

# Assessment and Impact of EMA Annexure 1: Industry Perspective

Wednesday November 4<sup>th</sup>, 2020

Glenn Wright, PDA, VP Science & Regulatory Affairs

Hal Baseman, ValSource, Co-Chair PDA Annex 1 Review Task Force



## History of Annex 1

1971 - Annex 1 first issued  
- Number of revisions since 1971 but no full revision

2012 - First proposal for full revision of Annex 1

2014 - Proposal for full revision re-issued

2017 - First draft of revision published for comment  
- Over 6,000 comments received

2020 - Second draft (ver 12) published for targeted stakeholder consultation



## Reasons for Revision

Some of the reasons for revision:

- Introduce Quality Risk Management (QRM) and Contamination Control Strategy
- Support and encourage new and innovative processes and technology
- Clarify ambiguities
- Add more detail
  - Current 2008 published version: 16 pages in length
  - 2020 draft: Just over 50 pages in length
- Restructure for more logical flow



## Regulatory Stakeholders

EU  
28 Member States

PIC/S  
54 Agencies

WHO  
194 Members

## Industry Stakeholders

Small Pharma

Big Pharma

Hospitals

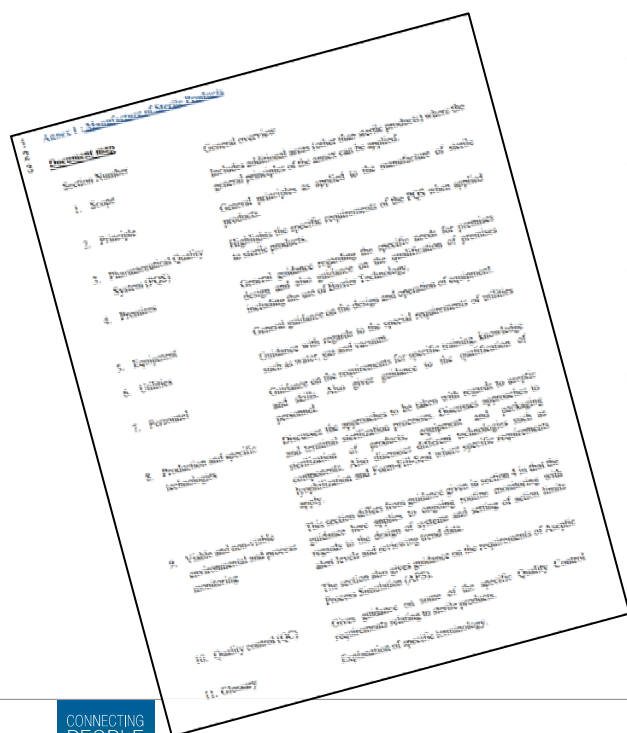
Suppliers

CMOs

Academic Institutions

Government/  
State  
Laboratories

## 2020 Targeted Consultation of Annex 1 Version 12



Section Number	Description
1. Scope	General overview Includes additional areas (other than sterile products) where the general principles of the annex can be applied.
2. Principle	General principles as applied to the manufacture of sterile products.
3. Pharmaceutical Quality System (PQS)	Highlights the specific requirements of the PQS when applied to sterile products.
4. Premises	General guidance regarding the specific needs for premises design and also guidance on the qualification of premises including the use of Diverted Technology.
5. Equipment	General guidance on the design and operation of equipment including the special requirements of utilities.
6. Utilities	Guidance with regards to the special requirements of utilities such as water, gas and vacuum.
7. Personnel	Guidance on the requirements for specific training, knowledge and skills. Also gives guidance to the qualification of personnel.
8. Production and specific technologies	Discusses the approaches to be taken with regards to aseptic and terminal sterilization processes. Discusses approaches to sterilization of products, equipment and packaging components. Also discusses different technologies such as hypofiltration and Euro-Filter and their specific requirements apply.
9. Viable and non-viable environmental and process monitoring	This section differs from guidance given in section 4 in that the guidance here applies to ongoing routine monitoring with regards to the design of systems and setting of action limits alert levels and recovering trend data.
10. Quality control (QC)	The section also gives guidance on the requirements of Acceptance Process Limitation (APL).
11. Glossary	Gives guidance on some of the specific Quality Control requirements relating to sterile products. Explanation of specific terminology

- Targeted Consultation with 16 Stakeholders (Identified in the notice)
- Stakeholders encouragement not to repeat comments from last public consultation and focus on specific sections
- PDA and other associations identified areas throughout the document where commenting was still needed
- EMA extended commenting deadline due to COVID to 20 July 2020, providing more time for comment collation/review before submission
- PDA coordinated a series of T-cons between associations to discuss the draft and identify themes where the associations were aligned
  - The group of associations submitted a joint letter to the EC / EMA on these themes
  - Each association also individually provided their own comments to the EMA



# Associations' Letter



- The Annex should be flexible to support the use of appropriate alternative approaches
- There must be clear interpretation of the Annex.
  - Avoid use of specific examples
  - Clear distinctions between similar but different technologies and approaches
- More work on the Annex is needed
- Associations stand ready to assist with training/education programs once the Annex is approved

Find the Letter at: <https://www.pda.org/pda-letter-portal/home/full-article/joint-associations-response-letter-on-eu-annex-1-draft>

# PDA's Commenting Activity

## Assessment and Impact of EMA Annexure 1: Industry Perspective

# Content and comments





## PDA commenting process

9

- Core Team: 12 experts from 10 companies from US, EU, ASIA, in addition to consultants and PDA. Most worked on PDA Aseptic Process PtC Parts 1 & 2.
- Solicited and considered comments from 10K plus PDA members
- Additional effort with BioPhorum on PUPSIT and BFSIOA on BFS
- Overall, 88 Comments endorsed by the PDA Science Advisory Boards (SAB) and BoD and sent to EMA

# Team commenting rules

- ✓ Follow the format set by EMA, where possible
- ✓ Should not add burden or requirements, unless it is needed for patient safety
- ✓ Keep clarity of intent and value of topic in mind
- ✓ If one team member does not understand intent of section, then public will not
- ✓ Take into consideration public comments, but not necessary repeat them
- ✓ Limit comments to most important ones - but recognize this is our chance to address issues on Annex that will have impact for many years
- ✓ Try to reach a consensus

Introduction of principles of Quality Risk Management & Contamination Control Strategy

New & Innovative processes & technologies:

- Reinforcing the need of manufacturers to keep up with current technologies
- Single use closed systems
- Disposable systems
- Rapid Microbial test methods

Clarify ambiguities – more detail needed

Restructure – more logical flow



## Quality Risk Management in 2020 Draft Revision (12)

- Manufacture of sterile products using principles of **QRM** to ensure contamination is prevented in final product.
- QRM applies to document in its **entirety**
- Processes, equipment, facilities and manufacturing managed in accordance with QRM principles to provide a **proactive** means of identifying, scientifically evaluating and controlling potential risks to quality. QRM priorities should include **good design** of facility, equipment and process ... (and monitoring)
- Where **alternative approaches** are used, should be supported by appropriate rationales and risk assessment and should meet intent of Annex.

*If regulators expect industry to use QRM to justify current approaches ...  
then QRM can be used to justify improved approaches.*

Contamination Control Strategy (CCS) – A **planned set of controls** for microorganisms, pyrogens and particulates, **derived from current product and process understanding that assures process performance** and product quality.

The controls can include parameters and attributes related to active substance, excipient and drug product materials and components, facility and equipment operating conditions, in process controls, finished product specifications, and the associated methods and frequency of monitoring and control.

\*Also from EU GMP Annex 15 and derived from ICH Q10.

Section Number	General Overview
1 Scope	<ul style="list-style-type: none"><li>• Additional areas where principles of Annex can be applied – <b>relevance to ATMP and low bioburden products?</b></li></ul>
2 Principles	<ul style="list-style-type: none"><li>• Principles as applied to manufacture of medicinal products. Includes <b>linkage of Contamination Control Strategy and QRM</b></li></ul>
3 Pharmaceutical Quality System	<ul style="list-style-type: none"><li>• Highlights the specific requirements of the PQS when applied to sterile medicinal products – <b>emphasizes QRM throughout</b></li></ul>
4 Premises	<ul style="list-style-type: none"><li>• Premises design and qualification of premises including the use of <b>barrier technology, cleanroom classification, qualification</b></li></ul>
5 Equipment	<ul style="list-style-type: none"><li>• Design, operation, and <b>decontamination/sterilization</b> of equipment</li></ul>
6 Utilities	<ul style="list-style-type: none"><li>• Requirements of utilities such as <b>water, steam</b>, gases, air and vacuum</li></ul>
7 Personnel	<ul style="list-style-type: none"><li>• Training knowledge, skills, <b>qualification, supervision</b></li></ul>

Section Number	General Overview
8 Production and specific technologies	<ul style="list-style-type: none"><li>• Aseptic and terminal sterilization processes - single use, <b>lyophilization and BFS/FFS/VFFS</b>, sterilization</li></ul>
9 Viable and nonviable EM and process monitoring	<ul style="list-style-type: none"><li>• Ongoing routine monitoring - setting of alert limits and reviewing trend data, <b>Aseptic Process Simulations</b></li></ul>
10 Quality Control	<ul style="list-style-type: none"><li>• Quality Control requirements relating to sterile medicinal products, <b>Sterility Testing</b></li></ul>
11 Glossary	<ul style="list-style-type: none"><li>• Explanation of terminology – <b>some added, some changed</b></li></ul>

## 2<sup>nd</sup> Consultation Request

**2. Scope of the consultation: This second consultation is intended to be focused and limited to paragraphs that raised concerns or were changed more significantly, as identified below.**

**2.1. Feedback on the concerns raised by stakeholders (30)**

Qualification & requalification of cleanroom	from § 4.25 to 4.35
Handling of water systems	from § 6.7 to 6.15
Integrity testing of large volume parenteral container	§ 8.21
Handling of sterilizing filter including pre-use post sterilization integrity testing (Pupsit)	§ 8.88 and 8.95 & 8.96
Handling of lyophiliser	from § 8.110 to 8.113
Sterility testing	§ 10.6 & 10.7

**2.2. Sections and/or paragraphs which were substantively modified (44)**

Definition and handling of barriers systems including disinfection/decontamination	from § 4.18 to 4.24
Handling of gas filters	from § 6.18 to 6.20 and 8.89 & 8.90
Personnel qualification & gowning	§ 7.5 & 7.6 and from 7.14 to 7.16
Aseptic production	from § 8.11 to 8.19
Moist heat sterilisation	from § 8.54 to 8.65
Personnel monitoring	§ 9.32 & 9.33
Aseptic process stimulation (APS)	§ 9.34 & 9.40 & 9.47
Quality control	§ 10.1

**2.3. Other significant comments, Please avoid re-submitting comments already submitted at the first consultation ...**



- Many 2018 comments addressed (e.g. PUPSIT, APS, moist heat sterilization)
- QRM alignment to Contamination Control Strategy
- APS as verification of process control
- Clarity between ‘hard goods’ and ‘terminally sterilised products’
- Lyophilizer sterilization frequency based on automated closed load systems or systems that exclude operator intervention
- Glossary definitions

## Some remaining concerns

- Need for further clarity
- Strengthen QRM option for alternate approaches
- Relevance to ATMPs and “other” new technologies
- RABS and Isolator differentiation
- Prescriptive examples can be restrictive, e.g. settling plates
- Qualification sequence
- Reliance on testing and APS to ensure process control
- PUPSIT as default, need to mention PUPSIT related risk
- Silent on VHP for indirect product contact surfaces

### Annex 1 should ...

1. Avoid opportunity for individual interpretation and varied enforcement
2. Reduce use of examples that may be interpreted as prescriptive requirements
3. Use scientifically sound terms and definitions (e.g. total particulates, PNSU)
4. Focus on process design to assure control, rather than testing and monitoring
5. Reduce regulatory burden where little value is expressed
6. Improve process reliability and product quality assurance
7. Anticipate the needs of the future
8. Allow for alternative approaches to address new technologies, therapies, improved methods

### Qualification and re-qualification of Cleanrooms

- Still need to clarify approach to classification, qualification, and requalification sequence and requirements (e.g. EMPQ performed during APS)
- Removed 5 µm classification, added 1µm particle size
- Need to align with ISO 14644

### Handling of Water Systems

- Not all water systems require pyrogen control (e.g. Purified Water)

### Integrity testing of large volume parenteral containers

- Containers closed by fusion should be subject to 100% integrity testing. But this is not feasible for all LVP (wrapped) presentations



## Some more key “stakeholder concern” topics and comments

### Handling of Lyophilizer

- Until capped, product removed from the lyophilizer should remain under Grade A conditions air supply
- Finishing of sterile products where grade A is required until capped?
- **Qualification of cycle dwell time**

### Sterility Testing

- Sterility test: suggested to be taken beginning, middle and end of the batch and **after any significant intervention** (e.g. open barrier door). It is suggested that sampling frequency should be justified and documented in a CCS.

### Handling of Sterilizing filter including Pre-use Post-use sterilization integrity testing (PUPSIT)

- Allows for risk-based approach to PUPSIT. **PUPSIT remains default method.** Small batch example and does not note PUPSIT related risk.
- Clarification of redundant filtration and positioning of filters needed.

8.88 The integrity of the sterilized filter assembly should be verified by integrity testing before use ...

**It is recognized that PUPSIT may not always be possible due to process constraints** (e.g. the filtration of **very small volumes** of solution). In these cases, an **alternative approach may be taken providing that a thorough risk assessment...** Points to consider in such a risk assessment should include but are not be limited to:

- i. In depth knowledge and control of the sterilization process to ensure potential for damage to filter is minimized.
- ii. In depth knowledge and control of the supply chain to include:
  - Contract sterilization facilities.
  - Defined transport mechanisms.
  - Packaging of the sterilized filter, to prevent damage to the filter during transportation and storage.
- iii. In depth process knowledge such as:
  - Specific product type, including particulate burden 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 particulate burden and clarify the product prior to the sterile filtration.

**Add: “Risk to the aseptic process”**



## Some key “substantially changed” topics and comments

### Definition and Handling of Barrier systems including disinfection/ decontamination

- Add clarity to differentiation between RABs and Isolators
- Make clear differences between RABs and Isolators and the sterility assurance of in-direct product contact parts
- **Glove integrity testing physical vs visual inspection/campaign or batch**
- Unidirectional airflow and demonstration in Isolators

### Handling of Gas Filters

- Gases should be of appropriate quality
- Should be tested as part of campaign manufacture

### Personal qualification and gowning

- Requirements state that personnel working in grade C and D should go through gowning qualification. Gowning qualification of personnel working with non critical activities in lower grade cleanrooms should include training but not full qualification based on the lower risks.
- **Restrict and supervise people entering without qualification**



## Some more key “substantially changed” topics and comments

### Aseptic production

- Suggested the use of the principles and measures taken shall be documented in the CCS.
- Should reference the processes already mentioned – use of barrier systems, sterilisation-in-place, robotics etc and defined in CCS
- The required intervention list should be in APS section and not in aseptic production

### Moist heat

- **Needed differentiation between porous loads, terminal sterilisation of products/fluid cycles and steam-in-place**
- Validation needs both minimum and maximum temperatures attained
- Need a validated air detector with periodic Bowie Dick for verification





## Some more key “substantially changed” topics and comments

### Personal Monitoring

- It is unclear what is intended by the statement that “Particular consideration should be given”. Unclear whether the intent is to include exit monitoring for all personnel regardless of activity
- A requirement to monitor all personnel entering the aseptic area and in exit also introduces risk by requiring additional presence of personnel / sampling media.

### Aseptic **Process Simulation** (APS)

- **Should not be the only means to validate the aseptic process. Should be part of the sterility assurance CCS program**
- Frequency of interventions based upon risk to process that cannot be detected by other means
- **Link to personnel qualification remains, but is questionable**
- Manual aseptic fill vs. process

### Quality Control

- 10.6 Point i. indicates in addition to pulling sterility samples at the beginning, middle, and end of a batch, **to also pull samples at a significant intervention** (e.g. interventions where the integrity of the barrier is breached) or an operator intervention into critical zones.
- Clarify lyophilizer load sterility testing sampling.

### Disinfection

- The requirement to have **different modes (rotation)** of action of disinfectant is still included

### Premises

- The section describes that transfer into an aseptic processing area should be carried out via a unidirectional process. **The term 'unidirectional' used in this context is confusing as it may be interpreted as UDAF.**
- "A warning system should be in place to instantly indicate and warn operators of any failure in the air supply or reduction of pressure differentials..."

### Equipment

- Defines direct and indirect product contact surfaces and sterilization requirement.
- **Some current Isolator design do not allow for indirect contact parts to be heat sterilised.**

Direct and indirect contact parts **used for aseptic processing** should be sterilized. Direct contact parts are those that the **sterile** 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~~ **the surface of critical items and components that contacts sterile product.** *Where indirect product contact equipment design does not allow for heat sterilization and installation, a risk assessment should address the use and control required for alternative methods to address product sterility.*

### VHP sterilization of stopper bowls in isolators

### Finishing

- It is not clear if CCI testing will be required for products not closed by fusion.

### Sterilisation

- Lacks clarity as most refers to terminal sterilisation
- Cycle review now part of batch certification
- All parameters should be defined, and **where critical** controlled, monitored and recorded.
- Need to understand what is critical

### Dry Heat

- Description of dry heat sterilisation is not accurate and confusing.
- Dry heat sterilizing/ depyrogenation tunnels should be configured to ensure that air flow protects the integrity and performance of Grade A sterilizing zone by maintaining pressure differentials and air flow through tunnel from higher grade area to lower grade area.



## Some more key “other significant” topics and comments

### Gaseous sterilisation e.g. Ethylene Oxide

- **Requirements and guidance for VHP decontamination are missing.** But since VHP is a widely used bio-decontamination method requirements and guidance is needed for this process to add clarity on expectations. The MHRA Blog ‘Fragility of VHP’ indicated the need for clarity.

### FFS & BFS

- **Appears to be “mixing” of aspects of FFS/VFFS and BFS processes.** They are two separate techniques that should be addressed separately. Many of the requirements under heading do not apply to BFS
- BFS Grade A air conditions should be Grade A air quality

### Environmental Monitoring EM

- EM and process monitoring "Sampling methods and equipment used should be fully understood. The recovery efficiency of the sampling methods chosen should be qualified."
- **5 µm and settling plates remain**
- Where processes have discarded product contact materials, discarded material should be simulated with media as part of APS.

## Aseptic Process Simulation

- “Verify” rather than “determine” aseptic process capability

## Campaign

- Add definition linked to time

## Cleanroom

- At rest and operational states aligned with ISO standard 14644-1

## Bio-contamination and Decontamination

- Alignment with modern industry practice and regulatory expectation

## Closed system, Aseptic connecting device, Iso-kinetic sampling head, Isolator

## Manual Aseptic Filling & Manual Aseptic Operation

- Differentiate filling for ATMP related processes

# Final thoughts

- Annex 1 preparation, review, and implementation by international team
- Significant levels of industry consensus
- Highlights need for further scientific analysis and evidence
- Clarity for avoidance of varied and mis-interpretation essential
- Industry offer to help with education
- Pandemic underscores need for alternate approaches to meet future circumstances
- Final release expected in mid '21 – implementation schedule to be decided
- Industry and regulators should and are listening to each other ... thus a good document, but better would be better



## Acknowledgements

- Gabriele Gori, GSK, Co-Chair PDA Annex 1 team and Di Morris, Co-Chair PHSS Annex 1 team
- Stephen Langille and Darius Pillsbury, ValSource
- PDA Annex 1 comment response team



Thank You

Any Questions?