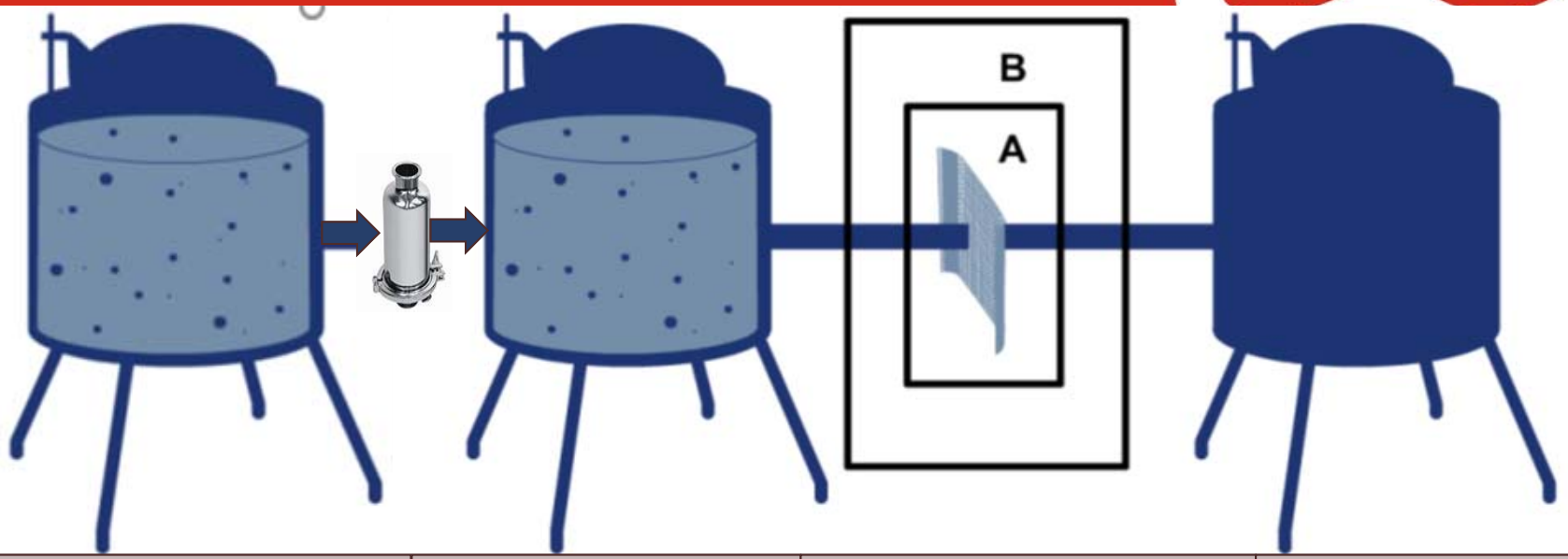
Aseptic Process Simulation (APS) Overview – Patrick Henderson

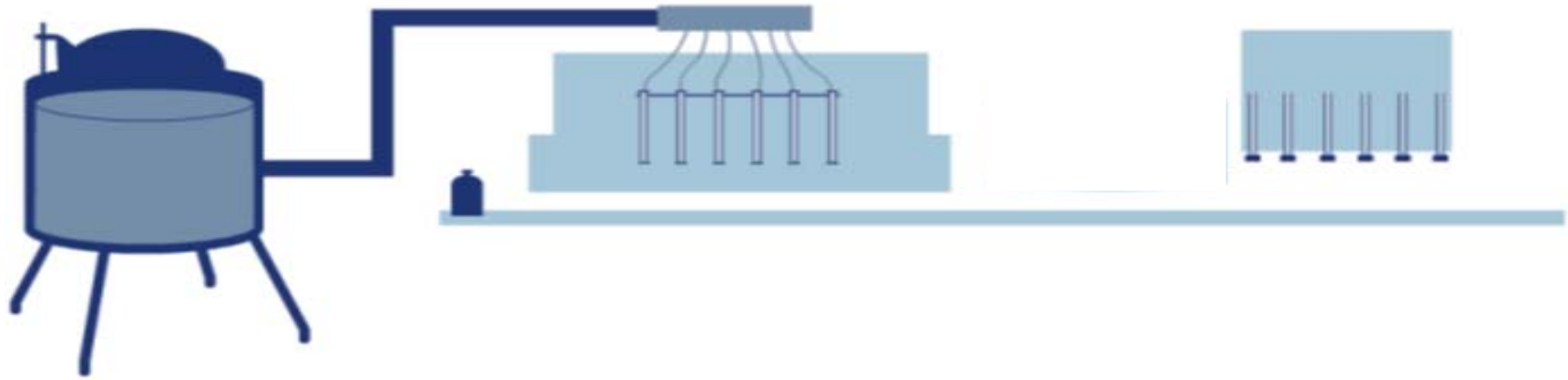
Indianapolis Parenteral Manufacturing

APS Formulation Process



3% Trypticase Soy Broth formulation	Bioburden reduction into a sterile tank	B = Grade B Area A = Grade A Sterile Filtration 0.22µm via POUF/IFT/FTR/ Tank-to-Tank Sterile Filtered	TSB in Sterile Filling Tank

APS Fill Process



Media transferred to filling manifold

Media is pumped through needles into Vials/Cartridges/ Syringes

Media filled units stoppered/capped/ plungered (or sent to lyophilization/capping)

APS Incubation Process

NLT 7 days

Media transferred to 20-25 °C Incubator NLT 7 days

Media transferred to 30-35 °C Incubator NLT 7 days

APS Growth Promotion Process

Media filled units sent to the Quality Control Purity Lab for Growth Promotion Assay:

- USP Sterility Test Isolates
- 4 Local EM Isolates (investigation related isolates)
- All must demonstrate growth

APS Acceptance Criteria

- All units demonstrate no growth (1 unit can pass with investigation)

Number of Units Incubated	Number of Contaminated Units	Action / Result
‹5,000	0	Pass
	1	Failure - cause for revalidation (three consecutive runs) following an investigation
5,000-10,000	0	Pass
	1	Investigation, including a consideration of a single repeat APS
	›1	Failure - cause for revalidation (three consecutive runs) following an investigation
›10,000	0	Pass
	1	Investigation
	›1	Failure - cause for revalidation (three consecutive runs) following an investigation

- All organisms must demonstrate growth during growth promotion assay requirements.

APS Challenge Factors

Risk Factor	Minimum Frequency Challenged
Filling Duration (on a set of equipment)	2X Annually
Unit size/Line Speed: • Smallest size/ high speed • Largest size / low speed	Annually
Equipment Set-up Hold Time	Annually
Maximum Personnel	Annually
Personnel Fatigue	Annually
Non-Routine Interventions/Manipulations	Annually
Routine Interventions	All APS
Sterile Hold Times (Tanks/Equipment/Components past expiry)	Annually
Processing Time Limits	Annually
Freeze Drying Process/Vial Transport (versus liquid fill)	Annually
Gas Purging/Overlay Activities	Annually

APS Program Governance

Global

- Global Quality Standard (GQS) 410, *Aseptic Process Simulation*

Site

- 001-007197, *Aseptic Process Simulation Program Strategy*
- 001-001693, *Use of Aseptic Process Simulations for Parenteral Product Aseptic Processing*

Line

- Line- specific Justification Documents
- Line- specific Annual Summary Reports
- Line- specific Annual Intervention Reports (Historical Data Analysis)
- Aseptic Process Simulation Protocols

Aseptic Process Simulation (APS) Program Introduction

Initial

- Initial 3X APS Validation is required for a **new aseptic fill line.**
- Challenges high risk contamination factors (e.g. duration and time limits, line speed, personnel, interventions, equipment set-up activities, etc.)
- Initial 3X APS Validation is required for a **new container closure** .
- 1X of 3X will be executed at full duration.

Revalidation

- Annual routine revalidation occurs at a **minimum of 2x/year** per line.
- Annual routine revalidation **utilizes a bracketing approach** to incorporate all contamination risk factors.
- Revalidation activities are not 'product specific', however, each filling line has unique challenges performed annually.

For Cause

- Additional revalidation activites may be required due to significant changes impacting the aseptic process or environment. These changes are evaluated via APS Risk Assessment FORM.