# ChemoLock™ 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 ChemoLock CSTD is a needlefree closed system drug transfer device (CSTD) that meets the definition of a CSTD that is 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 sampling size. Microbial Ingress test results are also included in the documentation submitted to the FDA in order to obtain 510(k) clearance. The ChemoLock CSTD was originally cleared under K131549 with the following Indications for Use: The ChemoLock Closed System Drug Transfer Device prevents the transfer of environmental contaminants, including bacterial and airborne contaminants, into the system and the escape of drug or vapor concentrations outside the system. The ChemoLock CSTD was subsequently cleared as part of the Diana™ Medication Transfer Set under K170110 which included the data outlined in this paper.[4]

## Introduction

The purpose of this microbial ingress study was to evaluate the ChemoLock 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 ChemoLock port, 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 microorganisms 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)

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 1-5x$10^3$ 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 demonstrate the suitability of the test method by showing microorganisms can be successfully recovered by following the test method in the protocol. This phase of the study was done following the below methods.

The ChemoLock port septum was inoculated in duplicate with an appropriate volume of inoculum to yield one $5x10^3$ 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 port 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 | Recovery (CFU/Device) | Positive Control Recovery Average (CFU) | Percent Recovery | Meets Criteria |
|---|---|---|---|---|
| *Staphylococcus aureus* | $1.9 \times 10^3$ | $2.0 \times 10^3$ | 95% | Yes |
| *Staphylococcus epidermidis* | $2.0 \times 10^3$ | $2.0 \times 10^3$ | 100% | Yes |
| *Pseudomonas aeruginosa* | $1.4 \times 10^3$ | $1.3 \times 10^3$ | 108% | Yes |
| *Klebsiella pneumoniae* | $1.9 \times 10^3$ | $2.4 \times 10^3$ | 79% | Yes |

## Sample Size

The study evaluated six replicate ChemoLock CSTD ports that were inoculated with 4 separate organisms and accessed 70 times. The number of activations 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 ChemoLock port septum was inoculated with the test organism before each activation. The port 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 port was then activated using the ChemoLock injector syringe assembly where 10 cc of normal saline was transferred through the port, 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 finally examined for growth.

This process was repeated for a total of 10 artificial contaminations, followed by an activation each day for 7 days. The total number of artificial contamination and fluid transfer events was 70.

### 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 procedure.

## Results

There was no microbial recovery on the negative controls. Results can be referenced in Tables 2–5 below.

Table 2. *Staphylococcus Aureus* Microbial Ingress Results

| Activation | | Replicate (CFU/filter) 1 | 2 | 3 | 4 | 5 | 6 | Inoculum Verification (CFU/Device) |
|---|---|---|---|---|---|---|---|---|
| DAY 1 | 1–10 | 0 | 0 | 0 | 0 | 0 | 0 | 1.1 X $10^3$ |
| DAY 2 | 11–20 | 0 | 0 | 0 | 0 | 0 | 0 | 1.7 X $10^3$ |
| DAY 3 | 21–30 | 0 | 0 | 0 | 0 | 0 | 0 | 1.4 X $10^3$ |
| DAY 4 | 31–40 | 0 | 0 | 0 | 0 | 0 | 0 | 1.2 X $10^3$ |
| DAY 5 | 41–50 | 0 | 0 | 0 | 0 | 0 | 0 | 1.2 X $10^3$ |
| DAY 6 | 51–60 | 0 | 0 | 0 | 0 | 0 | 0 | 1.2 X $10^3$ |
| DAY 7 | 61–70 | 0 | 0 | 0 | 0 | 0 | 0 | 1.1 X $10^3$ |
| Positive Control Replicate 1 (CFU/Filter) | | | | | | | | 39 |
| Positive Control Replicate 2 (CFU/Filter) | | | | | | | | 3 |

Table 3. *Staphylococcus Epidermidis* Microbial Ingress Results

| Activation | | Replicate (CFU/filter) 1 | 2 | 3 | 4 | 5 | 6 | Inoculum Verification (CFU/Device) |
|---|---|---|---|---|---|---|---|---|
| DAY 1 | 1–10 | 0 | 0 | 0 | 0 | 0 | 0 | 1.2 X $10^3$ |
| DAY 2 | 11–20 | 0 | 0 | 0 | 0 | 0 | 0 | 1.7 X $10^3$ |
| DAY 3 | 21–30 | 0 | 0 | 0 | 0 | 0 | 0 | 1.4 X $10^3$ |
| DAY 4 | 31–40 | 0 | 0 | 0 | 0 | 0 | 0 | 2.4 X $10^3$ |
| DAY 5 | 41–50 | 0 | 0 | 0 | 0 | 0 | 0 | 1.4 X $10^3$ |
| DAY 6 | 51–60 | 0 | 0 | 0 | 0 | 0 | 0 | 1.1 X $10^3$ |
| DAY 7 | 61–70 | 0 | 0 | 0 | 0 | 0 | 0 | 2.6 X $10^3$ |
| Positive Control Replicate 1 (CFU/Filter) | | | | | | | | 0 |
| Positive Control Replicate 2 (CFU/Filter) | | | | | | | | 3 |

Table 4. *Pseudomonas Aeruginosa* Microbial Ingress Results

| Activation | | Replicate (CFU/filter) 1 | 2 | 3 | 4 | 5 | 6 | Inoculum Verification (CFU/Device) |
|---|---|---|---|---|---|---|---|---|
| DAY 1 | 1–10 | 0 | 0 | 0 | 0 | 0 | 0 | 1.9 X $10^3$ |
| DAY 2 | 11–20 | 0 | 0 | 0 | 0 | 0 | 0 | 1.5 X $10^3$ |
| DAY 3 | 21–30 | 0 | 0 | 0 | 0 | 0 | 0 | 1.9 X $10^3$ |
| DAY 4 | 31–40 | 0 | 0 | 0 | 0 | 0 | 0 | 1.7 X $10^3$ |
| DAY 5 | 41–50 | 0 | 0 | 0 | 0 | 0 | 0 | 1.7 X $10^3$ |
| DAY 6 | 51–60 | 0 | 0 | 0 | 0 | 0 | 0 | 1.2 X $10^3$ |
| DAY 7 | 61–70 | 0 | 0 | 0 | 0 | 0 | 0 | 1.1 X $10^3$ |
| Positive Control Replicate 1 (CFU/Filter) | | | | | | | | 6 |
| Positive Control Replicate 2 (CFU/Filter) | | | | | | | | 6 |

Table 5. *Klebsiella Pneumoniae* Microbial Ingress Results

| Activation | | Replicate (CFU/filter) 1 | 2 | 3 | 4 | 5 | 6 | Inoculum Verification (CFU/Device) |
|---|---|---|---|---|---|---|---|---|
| DAY 1 | 1–10 | 0 | 0 | 0 | 0 | 0 | 0 | 1.3 X $10^3$ |
| DAY 2 | 11–20 | 0 | 0 | 0 | 0 | 0 | 0 | 1.1 X $10^3$ |
| DAY 3 | 21–30 | 0 | 0 | 0 | 0 | 0 | 0 | 1.1 X $10^3$ |
| DAY 4 | 31–40 | 0 | 0 | 0 | 0 | 0 | 0 | 1.5 X $10^3$ |
| DAY 5 | 41–50 | 0 | 0 | 0 | 0 | 0 | 0 | 1.3 X $10^3$ |
| DAY 6 | 51–60 | 0 | 0 | 0 | 0 | 0 | 0 | 1.1 X $10^3$ |
| DAY 7 | 61–70 | 0 | 0 | 0 | 0 | 0 | 0 | 4.2 X $10^3$ |
| Positive Control Replicate 1 (CFU/Filter) | | | | | | | | 8 |
| Positive Control Replicate 2 (CFU/Filter) | | | | | | | | 24 |

## Conclusion

Based on the results of the microbial ingress testing as reported above, it is determined that the ChemoLock system meets established criteria for microbial ingress. As part of the devices 510(k) clearance, data was provided to demonstrate the ChemoLock system's ability to prevent the transfer of environmental contaminants, including bacterial and airborne concentrations, 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 ChemoLock 510(k) Summaries K131549 and K170110
5. AAIPharma, Microbial Ingress Study for ChemoLock Connector Devices, August 2014