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Parenteral Drug Association

A Milestone Revision: What the Latest PDA TR22 Means for Aseptic Processing

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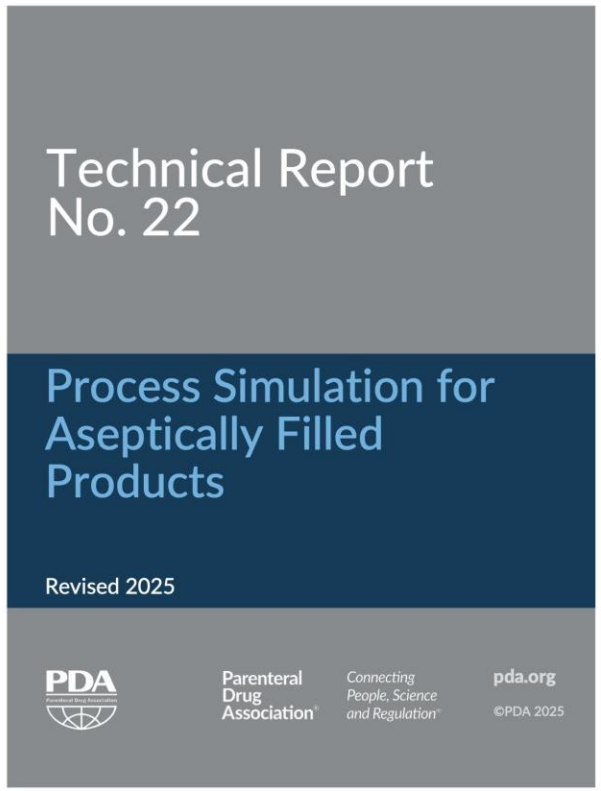
Connecting People, Science, and Regulation

Agenda

- Why TR22 Was Revised
- Alignment with Annex 1
- Key Principles and Prerequisites
- Risk-Based APS Design
- Interventions and Technology Considerations
- APS Duration and Acceptance
- Personnel Qualification
- Key Takeaways

Why TR22 Was Updated?



- **APS remains one of the most scrutinized areas during inspections**
- **Approximately one third of sterile and aseptic observations relate to APS for sterile products manufacturing**
- **Revised EU Annex 1 reframes APS as verification, no longer a standalone primary validation**
- **Industry needed clearer, standardized guidance aligned with modern technologies and barrier systems**
- **It was about time….prior revision was 2011**

Regulatory Drivers and Alignment with Annex 1

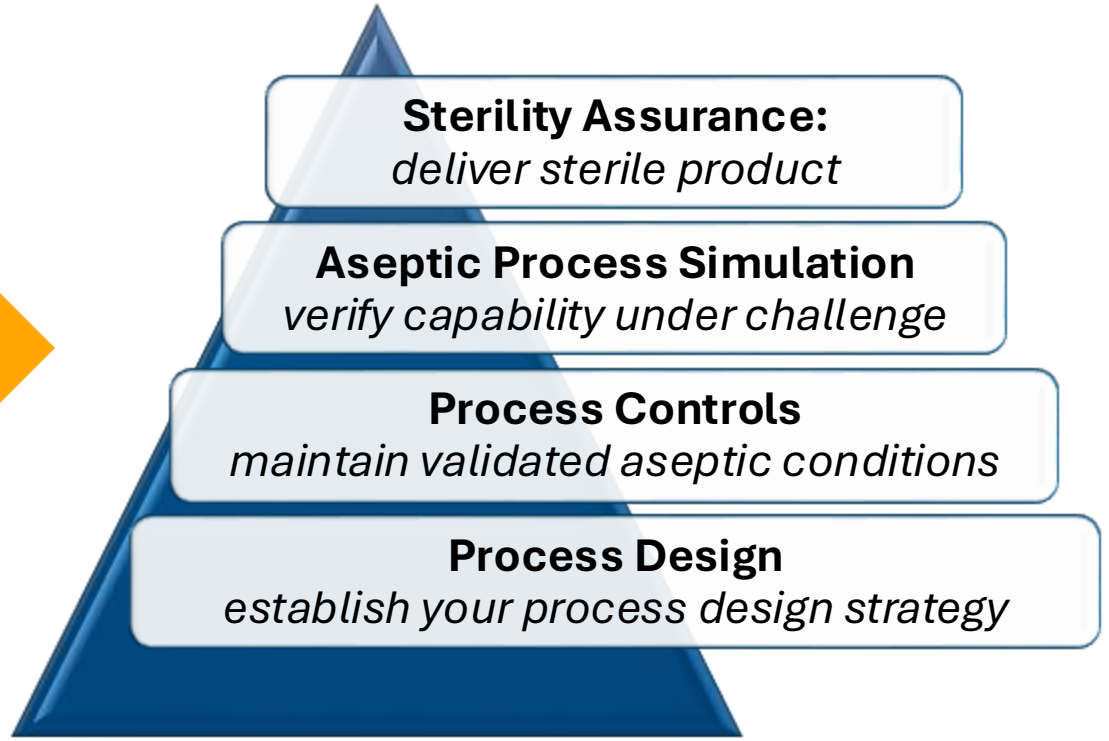
EU Annex 1 (2023) shifts perspective on APS from: a "primary validation tool" to *periodic verification*

- ✓Process design and system controls
- ✓APS must integrate with the site's CCS and effective controls
- ✓Ongoing monitoring and personnel training expectations
- ✓APS defined as simulation of the *entire* aseptic process
- ✓Clearer expectations described for frequency, scope, and justification
- ✓Pharmaceutical Quality System requirements & QRM tools

Structured Design

APS connects process design to sterility assurance by simulating real operations under controlled, yet challenging, conditions.

That's why EU Annex 1 calls APS a "periodic verification of control", not just a test, but evidence that the process still performs as designed.



APS Prerequisites

Here's a short list of things you need to…

..lock down BEFORE performing an APS.

Risk Management and Worst-Case Design

Worst-case conditions must be defined, justified, & documented:

- ✓Maximum personnel load
- ✓Slowest and fastest fill speeds
- ✓Maximum qualified hold times
- ✓Most complex container–closure configuration
- ✓Worst-case differs by technology (isolator, RABS, manual operations)

TR22 elevates QRM as the foundation of APS design

Interventions: Expanded Requirements and Clarity

TR22 introduces:

- **Intervention qualification expectations**
- **Disallowed or unapproved interventions**
- **Risk-based frequency using IREM (Intervention Risk Evaluation & Management Model)**
- **Handling of intervention-related units clarified (integral vs. non-integral)**

Inherent Interventions

Planned, required actions intrinsic to aseptic operations.

Examples: replenishing stoppers, glove disinfection, aseptic sampling.

Must be performed during APS with the same frequency & techniques as in production.

May be optimized or automated but cannot be fully eliminated.

Corrective Interventions

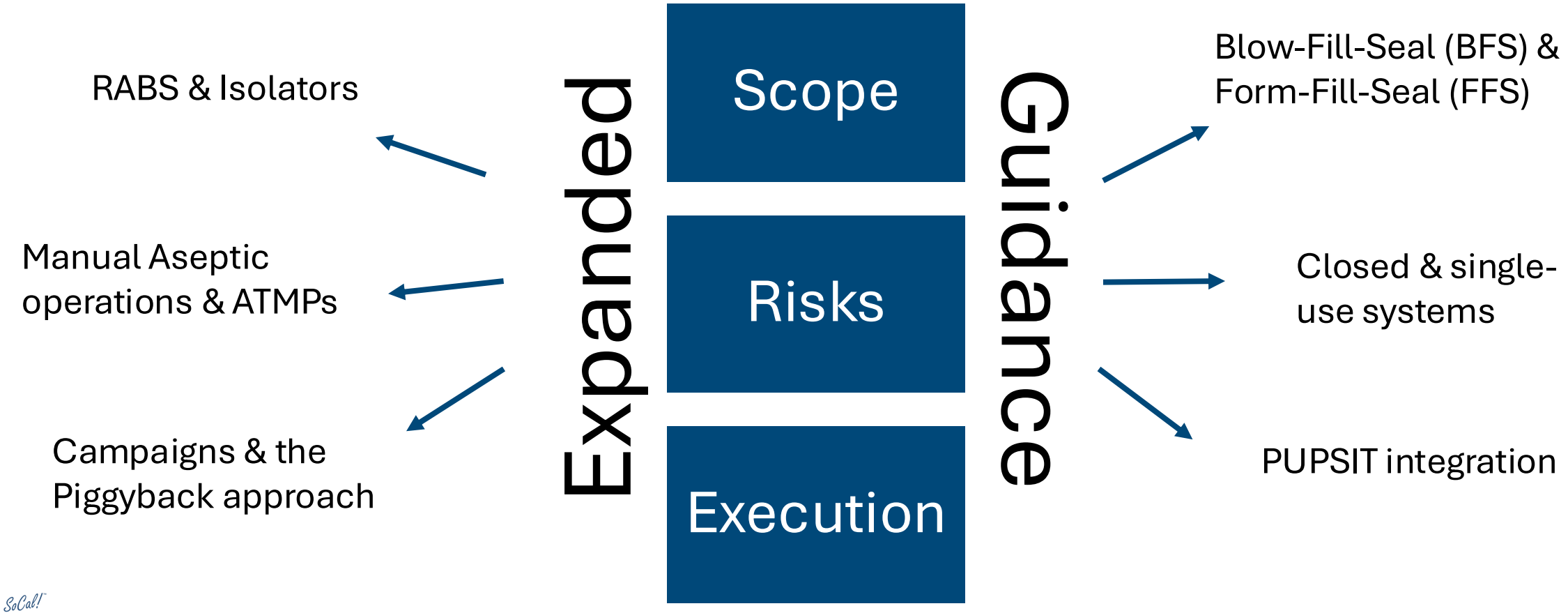
Unplanned actions required to address a deviation, issue, or process disturbance.

Examples: sensor reset, rail adjustment, or clearing blockages.

Should be risk-assessed before inclusion in APS.

Each corrective intervention in production should trigger root cause investigation & CAPA.

Technology-Specific Considerations



Means to achieve APS Duration

Duration = the time it takes to do the following:

- Equipment setup and preparation
- Sufficient filling and sealing of a representative number of units
- Adequate number, frequency, and types of interventions
- Transfer and aseptic connection of any surge tanks
- Maximum permitted hold times for products, components, and equipment
- Execution of routine environmental and personnel monitoring sampling
- Movement of personnel into and out of controlled environments (i.e., Grade B background for RABS) during shift changes (if applicable)
- Transfer and replenishment of components and materials, including loading of the isolator
- Replacement of filters during the aseptic process, if necessary
- Cleaning and sanitization procedures
- Visual inspection for glove integrity during use
- Consideration of unique operations or process-specific variables
- Simulation of campaign operations for extended durations

Means to achieve longer APS Duration Pt 2

TR22 cautiously provides flexible, risk-based strategies to achieve longer-duration simulations, when scientifically justified for certain circumstances:

- Intermittent media filling with idle periods
- Media followed by empty units
- Use of WFI during non-media segments
- Piggyback APS after production runs

If a risk assessment shows no duration-dependent effects, the APS does *not* need to exceed the process's maximum routine production time.

Growth Promotion Requirements

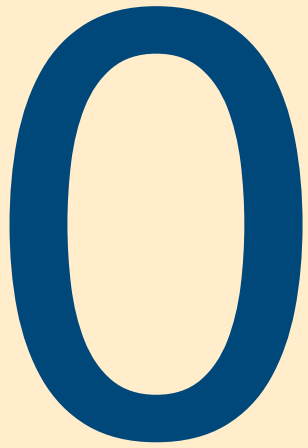
GOAL: confirms that the media could have supported growth if contamination were present along the simulated aseptic process.

Sample Collection	Method Criteria	Acceptance Criteria
• Collect samples from **beginning, middle, and end** of the APS batch to represent potential process. • **Start:** risk of nutrient loss from filtration. • **End:** risk of degradation from prolonged exposure. • Include **bulk media sample** prior to filling when justified. • Use aseptic technique and justify all sampling points	• Inoculate each sample with **<100 CFU** of required microorganisms. • Use robust **compendial strains** & **facility isolates,** justifying which are used. • Include **Gram+**, **Gram–**, **yeast**, and **mold** species. • Use the **same organisms** for bulk and post-incubation tests. • Design test to show media still supports growth after handling.	• Visible growth of all inoculated microorganisms = **Pass**. • Absence of growth = **Fail** & APS is rendered invalid, investigation required. • Unexpected growth (non-inoculated species) = investigate source, may require retest. • If GPT fails but APS shows contamination, the APS = Failed; investigation and repeat required.

Acceptance Criteria and Investigation of Positives

- Zero positives required for APS acceptance
- Any contaminated unit triggers a full, documented investigation
- TR22 provides a comprehensive list of what good looks like
- APS observation methods expanded

It's simple.
It's zero.



The target should be zero growth; any contaminated unit should result in a failed APS

- Detailed batch records & deviation documentation required
- Investigation expectations include:
  – Root cause analysis
  – Impact assessment
  – CAPA development
- APS positives indicate broader control issues, not isolated events

Understanding the Limitations of APS

APS does *not* qualify:
– Full process duration
– Maximum equipment usage times
– Environmental exposure limits
– Maximum hold times for sterile materials
– Human endurance or operator fatigue

These variables must be independently qualified and periodically verified

APS serves as *verification* of controls, not a universal validation tool

Personnel Qualification in the Updated TR22

Multi-level qualification model aligned with EU Annex 1 expectations:	L1: Entry-level access with foundational training
	L2: Routine aseptic activities under supervision
	L3: Full aseptic interventions and independent operation

- ✓ Annual requalification through APS or equivalent assessments
- ✓ Emphasis on aseptic technique, airflow awareness, & intervention proficiency
- ✓ Loss of qualification linked to performance, lapses, or deviations

How Digital Tools Strengthen APS Design & Execution

- VR-based operator training and intervention practice tools
- Standardized global templates and centralized training records
- Automated incubation and inspection systems
- Improved data integrity through integrated, multi-site data platforms
- Supports more reliable qualification, reduced variability, and better documentation

Expanded Appendix Examples:

New Appendices:

- Applying Risk-Based APS Frequency
- Intervention Simulation Frequency Based on Application of IREM
- Use of QRM to Define Inclusion and Frequency of Interventions during APS
- Aseptic Process Simulation (APS) Design for Lines Producing Single Dosage Form with Different Fill Volume
- Aseptic Process Simulation (APS) Design for Lines Producing Different Products or Dosage Forms
- Campaign Strategy Example for Isolator Line
- Design of the APS for an Advanced Therapy Medicinal Product (ATMP)

Conclusion and Key Takeaways

- TR22 (2025) is the most aligned guidance with current EU Annex 1 expectations including principles, glossary & design parameters
- APS is a *verification tool,* not the primary means of validating aseptic processes
- Strong emphasis on CCS, QRM, and scientific justification
- Expanded clarity on interventions, technologies, personnel qualification, and limitations
- Successful APS design requires true process understanding and site-specific risk evaluation

TR22 Statistics & Contributions

2 Expert CoLeads

2 PDA Project Managers

16 Industry Experts

3 Working Years

10+ Peer Reviewers

650 + Downloads

Co-Leads

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Thank you!

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