ChemoClave™ Closed System Transfer Device (CSTD) Microbial Ingress Study

Report of a study commissioned by ICU Medical, Inc. and conducted by AAIPharma Services Corp.

Background

The ChemoClave CSTD is a needlefree closed system transfer device (CSTD) that meets the definition recognized by USP ‹800› as "a drug transfer device that mechanically prohibits the transfer of environmental contaminants into the system and the escape of the hazardous drug or vapor concentrations outside the system."[1,2] To validate a CSTD's ability to "mechanically prohibit the transfer of environmental contaminants into the system," microbial ingress test methods have been developed and commissioned by ICU Medical, Inc.

The US Food and Drug Administration (FDA) has issued a guidance document related to microbial ingress testing as part of the premarket clearance 510(k) process for intravascular administration sets.[3] This guidance document serves to assist manufacturers in the development of appropriate test methods, types of microorganisms to consider in the study, and sample sizing. Microbial ingress test results are also included in the documentation submitted to the FDA to obtain 510(k) clearance. The ChemoClave Closed System Drug Transfer Device was cleared under K173477 with the following Indications for Use: The ChemoClave CSTD mechanically prohibits the transfer of environmental contaminants, including bacterial and airborne contaminants, into the system and the escape of drug or vapor concentrations outside the system.[4]

Introduction

The purpose of this microbial ingress study was to evaluate the ChemoClave CSTD's ability to prevent microbial contamination of the system during a worst-case, simulated use test model. The test model included the artificial contamination of the ChemoClave CSTD, followed by a decontamination process and multiple activations over a 7-day use life.

This white paper describes the methods including the types of challenge organisms used, the microbial recovery methods, sample size, controls, procedures including the inoculation methods, the environmental conditions, the validation methods, and the rationales used for these choices.[5]

Methods

Organisms (Four Bacterial Strains)

The organisms chosen for this study include 2 gram-negative and 2 gram-positive organisms, which represent normal microbiological flora found in a clinical setting. The target concentration of 1-5x10^3 represents a higher-than-expected microbial contamination load during worst-case clinical use.

- *Staphylococcus aureus* (ATCC 6538)
- *Staphylococcus epidermidis* (ATCC 12228)
- *Pseudomonas aeruginosa* (ATCC 9027)
- *Klebsiella pneumoniae* (ATCC 4352)

Microbial Recovery Study

The microbial recovery study is designed to accurately estimate the number of microorganisms present in the test solution to demonstrate a method to confirm microbial inoculum levels. This study was done following the below methods. The ChemoClave CSTD septum was inoculated in duplicate with an appropriate volume of inoculum to yield 1-5x10^3 colony-forming units (CFUs) of each test organism listed in the report under Organisms, and then allowed to dry for 1 minute at ambient conditions. After drying, the Clave™ needlefree connector was placed in 10 mL of sterile 0.9% sodium chloride and was mixed using a vortex mixer. The positive control was prepared by inoculating a 10 mL volume of 0.9% sodium chloride with the same inoculum volume used to inoculate the port, followed by 1 mL aliquots being plated to trypticase soy agar (TSA) and incubated at 30–35°C for 1–2 days.

After incubation, the lab performed the colony counts to determine the percent recovery as

$$\text{Percent recovery} = \frac{\text{CFU recovery fluid}}{\text{CFU inoculum count}} \text{ X } 100$$

The acceptance criteria of the percent recovery must be greater than 70%. As seen in Table 1, all microbial recovery testing meets this criterion.

Table 1. Microbial Recovery Studies Results

Test Organism	Device Recovery Average (CFU)	Positive Control Recovery Average (CFU)	Percent Recovery	Meets Criteria
*Staphylococcus aureus**	280	290	97%	Yes
Staphylococcus epidermidis	132	183	72%	Yes
Pseudomonas aeruginosa	188	230	82%	Yes
Klebsiella pneumoniae	150	151	99%	Yes

* Results are estimated; number of colonies recovered was greater than 250 CFU/plate

Sample Size

The study evaluated 6 replicate ChemoClave CSTD septa, which were inoculated with 4 separate organisms and accessed 14 times. The sample size represents the worst-case clinical use and is in alignment of the FDA's requirements for the microbial recovery of medical devices.

Inoculum Concentration

1-5x10^3 colony-forming units (CFUs) for each activation

Procedure

Each ChemoClave CSTD septum was inoculated with the test organisms before each activation. The ChemoClave CSTD was then disinfected with a 70% isopropyl alcohol (IPA) prep pad using an aggressive circular motion for not less than 3 seconds and allowed to dry. The ChemoClave CSTD was activated using the Spiros™ closed male luer syringe assembly, where 10 cc of normal saline was transferred through the ChemoClave CSTD, and the transferred saline was collected and filtered through a 0.45 μm cellulose nitrate filter. The filter was rinsed with 100 mL of 0.9% saline, transferred to a solidified plate of TSA, incubated for a minimum of 48 hours at 30–35 °C, and examined for growth.

This process was repeated for a total of 14 times using artificial contaminations, followed by 2 activations each day, for 7 days. The total number of artificial contamination and fluid transfer events was 14.

Positive Controls

The positive controls were performed in duplicate for each organism by performing the activation and testing procedure above without the 70% IPA disinfection step.

Negative Controls

Negative controls were performed following the same procedure as the test samples with the omission of the microbial inoculation.

Results

Results for the microbial ingress are shown in Tables 2–5. There was no microbial recovery on the negative controls.

Table 2. *Staphylococcus Aureus* Microbial Ingress Results

Activation		Replicate (CFU/Filter) 1	2	3	4	5	6	Inoculum Verification (CFU/Device)
DAY 1	1 2	0	0	0	0	0	0	1.7×10^3
DAY 2	3 4	0	0	0	0	0	0	1.8×10^3
DAY 3	5 6	0	0	0	0	0	0	1.1×10^3
DAY 4	7 8	0	0	0	0	0	0	1.2×10^3
DAY 5	9 10	0	0	0	0	0	0	1.1×10^3
DAY 6	11 12	0	0	0	0	0	0	1.4×10^3
DAY 7	13 14	0	0	0	0	0	0	2.2×10^3
Positive Control Average (CFU/Filter)								24

Table 3. *Staphylococcus Epidermidis* Microbial Ingress Results

Activation		Replicate (CFU/Filter) 1	2	3	4	5	6	Inoculum Verification (CFU/Device)
DAY 1	1 2	0	0	0	0	0	0	2.4×10^3
DAY 2	3 4	0	0	0	0	0	0	2.2×10^3
DAY 3	5 6	0	0	0	0	0	0	1.2×10^3
DAY 4	7 8	0	0	0	0	0	0	2.2×10^3
DAY 5	9 10	0	0	0	0	0	0	1.3×10^3
DAY 6	11 12	0	0	0	0	0	0	1.5×10^3
DAY 7	13 14	0	0	0	0	0	0	1.2×10^3
Positive Control Average (CFU/Filter)								61

Table 4. *Pseudomonas Aeruginosa* Microbial Ingress Results

Activation		Replicate (CFU/Filter) 1	2	3	4	5	6	Inoculum Verification (CFU/Device)
DAY 1	1 2	0	0	0	0	0	0	2.2×10^3
DAY 2	3 4	0	0	0	0	0	0	1.4×10^3
DAY 3	5 6	0	0	0	0	0	0	1.2×10^3
DAY 4	7 8	0	0	0	0	0	0	1.1×10^3
DAY 5	9 10	0	0	0	0	0	0	1.3×10^3
DAY 6	11 12	0	0	0	0	0	0	1.6×10^3
DAY 7	13 14	0	0	0	0	0	0	1.5×10^3
Positive Control Average (CFU/Filter)								106

Table 5. *Klebsiella Pneumoniae* Microbial Ingress Results

Activation		Replicate (CFU/Filter) 1	2	3	4	5	6	Inoculum Verification (CFU/Device)
DAY 1	1 2	0	0	0	0	0	0	2.0×10^3
DAY 2	3 4	0	0	0	0	0	0	1.1×10^3
DAY 3	5 6	0	0	0	0	0	0	1.4×10^3
DAY 4	7 8	0	0	0	0	0	0	2.3×10^3
DAY 5	9 10	0	0	0	0	0	0	2.4×10^3
DAY 6	11 12	0	0	0	0	0	0	2.2×10^3
DAY 7	13 14	0	0	0	0	0	0	2.2×10^3
Positive Control Average (CFU/Filter)								22

Conclusion

Based on the results of the microbial ingress testing as reported above, it is determined that the ChemoClave CSTD meets established criteria for microbial ingress. As part of the devices 510(k) clearance, data was provided to demonstrate the ChemoClave system's ability to prohibit the transfer of environmental contaminants, including bacterial and airborne contaminants, into the system as reflected in the devices Indications for Use statement.

References

1. The United States Pharmacopeial Convention. USP General Chapter ‹800› Hazardous Drugs – Handling in Healthcare Settings. Chapter 14: Administering. 2017
2. National Institute for Occupational Safety and Health (NIOSH): A Performance Test Protocol for Closed System Transfer Devices Used During Pharmacy Compounding and Administration of Hazardous Drugs. NIOSH Docket Number 288-A
3. Guidance for Industry and FDA Staff: Intravascular Administration Sets Premarket Notification Submissions [510(k)], US Department of Health and Human Services, Food and Drug Administration, 2008, Rockville, MD. http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070850.pdf
4. ICU Medical ChemoClave 510(k) Summary K173477
5. AAIPharma, Microbial Ingress Study on ChemoClave, September 2013