

Baxa Corporation

Aseptic Syringe Filling

Technical Paper

Processing sterile batch syringes with the Rapid-Fill™
Automated Syringe Filler.


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Introduction

Stedman's Medical Dictionary defines asepsis as, "A condition in which living pathogenic organisms are absent; a state of sterility."¹ Aseptic processing, therefore, is the manipulation and preparation of sterile products without introducing contamination. Pharmacies performing aseptic processing bring together drug product, containers and closures that have been sterilized separately. Strict aseptic procedures ensure that containers are filled and sealed in a high-quality environment, since the final products will not undergo further sterilization. Any manipulation of the sterile components prior to, or during, aseptic processing poses a contamination risk and necessitates careful control.

The purpose of this paper is to demonstrate that the Baxa Rapid-Fill™ Automated Syringe Filler uncaps, fills, recaps, and labels Rapid -Fill Syringe Strips in an aseptic manner.

Equipment

The Rapid-Fill Automated Syringe Filler (ASF) is a batch filling system for use in the hospital pharmacy to fill, cap and label sterile syringes. This is accomplished by feeding an integrated syringe strip into the Rapid-Fill ASF, then programming the number of syringes to be filled, the amount of ingredient for each fill, and the label information.

Upon initiation of the filling sequence, the Rapid-Fill ASF draws the syringe strip around the syringe drum, removes the syringe cap, engages the fill nozzle, fills the syringe to the specific amount, removes the fill nozzle, replaces the syringe cap, prints the label information and cuts the finished, labeled syringe from the strip. Filled syringes feed off of the drum where they slide down the out-feed chute into a finished syringe collection bag. This process continues until the specified number of syringes (the batch) is complete.

The Rapid-Fill Automated Syringe Filler was designed to facilitate aseptic processing within a sterile compounding area. The system fits inside a horizontal laminar airflow hood (LAH), or may be operated in a Class 100 cleanroom. When placed in an LAH, manipulation of the syringe and filling and capping operations are done inside the horizontal air flow. The Rapid-Fill ASF's syringe and drum covers provide protection from the "zone of turbulence" for the sterile, unfilled syringes prior to processing.

Test Description

To demonstrate the effectiveness of the Rapid-Fill ASF for aseptic processing, it was necessary to use the system to fill syringes under controlled conditions without contamination. For this test, an operator filled presterilized syringes with a culture medium rather than sterile drug product. Any exposure of the medium to the environment during the process, therefore, would allow the medium to become contaminated with microorganisms. After processing, the medium was incubated to allow any microorganisms to grow and be detected. Positive control syringes were processed in the same way as the media-filled syringes to demonstrate that the media supports organism growth.

¹ *Stedman's Concise Medical Dictionary for the Health Professions*. John H. Dirckx, Ed. Williams and Wilkins. 1999.

Test Media

The quality and sterility of the media used in this evaluation were critical to the success of the validation. The media used, Tryptic Soy Broth (TSB) is certified to support the growth of a wide spectrum of microorganisms likely to be present during manipulations. Acceptable microorganisms referenced in the United States Pharmacopoeia/National Formulary – USP XXI/NF XVI for sterility test growth promotion tests include Tryptic Soy Broth (TSB) for aerobic microorganism detection and Fluid Thioglycolate (FTG) for anaerobic microorganism detection.

Sample Size

The number of units tested in the media fill was large enough to yield a high probability of detecting low incidences of contamination. Under 21 CFR 10.90 (*Guidelines on sterile drug products produced by aseptic processing*), three thousand units (3,000) are sufficient to detect, with 95% probability, a contamination rate of one in one thousand.

Acceptance Criteria

The following criteria were used to indicate a successful test result.

1. All 3000 media-filled syringes must exhibit no growth.
2. All negative-control, sterile syringes must exhibit no growth.
3. All inoculated, positive-control syringes must exhibit growth.

Test Method

One hundred (100) unfilled, presterilized syringes were tested for sterility prior to filling as a negative control to show that the syringes used in the test were sterile before filling. Three positive-control syringes were drawn manually, using aseptic technique, from each of the nine media bags, then inoculated with bacillus to demonstrate that the growth media used supported organism growth under test conditions. A negative control syringe was obtained by manually and aseptically withdrawing media from each bag. The remaining media in each media bag used was tested also to ensure that the bags were not contaminated prior to filling or during the attachment of the tube set. A total of 3,000 syringes were filled with growth media (1,500 inside an LAH and 1,500 outside an LAH). All samples were sent to an independent laboratory and incubated at 30-35°C for 14 days. Samples were examined for turbidity (failure) every two days.

Test Set-Up for Syringes Filled Inside the LAH

The LAH was turned on for twenty-four hours prior to the media fill to ensure complete purging of the room air from the critical work area. Work surfaces and the sides of the laminar airflow hood were cleaned and sanitized before the filling began. A germicidal detergent (Lysol IC Quat) was used as a cleansing agent, and the sanitization was done with isopropyl alcohol 70%. The Rapid Fill ASF was cleaned, sanitized, and placed in the LAF hood.

Prior to performing the media fill, the media bags were visually checked for leaks by squeezing the bags lightly. Each bag was labeled with a sequential number. Operators wore gloves, gowns, and hairnets while performing the media fill. During the test filling, gloves were rinsed frequently with 70% Isopropyl Alcohol (IPA) and changed if their integrity was compromised (punctured or torn). A total of fifteen hundred (1,500) syringes were filled with media in the hood. Average velocity reading for the LAH was verified to be 92.3.

Test Procedure for Syringes Filled Inside the LAH

All procedures were performed at least 6 inches inside the front edge of the laminar airflow hood. The syringe fill volume was set to the maximum syringe volume of 12 mL. The first syringe of each strip of 200 was hand fed into the Rapid-Fill ASF, after which the machine automatically processed the remaining 199 syringes.

Test Set-Up and Procedure for Syringes Filled Outside the LAH

The test set-up and procedure for syringe filling was identical to that stated above, except that the Rapid-Fill ASF was operated on an open table instead of inside the LAH.

Microbial Monitoring

A baseline measure of environmental control was taken for each workbench used in the Rapid-Fill ASF syringe filling by measuring viable particle counts. This measure was taken to evaluate actual contamination conditions. Each workbench was tested for airborne microbial contaminants and surface microbial contaminants immediately following the completion of the media filling operation.

Results

Syringes Filled Using the Rapid-Fill Automated Syringe Filler

Quantity: 3,000 total syringes

Syringes Filled Inside LAH		Syringes Filled Outside LAH	
Day	Growth / No Growth	Day	Growth / No Growth
2	No Growth	2	No Growth
4	No Growth	4	No Growth
6	No Growth	6	No Growth
8	No Growth	8	No Growth
10	No Growth	10	No Growth
12	No Growth	12	No Growth
14	No Growth	14	No Growth

Negative Control Results (Unfilled Syringes)

Quantity: 100 syringes

Sample	Growth / No Growth
Negative Controls (100)	No Growth

Control Results (Filled Syringes)

Positive Control Unit Results					
Sample	Media Bag #	Growth/ No Growth	Sample	Media Bag #	Growth/ No Growth
1	1	Growth	1	6	Growth
2	1	Growth	2	6	Growth
3	1	Growth	3	6	Growth
1	2	Growth	1	7	Growth
2	2	Growth	2	7	Growth
3	2	Growth	3	7	Growth
1	3	Growth	1	8	Growth
2	3	Growth	2	8	Growth
3	3	Growth	3	8	Growth
1	4	Growth	1	9	Growth
2	4	Growth	2	9	Growth
3	4	Growth	3	9	Growth
1	5	Growth			
2	5	Growth			
3	5	Growth			

Negative Control Unit Results					
Sample	Media Bag #	Growth/ No Growth	Sample	Media Bag #	Growth/ No Growth
1	1	No Growth	6	6	No Growth
2	2	No Growth	7	7	No Growth
3	3	No Growth	8	8	No Growth
4	4	No Growth	9	9	No Growth
5	5	No Growth			

Media Bag Results

Media Bag #	Growth / No Growth
1	No Growth
2	No Growth
3	No Growth
4	*NA
5	No Growth
6	No Growth
7	No Growth
8	No Growth
9	No Growth

* Note: Bag 4 was contaminated after the validation during microbial testing and discarded.

Microbial Monitoring Results

With LAF Hood		Without LAF Hood	
Sample	Colony Forming Units (CFUs)	Sample	Colony Forming Units (CFUs)
<i>Air Sampling with Biotest RCS Air Sampler Results</i>			
1	7	1	5
2	0	2	2
<i>Air Sampling with Settling Plates Results</i>			
1	0	1	1
2	0	2	2
<i>Surface Sampling with Rodac Plates Results</i>			
1	0	1	0
2	0	2	0
3	1	3	0

Conclusion

Testing demonstrates that the Rapid-Fill Automated Syringe Filler fills syringes aseptically when operated using aseptic technique. The evaluation resulted in sterile syringes whether they were filled using the Rapid-Fill ASF operating inside a Laminar Airflow hood (LAH), or outside the LAH under environmentally controlled conditions.

No special precautions for environmental control were undertaken during the evaluation. The LAH samples were produced on the Rapid-Fill System under standard conditions in a room with no additional environmental controls. The non-LAH samples were filled in an electro-mechanical production area with no specific air handling equipment. Operators performing the testing wore gloves, gowns, etc. during the syringe filling, however in both cases there were other people working in the room in standard street clothing. This test was designed to determine the impact of aseptic technique and environmental conditions on the quality of the syringes filled by the Rapid-Fill ASF. The results provide a high level of confidence that the Rapid-Fill System aseptically fills syringes in a hospital pharmacy setting – with or without the use of a laminar airflow hood.

During the evaluation, a total of 3,000 syringes were filled with media using the Rapid-Fill Automated Syringe Filler (1,500 inside and 1,500 outside an LAH), and incubated for 14 days. All samples exhibited no growth. The negative control samples, and the original nine TSB growth media bags similarly demonstrated no growth. All positive control syringes (inoculated with bacillus) demonstrated growth. Test results match the expectations from the original proposal, and validate the purpose of the study which was to demonstrate that the Rapid-Fill ASF aseptically uncaps, fills, recaps, and labels sterile Rapid -Fill Syringe Strips in an aseptic manner.

The test results indicate that Pharmacists or technicians operating the Rapid-Fill Automated Syringe Filler, using aseptic technique and according to the procedures outlined in the Operator Manual, can meet current aseptic filling guidelines published by the American Society of Health-Systems Pharmacists (ASHP).