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FMEA-Integrated Aseptic Process Simulation for Sterile Ophthalmic Manufacturing

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ABSTRACT: Aseptic process simulation (APS), also known as media fill simulation, provides microbiological evidence of an aseptic manufacturing process under representative operating conditions. Integrating prospective Quality Risk Management (QRM) with APS may strengthen the identification and evaluation of contamination risk. An industrial-scale APS study assessed a sterile ophthalmic filling procedure using Soybean Casein Digest Medium (SCDM) in 5 mL LDPE containers under Grade A conditions with a Grade B background. A prospective Failure Mode and Effects Analysis (FMEA) was performed to identify contamination-related risks and define the controls before the APS. Routine and non-routine interventions were incorporated into the simulation, including equipment adjustments, component replenishment, line disturbances, simulated breakdowns and a 10-minute power interruption. Growth-Promotion Testing (GPT), sterility testing, physicochemical evaluation, environmental and personnel monitoring, microbiological container closure integrity (CCIT), and post-incubation stasis testing were performed. 9,100 filled units were transferred for inspection and incubation; after 14 days, no microbial growth was detected in any of the 9,100 incubated units. With 9,690 units equivalent received, 482 units equivalent sampled, 96 units equivalent representing media loss, 12 non-integral bottles rejected during filling, and 9,100 filled units, media accountability was reconciled to zero. GPT was satisfactory for *Candida albicans*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus*. Sterility testing showed no growth, environmental and personnel monitoring met predefined criteria, and 20/20 CCIT-challenged containers passed. The integrated findings show the complementary value of prospective FMEA and APS and support microbiological control of the evaluated aseptic ophthalmic filling process under the simulated conditions.

1. INTRODUCTION

Sterile ophthalmic products require stringent microbiological control because contamination may directly compromise patient safety. In aseptic manufacturing, sterility assurance is dependent on the coordinated control of environmental conditions, personnel practices, equipment performance, facility design, and validated procedures and monitoring rather than on a single step or process step. Contemporary sterile manufacturing guidance therefore emphasises an integrated contamination-control approach (European Commission, 2022; World Health Organisation, 2011).

APS is used to evaluate whether an aseptic manufacturing process can maintain microbiological control during simulated production. A microbiological growth medium is replaced in place of the pharmaceutical product in an APS; this medium is processed using representative equipment, environmental conditions, personnel activities, and interventions. The filled units' subsequent incubation provides an opportunity to detect any microbiological contamination that might have occurred during processing (Ministry of Health and Family Welfare, 2023; World Health Organisation, 2011).

The effectiveness of an APS depends on how closely the simulation represents actual manufacturing conditions; for this reason, representative interventions and process disturbances are therefore important components of simulation design. According to process knowledge and risk assessment, activities such as manual interventions, component replenishment, equipment adjustments, line disturbances, prolonged processing, and recovery from operational interruptions should be appropriately represented because they may create opportunities for microbial contamination (European Commission, 2022; World Health Organisation, 2011)

QRM provides a systematic framework for identifying and controlling risks to pharmaceutical quality. A risk-management technique, FMEA, evaluates possible failure modes based on factors like severity, likelihood of occurrence, and detectability (ICH Q9 (R1), 2023). Therefore, rather than relying just on the final media-fill outcome, performing FMEA before the APS execution can provide a prospective basis for identifying contamination-related risks and selecting representative process challenges (Elmadhoun et al., 2025).

The present study integrated prospective FMEA with a full-scale APS for a sterile ophthalmic filling process and evaluated the resulting microbiological performance using environmental and personnel monitoring, growth-promotion testing, sterility testing, microbiological CCIT, and post-incubation stasis testing. The purpose of the study was to ascertain whether, given the specific simulated manufacturing conditions, the integrated approach could provide converging evidence of microbiological control and process resilience.

2. MATERIALS AND METHODS

2.1 Study design and study site

A prospective industrial-scale APS was performed at Senses Pharmaceuticals Pvt. Ltd., Bengaluru, Karnataka, India, for a sterile ophthalmic filling procedure. The aseptic processing area consisted of a Grade A laminar airflow (LAF) workstation with a Grade B background.

The study design incorporated prospective FMEA prior to APS execution, and then representative routine and non-routine aseptic interventions were simulated. Environmental and personnel monitoring, physicochemical evaluation of SCDM, GPT, sterility testing, microbiological CCIT, and post-incubation stasis testing were employed to obtain microbiological and process-control evidence.

2.2 Growth medium, components and equipment

SCDM obtained from HiMedia Laboratories Pvt. Ltd. was used as microbiological growth medium. Sterile LDPE nozzles, sterile white HDPE caps, and sterile transparent LDPE ophthalmic bottles with a nominal 5 mL volume were employed in the simulation.

The filtration system consisted of a 0.2 μm pre-filter and a 0.22 μm sterilising-grade cartridge filter. During specified interventions, pharmaceutical-grade 70% isopropyl alcohol (IPA) was employed for sanitisation. A qualified six-head aseptic filling machine with a Grade A LAF and a Grade B background was used for the filling process.

2.3 Preparation and processing of SCDM

A 50 L batch of SCDM was prepared. Following preparation, the medium was moist-heat sterilised and then passed through a 0.2 μm pre-filter and a 0.22 μm sterilising-grade filter before being aseptically transferred to the filling system.

Under Grade A LAF with Grade B background conditions, the filtered medium was filled into sterile 5 mL LDPE bottles with fill volume range 5.0–5.2 mL. HDPE caps and LDPE nozzles were used following filling.

2.4 Media accountability

The quantities recorded during the filling process were used to evaluate media accountability. 49.420 L of media, 9690 units equivalent, were received for filling. 2,458.2 mL, 482 units equivalent, of media were sampled during the process. Media loss corresponded to 96 units, 489.6 mL. The total number of bottles filled, including integral rejected units, was 9,100. Twelve non-integral bottles rejected during filling were accounted for separately.

The media accountability was calculated as:

Media accountability = $F - (G + H + I + J)$

Where F = media received for filling, G = media sampled, H = media loss, I = non-integral rejected units and J = total filled units.

The recorded accountability was: $9,690 - (482 + 96 + 12 + 9,100) = 0$, indicating complete reconciliation of the media received for filling.

2.5 Aseptic process simulation and interventions

The APS was designed to reproduce routine aseptic manufacturing activities and contamination-relevant challenges. Routine activities included filtration assembly, machine setup and assembly, material charge, priming, fill-volume adjustment, in-process sampling, and equipment adjustments.

Non-routine interventions included repeated charging of bottles, nozzles, and caps; adjusting star wheels, sensors, screwers, and tracks; removing fallen bottles; simulating equipment jams and malfunctions; replacing Grade A environmental monitoring plates; active air sampling; and a controlled power-failure simulation.

The controlled power-failure simulation consisted of a 10-minute interruption. All personnel exited the filling room. Following a four-minute recorded area recovery period, environmental monitoring was carried out, and personnel re-entered following the defined recovery period. Bottles that were left in the filling machine, both filled and empty, were removed and rejected. The filling station was sanitised with 70% IPA before the process was resumed.

2.6 Prospective FMEA

A multidisciplinary prospective FMEA was conducted before APS execution. We assessed potential failure modes related to personnel, material transfer, filtration, filling machine setup, equipment adjustment, line clearance, incubation, documentation, and other operations related to contamination. A three-point scoring system was used for severity (S), probability of occurrence (P), and detectability (D). The following formula was used to calculate the Risk Priority Number (RPN):

$$RPN = S \times P \times D$$

Risk-control measures were established for identified failure modes before the execution of the APS. Therefore, rather than as an assessment performed after obtaining the media-fill outcome, the FMEA served as a prospective risk-management activity.

2.7 Environmental and personnel monitoring

Viable environmental monitoring was carried out during the APS using active air sampling, passive air sampling using settle plates, and surface monitoring using contact plates. In accordance with the facility environmental monitoring program, sampling was performed at predetermined locations in Grade A and Grade B areas. Personnel monitoring was carried out following aseptic operations using glove and gown contact-plate monitoring. The applicable environmental and personnel monitoring acceptance criteria were used to evaluate the observations (FDA, 2004).

2.8 Physicochemical evaluation of SCDM

The prepared SCDM was evaluated for physical appearance, pH, and specific gravity. The pH was measured against the specified 7.0-7.5 acceptable limits.

2.9 Growth Promotion Testing and Stasis Testing

Staphylococcus aureus, *Pseudomonas aeruginosa*, and *Candida albicans* were used in GPT to evaluate the SCDM's capability to promote growth. GPT was performed before the APS, and post-incubation growth-promotion/stasis tests were carried out following the designated incubation period.

2.10 Sterility testing

Sterility testing was carried out on representative samples associated with the APS, such as filtered media, process and packaging-component samples, compressed air, priming medium, and leftover medium. The dual-temperature conditions of 20-25°C and 30-35°C were used for the incubation of the samples.

The acceptance criteria are the absence of visible microbial growth during the specified incubation period (United States Pharmacopeial Convention, 2024).

2.11 Microbiological container closure integrity testing

A microbiological challenge method was used to carry out CCIT. *Pseudomonas aeruginosa* (ATCC No. 8532) was used to challenge representative filled containers under the given challenge conditions. The challenged containers were incubated at 30–35°C for 14 days after being immersed for not less than 30 minutes. The acceptance criterion is the absence of microbial growth following incubation for the microbiological challenge assessment (Parenteral Drug Association, 2025).

2.12 APS acceptance criterion

Acceptable filled units were incubated for a total of 14 days at the specified dual-temperature conditions after the APS was completed. The primary APS acceptance criterion was the absence of visible microbial growth in any incubated unit.

3. RESULTS AND DISCUSSION

3.1 Prospective FMEA and risk-based APS design

The prospective FMEA identified contamination-related risks associated with personnel intervention, material transfer, filtration, filling-machine setup, equipment adjustment, line clearance, incubation, and documentation. Failure types were evaluated; the initial RPN values varied from 8 to 18. Risk control measures included aseptic training and gowning qualification, approved filtration assembly procedures, validated transfer and disinfection procedures, SOPs and checklists, QA verification, trained intervention personnel, calibrated incubation systems, and GDP-based documentation controls (Table 1).

The risk assessment provided a prospective basis for selecting process activities and interventions for APS. This approach is consistent with the QRM principle, which states that risks should be identified, examined, evaluated, and controlled with a level of formality appropriate for the specific process (ICH Q9 (R1), 2023). As a result, the FMEA served a preventive role, and APS subsequently provided experimental evidence of microbiological control under the selected operating conditions.

Table 1. Prospective FMEA of contamination-related process risks

Process/activity	Potential failure mode	Potential effect	S	P	D	Initial RPN	Risk-control measure	Residual S	Residual P	Residual D	Residual RPN
Personnel intervention	Improper aseptic technique	Microbial contamination	3	3	2	18	Aseptic training, gowning qualification, SOP adherence and supervision	3	1	1	3
Material transfer	Improper transfer of components	Contamination of sterile pathway	3	3	2	18	Validated transfer/disinfection procedure	3	1	1	3
Filtration	Filter assembly error	Loss of microbial barrier	3	2	2	12	Approved assembly procedure and integrity testing	3	1	1	3

Filling-machine setup	Incorrect assembly/setup	Contamination or process interruption	3	3	2	18	SOP, checklist and QA verification	3	1	1	3
Equipment adjustment	Excessive/incorrect intervention	Exposure of sterile pathway	3	3	2	18	Trained personnel and defined intervention procedure	3	1	1	3
Line clearance	Incomplete clearance	Mix-up/contamination risk	3	3	2	18	SOP, checklist and QA verification	3	1	1	3
Incubation	Incorrect incubation condition	Failure to detect contamination	3	2	2	12	Calibrated incubators and alarms	3	1	1	3
Documentation	Incomplete records	Loss of traceability	2	2	2	8	GDP, review and audit trail	2	1	1	2

Abbreviations: S- severity; P- probability; D- detectability; RPN- Risk Priority Number; GDP- good documentation practice; QA- quality assurance.

3.2 APS execution and media accountability

The APS was performed using a 50 L SCDM batch on a six-head filling machine operating at 88.1% machine speed. Filling operations were performed from 07:41 on July 30, 2025, until 02:12 on July 31, 2025; 5 operators were directly involved in filling, plugging, and capping operations. 9,100 filled units were transferred for inspection before being incubated. Twelve non-integral bottles that were rejected during filling were not included in the incubated population and were accounted for individually. With 9,690 units equivalent received, 482 units equivalent sampled, 96 units equivalent reflecting media loss, 12 non-integral rejected units, and 9,100 filled units, media accountability was reconciled to zero. Thus, the recorded media quantities were completely reconciled.

After the specified 14-day incubation period, there was no visible microbial growth in any of the 9,100 incubated units. Thus, the APS was reported as PASS since it satisfied the specified acceptance criterion.

3.3 Routine and non-routine interventions

APS incorporated a broad range of process challenges: component replenishment, machine assembly and setup, equipment adjustments, solution priming, fill-volume adjustment, line disturbances, jam clearance, fallen-bottle removal, simulated breakdowns, maintenance-related intervention, environmental monitoring interventions, personnel-related challenges, room disturbance, and power interruption (Table 2).

Table 2. Routine and non-routine interventions incorporated into the APS

Intervention category	Intervention
Component replenishment	Bottle, nozzle and cap charging
Equipment assembly/setup	Machine-part assembly, initial machine setup and needle centering
Equipment adjustment	Star wheels, tracks, sensors, screwdriver and bottle orientator
Process intervention	Bulk tank connection, solution priming and fill-volume adjustment

Line disturbance	Jam clearance, fallen-bottle removal and breakdown simulation
Maintenance intervention	Capping-belt replacement
Environmental intervention	Active-air sampling and Grade A plate replacement
Personnel-related challenge	Maximum personnel and operator fatigue
Room disturbance	Filling-room door opening
Power interruption	10-minute power-failure simulation followed by recovery and sanitisation

The controlled power-failure simulation provided a specific recovery challenge. The interruption occurred once and lasted about ten minutes. After all personnel exited the filling room, a 4-minute area recovery period was observed. The filling station was cleaned with 70% IPA before operations resumed; personnel were re-entered in accordance with the established recovery procedure, and any affected bottles remaining inside the filling machine were removed and rejected.

No microbial contamination was detected among 9100 incubated units following these interventions; the results validate the efficacy of the specific recovery and restart controls evaluated in this APS, but it should not be used as evidence that all potential power-loss scenarios would be inherently safe.

3.4 Physicochemical characteristics and growth promotion

The prepared medium was clear and free from visible particles, while the dehydrated SCDM was yellow and flowed freely. The in-process pH was 7.08, and the QC pH result was 7.10, both within the specified range of 7.0-7.5. Specific gravity was 1.0086 g/mL. (Table 3). GPT demonstrated the growth of *Candida albicans*, *P. aeruginosa*, and *S. aureus*. Post-incubation stasis testing also demonstrated retained growth-promotion capability. The interpretation of the negative APS result depends on the GPT results. The absence of microbial growth in the incubated APS units cannot simply be ascribed to the medium's inadequate growth-supporting capability. Growth promotion retention during the post-incubation stasis evaluation provided additional evidence for the validity of the negative APS observation.

Table 3. Physicochemical evaluation and growth-promotion testing of SCDM

Parameter	Observation	Acceptance criterion	Result
Appearance—dehydrated medium	Yellow, free-flowing	As specified	Pass
Appearance- post-filtration	Clear	As specified	Pass
pH: in-process	7.08	7.0 - 7.5	Pass
pH: QC result	7.10	7.0 - 7.5	Pass
Specific gravity	1.0086 g/mL	As specified	Pass
GPT: <i>S. aureus</i>	Growth observed	Growth required	Pass
GPT: <i>P. aeruginosa</i>	Growth observed	Growth required	Pass
GPT: <i>C. albicans</i>	Growth observed	Growth required	Pass
Post-incubation GPT/stasis	Growth promotion retained	Growth promotion required	Pass

3.5 Environmental and personnel monitoring

Microbiological control was demonstrated by environmental monitoring throughout the APS (Table 4). While Grade A active air monitoring showed 0 CFU/m³ at all nine monitored locations, Grade B active air monitoring revealed 0 CFU/m³ at all four monitored locations. At each of the eight locations under observation, Grade A settle plates showed 0 CFU/4 h. Grade B

settle-plate monitoring showed 0 CFU/4 h in 13 places and 1 CFU/4 h at two locations; these results remained within the acceptable criterion. At all 11 monitored locations, Grade A contact plates showed 0 CFU/plate. Grade B contact plates remained within the specified limit, with 0 CFU/plate at 11 locations and 1 CFU/plate at two locations. No fungal recovery was reported in the environmental monitoring observations. Personnel monitoring covered 30 body-location sites involving five operators. With a maximum recovery of 1 CFU/plate, 23 sites showed 0 CFU/plate and 7 sites showed 1 CFU/plate. Every observation stayed within the applicable acceptance criteria. An independent line of evidence supporting the negative APS result is provided by the environmental and people monitoring results. The absence of recovery in Grade A monitoring, together with the limited Grade B recoveries remaining within predefined criteria, was consistent with maintenance of microbiological control during the simulation.

Table 4. Environmental and personnel monitoring during APS

Monitoring method	Area	n	Bacterial recovery	Fungal recovery	Acceptance criterion	Outcome
Active air sampling	Grade A	9	0 CFU/m ³	0 CFU/m ³	<1 CFU/m ³	Complies
Active air sampling	Grade B filling room	4	0 CFU/m ³	0 CFU/m ³	NMT 10 CFU/m ³	Complies
Settle plates	Grade A	8	0 CFU/4 h	Nil	<1 CFU/4 h	Complies
Settle plates	Grade B	14	0 CFU at 13 locations; 1 CFU at 2 locations	Nil	NMT 5 CFU/4 h	Complies
Contact plates	Grade A	11	0 CFU/plate	Nil	<1 CFU/plate	Complies
Contact plates	Grade B	12	0 CFU at 11 locations; 1 CFU at 2 locations	Nil	NMT 5 CFU/plate	Complies
Personnel/gown monitoring	Personnel	30 sites	23 sites: 0 CFU/plate; 7 sites: 1 CFU/plate	—	Applicable Grade A/B limits	Complies

3.6 Sterility testing

Under the specified incubation conditions, no microbiological growth was detected in representative sterility samples that included filtered medium, PPM bottle, PPM nozzle, PPM cap, compressed air, priming medium, and residual medium (Table 5), and the overall sterility result was pass. Although these findings provide corroborating microbiological evidence, they should not be interpreted as independent proof of the overall sterility manufacturing process. Instead, their value lies in their concordance with the APS, growth-promoting results, environmental monitoring, and personnel monitoring.

Table 5. Sterility testing of APS-associated samples

Test sample	Result
Filtered medium	No growth
PPM bottle	No growth
PPM nozzle	No growth
PPM cap	No growth
Compressed air	No growth

Priming medium	No growth
Leftover medium	No growth
Overall sterility result	Pass

3.7 Microbiological CCIT

Twenty filled containers were subjected to microbiological CCIT using *P. aeruginosa*. All 20 challenged units passed, with 0 failures after the defined exposure and 14-day dual temperature incubation at 20-25°C & 30-35°C (Table 6).

The 20/20 CCIT results support the performance of the tested container-closure configuration under the conditions used. By providing additional evidence concerning the microbiological barrier of the filled container evaluated in the study, it complements the APS result.

Table 6. Microbiological container closure integrity testing

Parameter	Result
Method	Microbiological challenge test
Challenge organism	<i>Pseudomonas aeruginosa</i>
ATCC/lot	8532
Challenge concentration	10 ⁻⁶ dilution
Exposure	Immersion for NLT 30 min
Incubation	30–35°C
Incubation period	14 days
Units tested	20
Units passed	20
Units failed	0
Overall result	Pass

3.8 Integrated interpretation of APS findings

The principal outcome of the study was the absence of microbial growth in all 9,100 incubated units, despite the incorporation of both routine and non-routine interventions. Multiple complementary evidence streams, including prospective FMEA, environmental monitoring, personnel monitoring, GPT, stasis testing, sterility testing, and microbiological CCIT, supported the conclusions.

Before execution, the FMEA identified probable contamination sources and established preventive controls in place. The controlled process was then given an experimental challenge by APS. The processing environment and operators remained within the applicable microbiological control limits, as evidenced by environmental and personnel monitoring. GPT and stasis testing demonstrated that the medium retained growth-supporting capabilities. While CCIT demonstrated that the tested container-closure arrangement performed successfully, sterility testing showed no growth in the evaluated supporting samples.

Therefore, the absence of contamination in 9,100 incubated units should be interpreted as part of a converging body of evidence rather than an isolated finding. This integrated approach is consistent with the principle that APS is a part of a larger strategy for sterility assurance and contamination control.

The findings also demonstrate how compatible FMEA and APS are. While APS offers direct experimental data under simulated production conditions, FMEA is preventive and prospective. Neither strategy takes the place of the other. Instead, integrating them offers a methodical way for connecting recognised contamination hazards to representative process challenges.

The study was conducted at a single manufacturing site using one filling configuration and one full-scale APS campaign. As a result, the findings demonstrate performance in the particular circumstances examined and should not be applied to all sterile ophthalmic procedures. Stronger evidence of reproducibility and broader process robustness would come from repeated APS programs and evaluation across additional configurations.

4. CONCLUSIONS

Prospective FMEA integrated with industrial-scale APS provided a structured risk-based approach for evaluating microbial control in the investigated sterile ophthalmic filling process. After the specified 14-day incubation period, no microbial growth was found in any of the 9,100 units that were incubated. Representative routine and non-routine interventions, such as equipment modifications, component replenishment, line disturbances, simulated breakdowns, and a controlled 10-minute power-failure challenge, were included in the APS. Monitoring of the environment and personnel remained within predetermined acceptable criteria. GPT demonstrated that the specified challenge organisms grew satisfactorily, and post-incubation stasis testing confirmed growth-promotion capability. All 20 microbiologically challenged containers passed CCIT, and sterility testing revealed no microbial growth in the evaluated samples.

The concordance of these findings supports microbiological control of the evaluated aseptic process under the simulated conditions. The study demonstrates the value of combining prospective QRM/FMEA with APS and complementary microbiological assessments rather than relying on a single sterility-assurance measure.

The findings are specific to the evaluated process, equipment configuration and simulation conditions. Further repeated APS campaigns and evaluation of additional process configurations are recommended to strengthen evidence of long-term reproducibility.

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7. AUTHOR CONTRIBUTIONS

Conceptualisation: Tejashwini k; methodology: Guna Shree SH; investigation: Shreesha S and Sanjana S; data curation: Ishwarya M; formal analysis: Thanuja KR and Sabarisan D; writing-original draft: Tejashwini k; writing-review and editing: Sangeetha G; All authors approved the final manuscript.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

9. ETHICS STATEMENT

No human or animal research was conducted as part of this study; therefore, ethics committee approval was not applicable.

10. DATA AVAILABILITY

The data supporting the findings of this study are contained within the manuscript and its tables. Additional process records are subject to institutional confidentiality and may be made available by the corresponding author subject to appropriate authorisation.

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