sufficient to assess the performance of those activities identified in a risk assessment as having the potential to introduce contamination.

-The duration of the process simulation should be risk based and designed to simulate the conditions which provide the greater likelihood of uncovering process contamination (i.e., worst case conditions).

- Each company should determine appropriate risk based rationale and approaches applicable to their unique operations by means of documented risk assessment and process simulation design.

PDA Annex 1 : selection of comments

Topic: Unidirectional air flow (5.3).

-The maintenance of unidirectional airflow should be demonstrated and validated across the whole of the grade A area

Comment:

-This implies that a Grade A (unidirectional) airflow is required within an isolator. Considering that all air within an isolator is entirely HEPA filtered and isolated from potential contamination, turbulent airflow within a closed isolator may be acceptable if supported by operational qualification demonstrating the maintenance of acceptable particulate levels (ISO 5 air borne particulate) and grade A viable levels.

PDA Annex 1 : selection of comments

Topic: Clean room periodic requalification (5.29)

-Clean rooms should be requalified periodically and after changes to equipment, facility or processes based on the principles of QRM. For grade A and B zones, the maximum time interval for requalification is 6 months. For grades C and D, the maximum time interval for requalification is 12 months.

Comment:

-ISO 14644-1 and 2 recommend classification based on a risk assessment, typically at one year. Revision should be consistent with ISO 14644 recommendations .

PDA Annex 1 : selection of comments

Topic: Non viable monitoring (9.13) .

-Table 5 sets limits (20) for 5 µm particle monitoring for Grade A environments.

Comment:

-Limits should not be applied for ≥5 µm particle monitoring for Grade A environments, due to the sampling limitations, as noted in ISO 14644-1.2:2014.

-It would be more effective to recommend that companies focus on the overall *trend* of ≥5 µm particle monitoring rather than individual numbers based on the low accuracy of the measurement. It should also be noted that clean room environmental performance issues, anticipated by the ≥5 µm particle monitoring, would be well represented with ≥ 0.5 µm particle monitoring. Therefore, there is a low risk of an issue arising that would be missed due to the lack of absolute ≥5 µm particle monitoring limits

PDA Annex 1 : selection of comments

Topic: Rotation of disinfectants (5.31).

-The statement “More than one type of disinfecting agent should be employed” appears to recommend or require the rotation of disinfectants (with different antimicrobial agents)

-Comment:

-PDA position as stated in technical reports and the aseptic processing points to consider, as well as scientific literature suggests that micro-organisms would not adapt to disinfectants (in contrast to antibiotic-resistance). In addition, this may lead to higher residue levels, without material benefit.

-Suggested the removal of recommendation for multiple disinfecting agents (but to keep the periodic use of a sporicidal agent)

PDA Annex 1 : selection of comments

Topic: In-direct contact surfaces (6.6)

-All critical surfaces that come into direct contact with sterile materials should be sterile.

Comment:

-For large equipment e.g., stopper bowls and tracks in isolators where it is not possible to pre-sterilize and install the items adequately without introducing additional contamination risk, a risk assessment should be used, including an evaluation of the effectiveness of VHP (or other treatment in-place) capability to remove all microorganisms that may be present: precautions should be taken to ensure the effectiveness of the in place sterilization method, including

a) Removal of any substances or residues that could reduce effectiveness of the sterilization process (e.g. oily substances)

b) Pre-treatment of materials to reduce bioburden steps (e.g. offline sterilization or decontamination)

c) Limited exposure of items to sources of contamination

d) Monitoring and sampling of sterilized or decontaminated items at the end of the fill/ production run

PDA Annex 1 : selection of comments

Topic: Lyophilizer sterilization. (8.106)

-Section 8.106 requires sterilization of the lyophilizer before each load.

Comment:

-Under certain circumstances, which may include but are not limited to the use of automated lyophilizer loading/unloading technologies, RABS for lyophilizer loading/unloading, a successful history of aseptic process simulations and sterility assurance, the sterilization frequency of lyophilizers may exceed after each load. In addition, excessive sterilization cycles may cause quicker aging and damaging of the lyophilizer. A frequency of sterilization based upon QRM principles is therefore suggested as implied in ISO standard 13408 – 3, Aseptic processing of health care products (Part 3:Lyophilization).

-The lyophilizer should be sterilized according to a predetermined frequency defined based on a risk assessment which takes into consideration technology and controls related to loading and unloading, to prevent contamination between cycles

PDA Annex 1 : selection of comments

Topic: Container Closure Integrity Testing (8.18).

-Section 8.18 prescribes 100% integrity testing of containers sealed by fusion. Samples of other containers should be checked for integrity utilising validated methods and in accordance with QRM, the frequency of testing should be based on the knowledge and experience of the container and closure systems being used. A statistically valid sampling plan should be utilized.

Comment:

The incorporation of a risk based approach, based on sound scientific principles is a welcome addition to the Annex. The focus should not be on end-point testing, but should embrace QRM principles with due consideration of the sealing process design, validation, and process controls (also for containers sealed by fusion).

PDA Annex 1 : selection of comments

Topic: Isolator and Gloves integrity (5.21)

-Integrity testing of the barrier systems and leak testing of the isolator and the glove system should be performed using visual, mechanical and physical methods. They should be performed at defined periods, at a minimum of the beginning and end of each batch, and following any intervention that may affect the integrity of the unit.

Comment:

-Suggested to clarify that interventions that pose a risk to the integrity of the gloves or isolator should be avoided where possible. Where they cannot be avoided, the integrity of gloves and isolator should at least be visually inspected after such interventions.

PDA Annex 1 : selection of comments

Topic: WFI - Water Systems (7.8)

-Water for injections (WFI) should be produced from purified water, stored and distributed in a manner which prevents microbial growth, for example by constant circulation at a temperature above 70°C. […]

Comment:

-It is recommended to align the requirements with whose of the current Pharmacopoeia (EP, USP, JP, FB) for WFI .

-Regarding the need for hot recirculation (>70°C): recirculation of WFI at lower temperatures with periodic sanitization has been proven to be effective and validated in many instances. Recirculating systems below 70°C should be sanitized periodically based upon monitoring and risk assessment and in a manner that does not compromise WFI quality

PDA Annex 1 : selection of comments

Topic: Pure Steam .

-Section 7.17 recommends or requires the use of “Purified water with low level of endotoxin” as feed to a pure steam generator.

Comment:

- Feed water to Pure Steam generator does not require purified water to meet pure steam quality specifications. There may be no endotoxin limit (as there is no endotoxin limit for Purified Water) for a properly designed generator that has entrainment separation capability to prevent the carryover of endotoxin in the distillate.

-Replace current recommendation to align with clean steam generator design criteria. “7.17 Feed water to a pure steam (clean steam) generator should comply with drinking water standards as a minimum. Feed water should be treated and pure steam generators designed and operated in a manner to ensure that the quality of steam produced meets defined chemical and endotoxin levels. For steam generators supplying steam to moist heat sterilizers, porous hard-goods loads steam condensate must meet the compendial requirements for WFI”

PDA Annex 1 : selection of comments

Topic: Sterilization by heat (8.47 and 8.52)

-Section 8.47 contains statements that as written apply only to porous hard goods and should be broadened to accurately cover liquid loads which use superheated water.

-Section 8.52 describes equilibration time which is not applicable to liquid loads and therefore only applies to porous hard good loads. This is not a consideration for liquid loads due to the lag in heat penetration temperature when compared to chamber temperature.

Comment:

-Modify language to clarify intent (i.e. specify what is applicable to porous hard goods and add the requirements specific for liquid products).

PDA Annex 1 : selection of comments

Topic: Point of Fill Filtration (8.15).

-Section 8.15 states that the final sterile filtration should be carried out as close as possible to the filling point.

Comment:

- This statement requires clarification. In the case of some single use systems, the filter may not be positioned very close to the filling system. Misinterpretation of this requirement may dissuade the use of such systems or promote designs that add intervention risk.

- It is recommended to modify language to clarify intent. The final sterile filtration should be carried out downstream of aseptic connections wherever possible.

Conclusions

PDA welcomes the revised Annex 1 and acknowledges the tremendous effort to revise the GMP annex to integrate new concepts (e.g. quality risk managements) and to facilitate introduction and implementation of innovative technologies, therefore paving the way of the regulatory framework for the next decades of sterile product manufacture.

PDA has identified areas where, because of the complexity of the subject matter and varying experience of companies, there may be the potential for misinterpretation that may result in quality and compliance risk. The clarity of language and intent are essential to the best understanding of the principles presented. Where intent is not fully understood, ambiguity exists that may lead to confusion and lack of appreciation of important recommendations.

PDA offered comments to the European Commission with the purpose to contribute to the further improvement of the revised Annex 1 and welcome a dialogue with the Regulatory Agencies.

Acknowledgements

PDA Annex 1 Comment Task Force

- Masahiro Akimoto (Toray)
- Hal Baseman (Valsource), Co-chair
- Jette Christensen (Novo Nordisk)
- Veronique Davoust (Pfizer)
- Phil De Santis (Consultant)
- Guenther Gapp (Consultant)
- Gabriele Gori (GSK Vaccines), Co-chair
- Richard Johnson (PDA)
- Salim Mamujee (Kite Pharma)
- William Miele (Pfizer)
- Janie Miller (PDA)
- Vincent O'Shaughnessy (Amgen)
- Darius Pillsbury (Adaptimmune)
- Mike Sadowski (Baxter)
- Ed Tidswell (Merck)
- Geert Vandenbossche (Novartis)

Thanks also to the many other colleagues who provided their contribution as part of the PDA Advisory Boards

Thank-you!