Practice 004:

Table 1. Aseptic Processing Facilities Environmental Monitoring Frequency - In Operation Conditions

		In Operation				
Type of Sample	**Sampling Method**	**Grade A**	**Grade B (Grade A Background)**	**Grade B (Non-Grade A Background)**	**Grades C[1]**	**Grade D[1]**
Microorganisms in Air	**Passive**	All Sites, Continuous[2]	All Sites - 1 x Each Shift	All Sites - 1 x Each Day	None	None
	Active	All Sites - 1 x Each Shift	All Sites - 1 x Each Shift	All Sites - 1 x Each Day	2 x Per Week	1 x Per Week
Microorganisms on Surfaces & Equipment	**Contact Plates &/or Swabs**	All Sites - End of Each Batch[3] or 1x daily whichever is more frequent	All Sites - 1 x Daily	All Sites - 1 x Daily	1 x Per Week	1 x Per Week
Microorganisms on Product Contact Surfaces	**Contact Plates &/or Swabs**	All Sites - End of Each Batch[3]	None	None	None	None
Personnel Monitoring Gown / Gloves	**Touch & Contact Plates**	1 x Each Shift	1 x Each Shift	1 x Each Day	None	None
Total Airborne Particulates	**Particle Counter**	Continuous[4]	1 x Per Shift	1 x Per Day	1 x Per Week	1 x Every 2 Weeks
Temperature & Humidity	**Calibrated Sensors**	If Product Requires	If Product Requires	If Product Requires	If Product Requires	If Product Requires
Room Pressure Differential	**Calibrated Sensors**	Continuous	Continuous	Continuous	Continuous	Continuous

(1) Sample site rotation acceptable in Grade C and Grade D areas.
(2) Settle plates exposed all of the time with immediate replacement of a fresh plate at the end of the validated exposure time.
(3) If operating on **Campaign*** basis, sample at the end of each campaign.
(4) Continuous while in operation. It is accepted that it may not always be possible to demonstrate conformity with particulate standards at the point of fill when filling is in progress, due to the generation of particles or droplets from the product itself.

Table 2. Action Levels for Microorganisms and Total Airborne Particulates[a]

	Grade	Total Airborne Particulates ≥0.5µm Per m^3 At Rest	Total Airborne Particulates ≥0.5µm Per m^3 In Operation	Total Airborne Particulates ≥5 µm Per m^3 [d]	Total Airborne Particulates ≥5.µm Per m^3 [d]	Active Air Sample cfu/m^3	Passive Air Sample cfu/plate	Product Contact Surface cfu/plate	Non-Product Contact Surface cfu/plate	Floor Surface cfu/plate	Personnel gloves cfu/glove	Personnel gown cfu/plate
APA	A	3500 (100)[b]	3500 (100)[b]	≥1	≥1	≥1	≥1	≥1	≥3	≥5	≥1	≥1
	B	3500 (100)[b]	350,000 (10,000)[b]	≥1	2000 (57)[b]	≥10	≥5	N/A[c]	≥5	≥10	>5	≥5
PAA	C	350,000 (10,000)[b]	3,500,000 (100,000)[b]	2000 (57)[b]	20000 (570)[b]	≥100	≥50	N/A	≥25	N/A	N/A	N/A
	D	3,500,000 (100,000)[b]	N/A	20000 (570)[b]	N/A	≥200	≥100	N/A	≥50	N/A	N/A	N/A

a. Action levels shall be established at each Site based on periodic review of historical data but must not exceed the levels shown in Table 2.

b. Represent the number of total airborne particles per cubic foot of air.

c. N/A is Not Applicable

d. Applicable to products marketed in the EU. See Regulatory Exception.

Figure 1. Decision Tree for Sterilization of Aqueous Products (Ref 12)

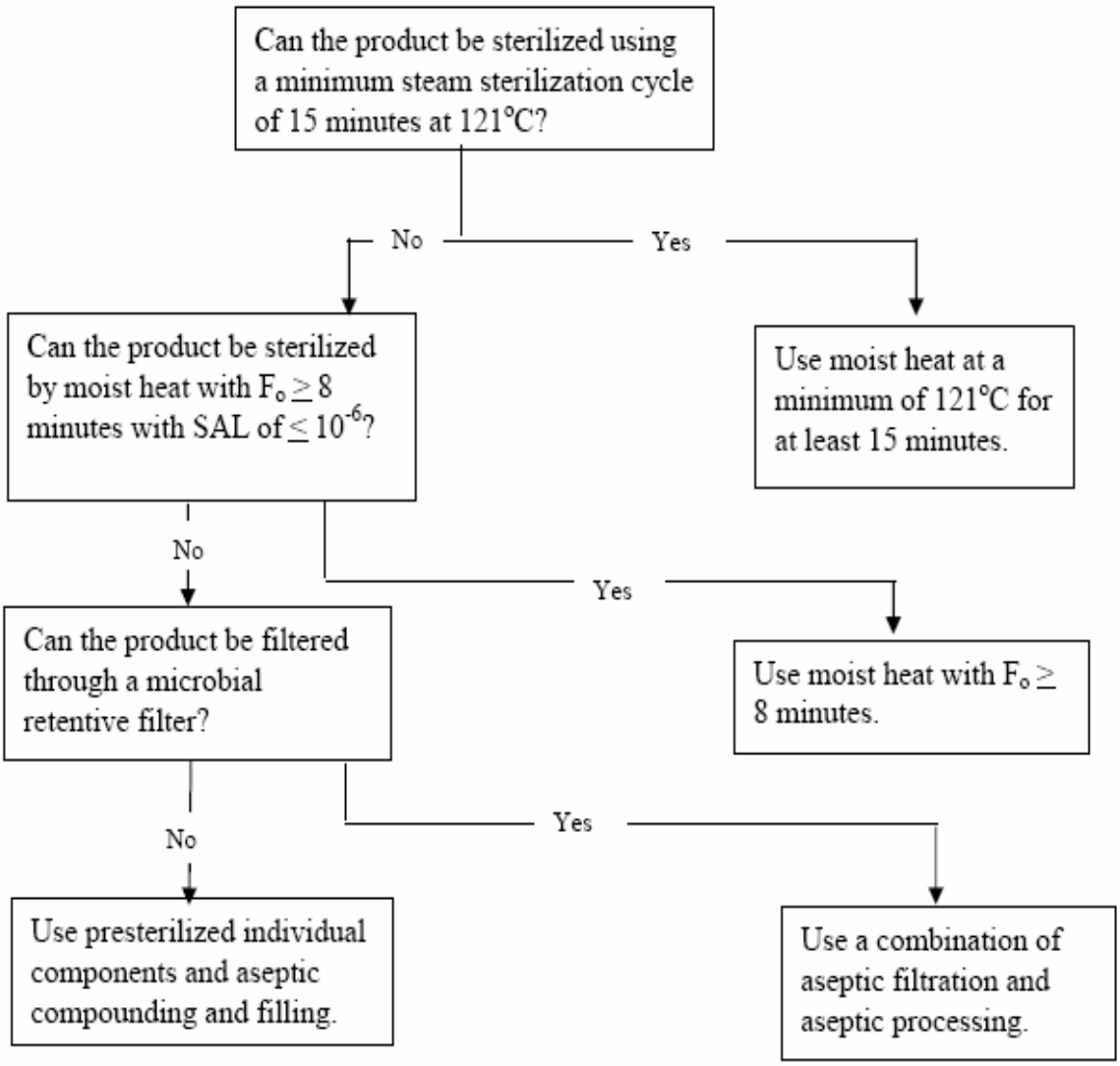

Table 1. Processing Controls for Terminally Sterilized Parenteral Drug Products

Processing Controls	**Drug Products Prepared using Aseptic Processing Conditions**	**Drug Products Prepared using Non-Aseptic Processing Conditions**
Compounding Environment	Minimum Grade C	Minimum Grade C
Final Filtration	0.22 micron porosity	0.45 micron porosity
Pre-sterilization Bioburden Monitoring	Monitor bulk solution prior to the final sterilization step	• Monitor bulk solution prior to the **Final Filter***, • Monitor filled containers for total aerobic microbial count, and • Perform heat shock screening for spore formers.
Filling/Sealing Environment **Air Classification***	Grade A Environment with a Grade B Background	Minimum Grade C Environment with **HEPA Filtered*** unidirectional airflow over filling/sealing equipment
Containers/Closures	Sterile, pyrogen free	Clean, pyrogen free
Time between Container Sealing and Sterilization	Validated time interval	Validated time interval

Figure 1 – Large Scale Media Fill Acceptability Decision Tree