

EMA's Annex 1 - 2022 Preparation & Perils

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Disclaimer

- ◆ This presentation is based solely upon the opinions of the author.
- ◆ It does not represent the views of the Parenteral Drug Association, United States Pharmacopeia, the USP Microbiology Expert Committee or anyone else.

Background

- ◆ This a major revision of Annex 1 – Manufacture of Sterile Medicinal Products.
- ◆ Its origins lie in the MHRA Orange Guide of 1970's.
- ◆ Many of the core principles from that era remain unchanged and hence it manages to conflict with industry practices, scientific principles and other regulatory / pharmacopieal guidance documents.
- ◆ **It's regulation not guidance!** There's no easy provision for alternative practices as explicitly stated in FDA's Aseptic Guidance.

Science or Compliance



Galileo Galilei

- ◆ Annex 1 defines expectations for sterile product manufacture that:
 - contradict contemporary objective science
 - require additional sampling & testing
 - denigrate numerous technology advances

- ◆ Annex 1 wrongly promotes:
 - Regulation over innovation / continuous improvement
 - Evidence of absence as proof of success
 - 1970's era practices & designs over novelty
 - Monitoring over process control



Pope Urban VIII

The Core Principles Behind Annex 1 - 1

- ◆ Firms must establish a comprehensive Contamination Control Strategy addressing its sterile product manufacture.
 - Design of both the plant and processes
 - Premises and equipment
 - Personnel
 - Utilities
 - Raw material controls – including in-process controls
 - Product containers and closures
 - Vendor approval – integrity of data transfer
 - Management of outsourced services – production, testing

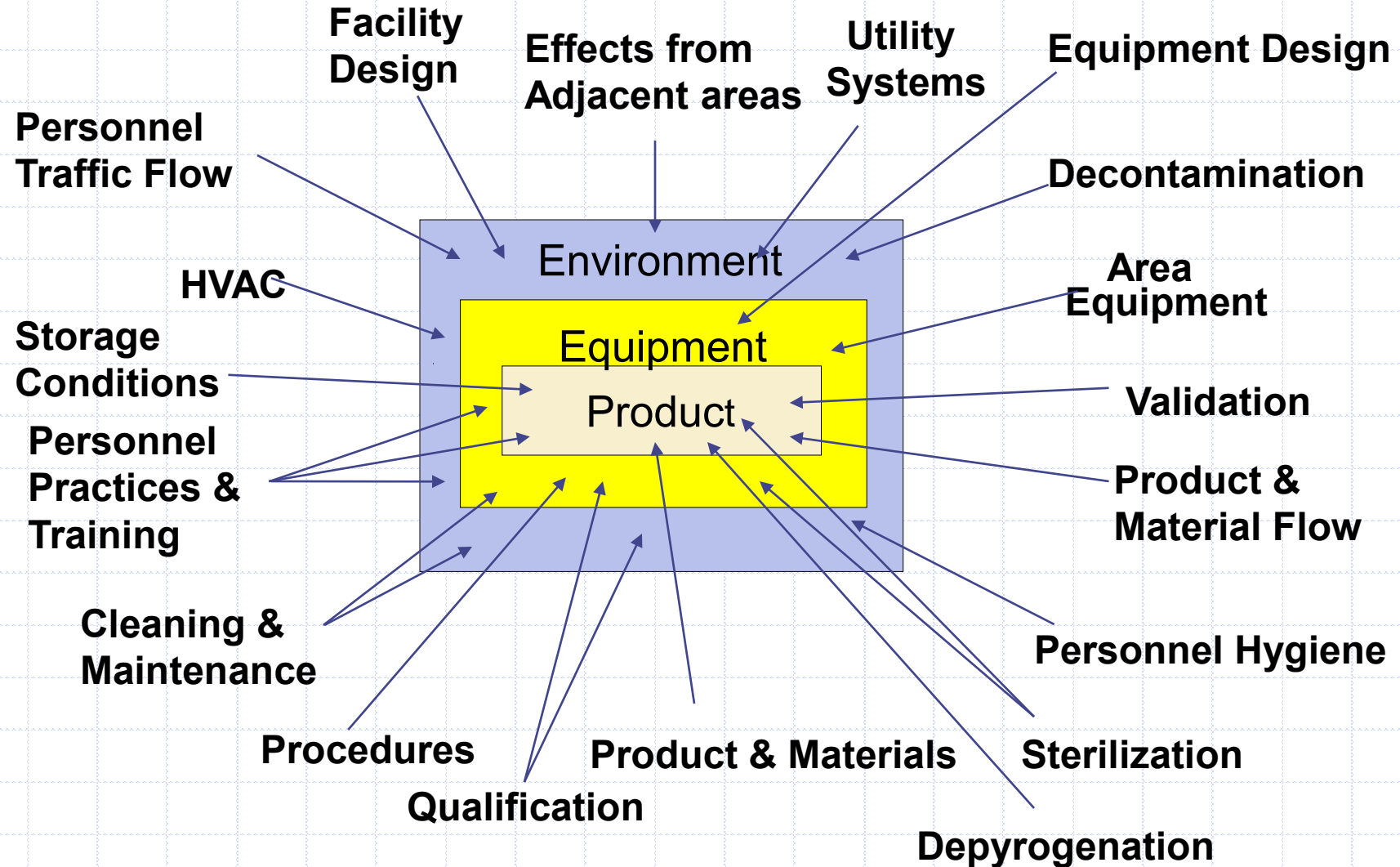
The Core Principles Behind Annex 1 - 2

- Process risk management
- Process validation
- Validation of sterilisation processes
- Preventative maintenance
- Cleaning and disinfection
- Monitoring systems
- Prevention mechanisms – trend analysis, detailed investigations.
- Continuous improvement based on information from above.

Contamination Control Strategy

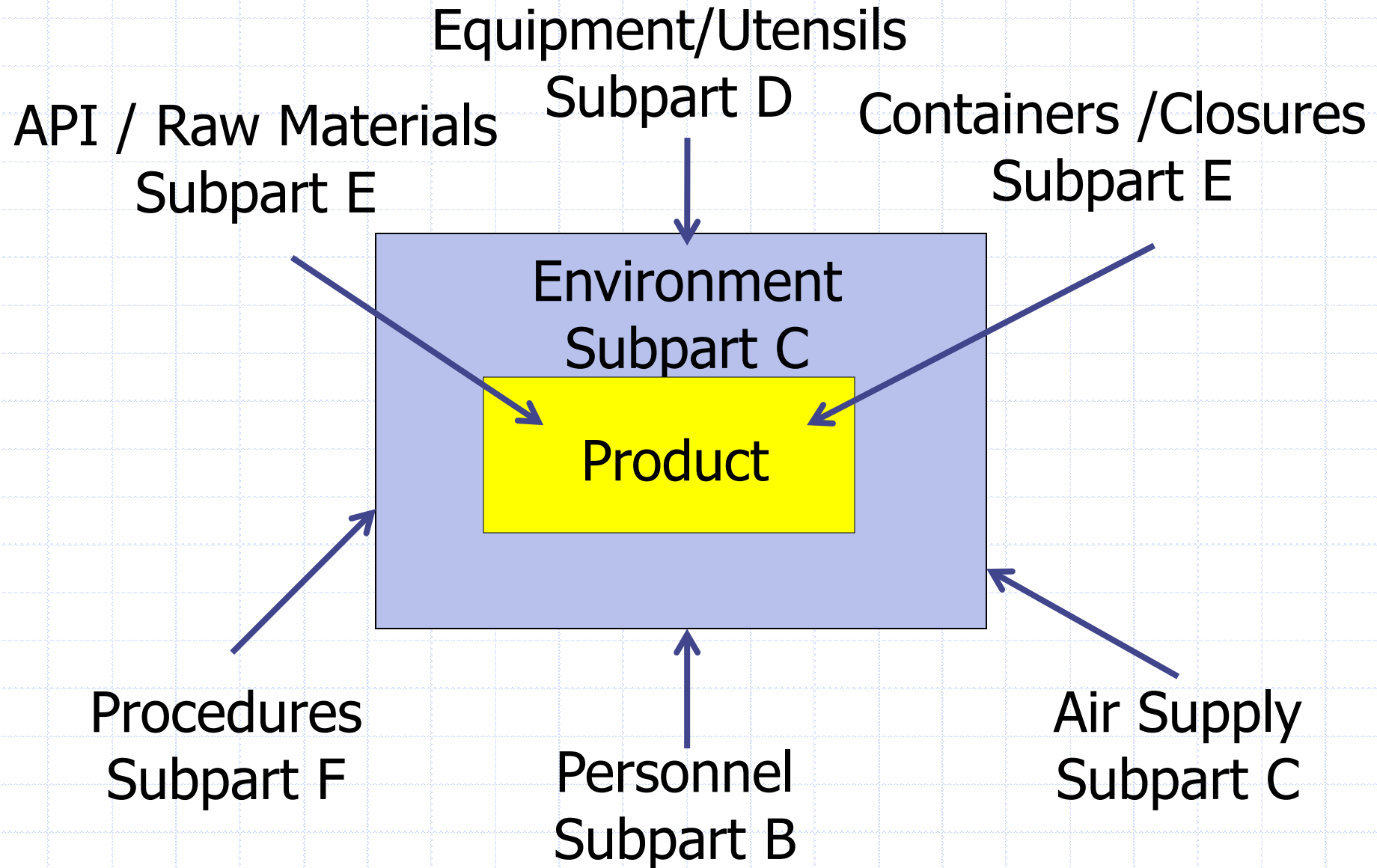
- ◆ There is **NO** requirement to develop a new CCS in response to the final Annex 1 version. Nearly all firms have document(s) outlining their approaches in some form or another – Site Master File, Validation Policy, Validation Master Plan, etc.
- ◆ The goal is to ensure that all of the identified requirements have been incorporated into the firm's operating practices and procedures. The CCS should point to the supportive materials.

Influences on Sterile Products



Adapted from Leonard Mestrandrea

Asepsis & US 211 CGMP Regulations



From USP, <1211>, Effective 2019

Sterility Assurance Sterility by Design

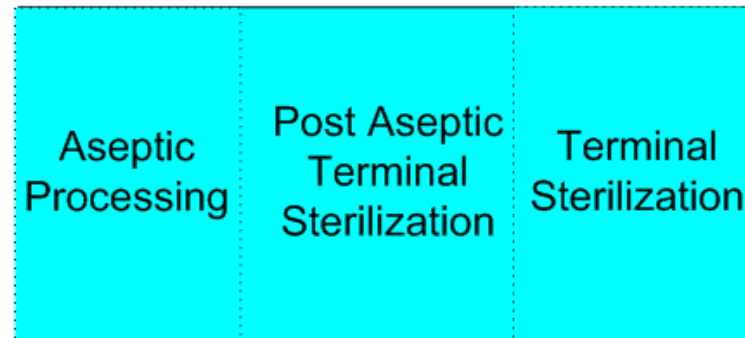
Personnel

Utilities

Containers -
Closures

API / Raw
Materials

Sterilization



Procedures

Facilities

Equipment

Decontamination

Depyrogenation

Monitoring

Air, Surface & Personnel Monitoring
Sterility Testing
Process Simulation

Quality Risk Management

- ◆ This is to be considered in all aspects of the CCS/
- ◆ *"... applying the principles of Quality Risk Management (QRM), to ensure that microbial, particulate and endotoxin/pyrogen contamination is prevented in the final product."*
- ◆ In principle, there should be no objection, however some of the required actions may actually increase the risk of contamination ingress. More on this later.



Premises

Contamination Control Overall

- Classification & Monitoring – both are needed in any new installation, but the Annex's content differs from standard practice.

Classification
(Chapter 4)

| Grade | Maximum limits for total particle $\geq 0.5 \mu\text{m}/\text{m}^3$ | | Maximum limits for total particle $\geq 5 \mu\text{m}/\text{m}^3$ | |
|-------|------------------------------------------------------------------------|----------------------------------|----------------------------------------------------------------------|----------------------------------|
| | at rest | in operation | at rest | in operation |
| A | 3 520 | 3 520 | Not specified ^(a) | Not specified ^(a) |
| B | 3 520 | 352 000 | Not specified ^(a) | 2 930 |
| C | 352 000 | 3 520 000 | 2 930 | 29 300 |
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Monitoring
(Chapter 9)

| Grade | Maximum limits for total particle $\geq 0.5 \mu\text{m}/\text{m}^3$ | | Maximum limits for total particle $\geq 5 \mu\text{m}/\text{m}^3$ | |
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- As facilities transition from installation to operation, the sampling locations / frequency are gradually reduced. Annex 1 goes the other way, by adding requirements during monitoring.
- Still doesn't align fully with ISO 14644.

Cleanrooms, RABS and Isolators - 1

- ◆ These are very different systems with very different performance capabilities. The annex blurs the distinction between them and treats them as near equals. The greatest number and most rigorous requirements are for isolators. RABS have fewer restrictions, while cleanrooms have the least.
- ◆ This disincentivizes the best available technology, making it more likely that firms will use less capable systems. It might result in continued implementation of new manned cleanrooms for aseptic processing.

Cleanrooms, RABS and Isolators - 2

- ◆ *"Restricted Access Barrier Systems (RABS) or isolators are beneficial in assuring required conditions and minimizing 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."* [4.3]
- ◆ Is this sufficient to further the use of advanced technologies when there are added constraints on their use in this same section? Respect also the denigration of vapor processes for sterilization (see section on equipment).

Annex 1 – Other Facility Issues

- ◆ Airlocks & passthroughs get considerable mention.
- ◆ Smoke studies are given added emphasis for all Grades and performed on a periodic basis.
- ◆ Decontamination practices must be validated.
- ◆ Glove practices for RABS & isolators are detailed. No mention is made of operator gloves in manned cleanrooms.
- ◆ There's not much impetus for the use of better technologies.



Equipment

Sterilization of Equipment - 1

- ◆ *"Particular attention should be given when the adopted product sterilisation method is not described in the current edition of the Pharmacopoeia, ..." [8.37]*
- ◆ This is problematic as the EP describes only steam, dry heat, ionizing radiation, and gas (only ETO is mentioned).
- ◆ Vapor sterilization for RABS & isolators where direct and indirect contact parts (*"e.g. sterilised items such as stopper bowls and guides, and sterilised components"*) are sterilized would be non-compliant. [5.5]
- ◆ This has the potential to become a major problem which cannot be easily addressed. Is USP <1229> considered?

Sterilization of Equipment - 2

- ◆ Aside from the limited and very restrictive requirements for the allowed sterilization processes – steam, dry heat, radiation, filtration and ETO nothing else is permitted.
- ◆ The use of ETO is discouraged ("*...where no other method is practical.*") [8.74]
- ◆ This eliminates a host of other sterilization methods including other gases (NO_2 , ClO_2 , O_3), liquids, vapors and other less common but increasingly useful methods.
- ◆ Deferring to *Europoean Pharmacopiea* for this is troubling. Will inclusion of other methods in USP <1229> *Sterilization* satisfy EMA?

Preparation for Sterilization

- ◆ *"Validation studies should take into account the product composition, storage conditions and **maximum time** between the start of the preparation of a product or material to be sterilised and its sterilisation."* [8.36] [8.17]
- ◆ Time limits are imposed on the interval between preparation and sterilization for equipment, components and containers.

Biological Indicator results are secondary!

- ◆ *"Suitable BIs placed at appropriate locations should be considered as an additional method to support the validation of the sterilisation process... ..BI results in isolation should not be used to override other critical parameters and process design elements."* [8.42]
- ◆ This is the opposite of what many have experienced with FDA investigators!

Steam Sterilization Complications Added

- ◆ *"For autoclaves capable of performing prevacuum sterilisation cycles, the temperature should be recorded at the chamber drain along with load probes throughout the sterilisation period."* [8.58]
- ◆ The use of load probes has been largely abandoned across the US industry as lacking real utility.

More Steam Sterilization Complications

- ◆ *"There should be adequate assurance of air removal prior to and during sterilisation when the sterilisation 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 the use of an air detector system."* [8.61]
- ◆ There's a fixation on steam sterilization requirements derived from HTM-10 which first appeared in the 1980's.



Utilities

Steam Quality

- ◆ *"Other aspects of the quality of pure steam used for sterilisation should be assessed periodically against validated parameters."* [6.17]
- ◆ This may be helpful as it appears to allows firms to their own limits.



Personnel

Personnel focused detail in Annex 1 revision

- ◆ Increased emphasis on training throughout.
- ◆ Dedicated garments to be worn under aseptic gowns.
- ◆ 'Sterile' eye covering are expected.
- ◆ Facility socks for personnel.
- ◆ Disinfected shoes are expected.
- ◆ No personal clothing in gown rooms for Grades B & C.
- ◆ Individual smoke study evaluation of operator aseptic technique.
- ◆ Procedures in place for operator dis-qualification and re-qualification after re-training.



Production & Specific Technologies

Terminal Sterilization expectations

- ◆ *"Where the CCS identifies that the product is at an unusual risk of contamination from the environment because, for example, the filling operation is slow, the containers are wide necked or are necessarily exposed for more than a few seconds before closing, then the product should be filled in a grade A with at least a grade C background."* [8.4]
- ◆ This isn't wholly new. Does the added detail imply increased use of Grade A will be expected?

Sound Advice to Listen to

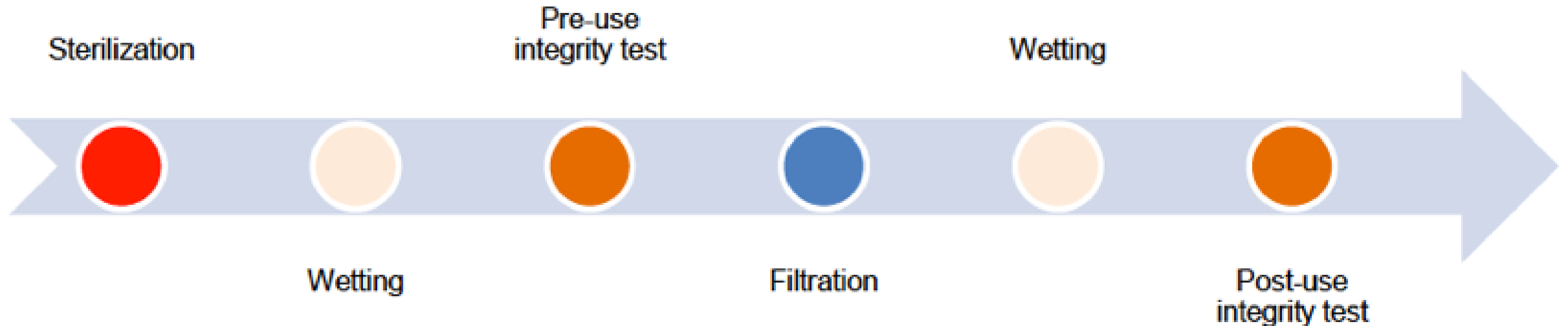
- ◆ *"Aseptic manipulations should be minimized through the use of engineering design solutions such as preassembled and sterilised equipment."* [8.15]
- ◆ *"There should be an authorized list of allowed and qualified interventions, both inherent and corrective, that may occur during production. Interventions should be carefully designed to ensure that the risk of contamination of the environment, process and product is effectively minimized."* [8.16]

Added Leak Testing Requirement

- ◆ *"Final 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... ...visual inspection alone is not considered as an acceptable integrity test method unless associated with mechanical/automated or semi-automated methods."* [8.21]
- ◆ This mandates new practices for BFS and FFS products. Does this expectation extend to terminally sterilized SVP and LVP containers?

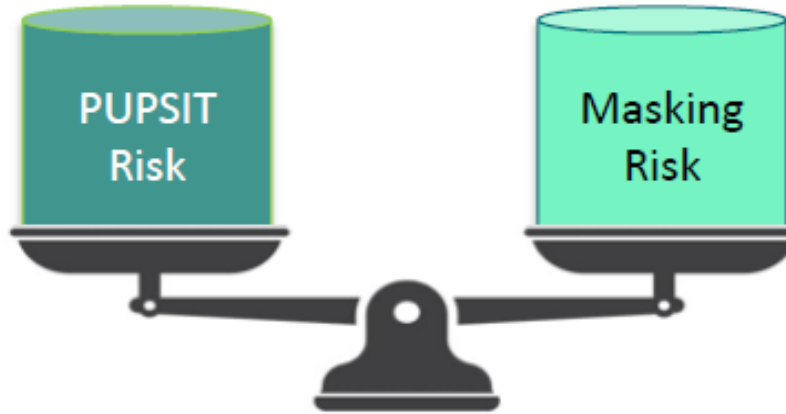
PUPSIT

- ◆ Expectations on this persist. PDA has supported several studies with filter manufacturers / users in efforts to resolve it to everyone's satisfaction. Incident rate of false negative potential was reported as less than 1%. Long term resolution is unclear.



PUPSIT Risk Balance

- Increased complexity of the filtration set-up
- Manipulation of the sterilized filtrate side
- Microbial ingress of the filtrate side
- Product dilution with wetting fluid
- With product wetting, unknown effects on the product by the test gas and time



- Flawed filter will not be detected by the post-use test
- Microbial penetration potential not being detected
- Sterilization process detriments are not detected
- ...

PUPSIT Clarified

- ◆ Pre-Use Post-Sterilization Integrity Test is intended to show that filters have not been damaged by the sterilization process.
- ◆ There's no need for PUPSIT if the process used to sterilize the filters has been validated. It only adds complexity and increases risk. This is why the current version of Annex 1 offers an alternative to PUPSIT.
- ◆ The issue of filter "healing" due to the accumulation of particles during the filtration process is different. That may lead to a non-integral filter passing the post-filtration integrity test.
- ◆ Comparison of the pre- and post-filtration integrity test values eliminates this concern, therefore **ALWAYS** perform a pre-filtration integrity test.

Closed and Single Use System Confusion

- ◆ *"The use of closed systems can **reduce** the risk of extraneous contamination... Closed systems should always be designed to **reduce the need for manual manipulations ...**"*[8.131]
- ◆ This severely understates their capability. Eliminate would be a better term.
- ◆ *"... For aseptic processing... ...the system should be **located in grade A.**"*[8.134]
- ◆ This is inconsistent with how closed systems are used in many applications / firms. Many single use systems are also closed systems; there should be substantial overlap between the two sections unfortunately there is not.

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Environment & Process Monitoring

5 Micron Particle Monitoring is here to stay

Table 6: Maximum permitted limits for total particle concentration monitoring.

| Grade | Maximum limits for total particle $\geq 0.5 \mu\text{m}/\text{m}^3$ | | Maximum limits for total particle $\geq 5 \mu\text{m}/\text{m}^3$ | |
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Note 2: The occasional indication of macro particle counts, especially $\geq 5 \mu\text{m}$, within grade A may be considered to be false counts due to electronic noise, stray light, coincidence loss, etc.

Personnel Monitoring Contradictions?

- ◆ *"Monitoring should include sampling of personnel at periodic intervals during the process. Sampling of personnel should be performed in such a way that it will not compromise the process. Particular consideration should be given to monitoring personnel following involvement in critical interventions ..."* [9.25]
- ◆ Is this rational? Increased personnel activity typically means increased contamination risk! Sampling personnel and allowing them to continue to work in the environment is a poor practice.

Viability Monitoring

Table 7: Maximum action limits for viable particle contamination

| Grade | Air sample Cfu /m³ | Settle plates (diam. 90 mm) Cfu /4 hours^(a) | Contact plates (diam. 55mm), Cfu / plate^(b) | Glove print, Including 5 fingers on both hands Cfu / glove |
|--------------|------------------------------------------|-----------------------------------------------------------------------|-----------------------------------------------------------------------|-------------------------------------------------------------------------------|
| A | No growth ^(c) | | | |
| B | 10 | 5 | 5 | 5 |
| C | 100 | 50 | 25 | - |
| D | 200 | 100 | 50 | - |

- (c) It should be noted that for grade A, any growth should result in an investigation.
- ◆ Well intended requirement, but one that proves little or nothing. Presence of microorganisms doesn't confirm contamination of filled units. Absence of microorganisms doesn't establish sterility of filled units. What does this really accomplish?

Process Simulation Raised Requirement

- ◆ *"The target should be zero growth. Any contaminated unit should result in a failed process simulation and the following actions should occur: ..."*
- ◆ *"...A sufficient number of successful, consecutive repeat media fills (normally a minimum of 3) should be conducted in order to demonstrate that the process has been returned to a state of control." [9.46]*
- ◆ No disagreement with the intent, but the required actions are numerous and restrictive.



Quality Control

A Reduction in Emphasis

- ◆ The latest revision of the Annex (V13) reduces the emphasis on sampling and testing as a means of assuring the safe production of sterile products that was present in the earlier drafts.
- ◆ This is a welcome sign.



Concluding Remarks



The Best of Annex 1

- ◆ The latest revision reduces the earlier emphasis on sampling and testing which emphasized Quality Control rather than Quality Assurance.
- ◆ While not making an explicit statement it speaks to many of the precepts of 'Sterility by Design' as found in USP <1211> *Sterility Assurance*. This is certainly encouraging.

The Worst of Annex 1

- ◆ The document errs where it endeavors to define technology requirements from an outdated perspective.
- ◆ Its treatment of RABS and isolation technology, closed and single use systems and sterilization processes include numerous flaws and outdated perspectives.

FDA's Position on Annex 1 is Unknown

- ◆ FDA's 2004 aseptic guidance is nearly 2 decades old, and while the revised Annex 1 is imperfect it does reflect an updated regulatory perspective on the many advances in sterile product manufacturing since that time.
- ◆ As a member of PIC/S, FDA has presumably been involved in the development of the revision throughout and will adhere to its precepts.

Thanks for Your Attention!



Questions?

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