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# Evaluation of the CLAVE<sup>®</sup> technology and resistance to microbial ingress

## Background

Contamination of the vascular access device is a substantial risk to patients in today's healthcare environment. The CDC estimates that there are a minimum of 250,000 incidents of Catheter Related Bloodstream Infections (CRBSI) annually in the United States.<sup>1</sup> It is believed that there are two portals for bacterial entry on a vascular access device; the extraluminal, or dermal entry point of the catheter, and the intraluminal, or hub of the catheter which is used to administer fluids and medications. In 1993 The CLAVE NeedleFree Connector was developed to protect the hub and intraluminal pathway of catheters. The CLAVE is a Microbiologically and Mechanically Closed Connector which permits access to the catheter via use of a luer lock connection: No Needles. The U.S. Food and Drug Administration (FDA) which, regulates medical device manufacturers and provides guidance to companies developing products has become concerned with the number of reports of infectious complications related to the field of connectors. The FDA publishes a document entitled *Intravascular Administration Sets Premarket Notification Submission [510(K)]*.<sup>2</sup> In 2005 the FDA revised this document to include a new guidance for the submission of needlefree connectors relating to Microbial Ingress. While only new devices seeking approval are required to conduct this study, ICU Medical independently contracted with Nelson Laboratories of Salt Lake City, Utah to perform the required testing. The results are reported herein.

## Introduction

Microbial Ingress Testing is the evaluation of a product's design and its ability to resist the passage of micro-organisms under a simulated use model. It is important to understand that the intent of the study is to demonstrate that under normal use the device will assist in protecting the vascular access device against intraluminal bacterial contamination. As the catheter hub has been identified as the primary culprit for catheter contamination, it is important that a needlefree device offers the best technology to protect that hub.

The Centers for Disease Control (CDC) makes recommendations regarding the use of needlefree connectors as accessories to intravascular administration sets in their guidance document *Guidelines for the Prevention of Intravascular Catheter-Related Infections* (2002).<sup>3</sup> The specific guidelines are as follows:

IX(B)(2) Change (needleless) caps no more frequently than 72 hours or according to the manufacturer's recommendations.

IX(B)(4) Minimize contamination risk by wiping the access port with an appropriate antiseptic and accessing the port only with sterile devices.

The purpose therefore of Microbial Ingress Testing is to demonstrate that if these actions are taken that the risk of bacterial contamination should be small. Most importantly it is to show that if the device is swabbed (disinfected) then the subsequent connection using a sterile device will offer a connection that does not transmit bacteria. More simply, a Microbial Ingress study should demonstrate that when a device is swabbed, that no bacteria are thereafter passed through, meaning the actual function of swabbing was effective and there are no areas in the device that are harboring bacteria.

Historically the FDA guidance document did not offer specific requirements for the study and therefore many devices were approved under a non-standard form of test, or otherwise, however the Manufacturer wanted to test them.

The latest FDA guidance document that was put out in 2005 gave much more specific direction on how a device should be tested than in previous years. The guidance document recommends testing the device under extreme use conditions, such as repeated insertions into the female luer or pre-slit septum and static insertion over a period of hours. This model is intended to represent a product's use life which would include both intermittent and continuous infusions.

## FDA Guidance Requirements

1. Inoculation of the device should be a minimum of  $10^3$  CFUs of a bacteria commonly associated with skin or IV line contaminants (such as *Staphylococcus epidermidis* or *Staphylococcus aureus*).
2. Allow the inoculated surface to dry for 1 minute.
3. Disinfect the inoculated surface with 70% Isopropyl Alcohol and allow to dry.
4. Access with a needle, or blunt cannulae attached to a syringe.

\*\*\*Repeat steps 1-4 at least 5 times over a period of 24 hours. After the final access you should inject growth media containing 5% BSA into the septa and count the micro-organisms going through the septa. We recommend you run positive and negative samples concurrently.

Development of the Methods and Protocols was based on this document in addition to consultation with the FDA. Discussions with the FDA revealed that they were seeking additional elements which would be seen as favorable including a test period of 72 hours and the testing of at least 4 different bacteria, including Gram negative and Gram positive strains.

## Methods

In order to validate the CLAVE's ability to resist Microbial Ingress, a protocol was developed and executed by Nelson Laboratories of Salt Lake City Utah. Based on communications with the FDA, four bacterial strains were selected for the study as follows:

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

Twenty Four (24) Test samples were prepared in addition to eight (8) negative control and eight (8) positive control samples. Sterile Phosphate Buffered Saline (PBS) was prepared as the flush solution for the repeat activations. Soybean casein digest broth (SCDB) containing 5% bovine serum albumin was prepared for the extended activation samples. Preparation of the test samples, microorganisms and additional materials were all completed in accordance with Good Laboratory Practice (GLP) standards.

## Procedures

For a three day period the test samples were subjected to a rigorous use simulation which followed the FDA guidance document. Each sample was subjected to an inoculation of a minimum of  $10^3$  CFU of the subject microorganism and allowed to dry for at least 1 minute. Each sample was then disinfected using a 70% (IPA) wipe using an aggressive circular motion for three (3) seconds. The sample was then accessed using a sterile 10mL syringe filled with saline which was then infused through the device and collected in a filter funnel unit. This entire process was completed four (4) additional times per day for three days. Each test sample received a total of fifteen (15) each; Inoculation, IPA swab and then push of 10mL of saline.

At the end of the repeat use simulation, the samples were subjected to two more activations; One four hour extended activation using a sterile 10mL syringe, and then a final activation where the SCDB with bovine serum albumin was flushed through the device and captured in the filter units.

The Positive Control samples were processed by eliminating the IPA wipe procedure and the Negative Control Samples were processed by eliminating the inoculation procedure. All collections from the simulated use flushes were incubated for seven days and then bacterial counts were analyzed.

## Results

Of the four bacterial strains, all showed zero (0) counts of CFU at completion of the study, demonstrating that the CLAVEs did not become contaminated during the repeat use simulation or extended activation procedures. The challenge inoculation counts for positive controls were:

*Staphylococcus aureus* = 21000 CFU  
*Staphylococcus epidermidis* = 2200 CFU  
*Klebsiella pneumoniae* = 28000 CFU  
*Pseudomonas aeruginosa* = 11000 CFU

The Negative Control Samples all demonstrated zero (0) CFU counts. The positive control samples all showed bacterial contamination, however more than half of the bacterial counts showed a significant reduction from the inoculation counts with *NO* disinfection procedure.

## Conclusions

In all cases the CLAVE was effective at preventing Microbial Ingress when subjected to a rigorous simulated use model. It was further found with the positive control samples that the CLAVE technology which includes the dedicated internal fluid pathway, was largely effective at preventing Microbial Ingress even when the IPA swab was not done. The CLAVE may be considered an effective tool to assist in the prevention of catheter hub contamination and otherwise intraluminal bacterial colonization.

## Summary Table

| Microorganism                     | Extended Activation (CFU) | SCDB Flush (CFU) | Positive Control Log Reduction |
|-----------------------------------|---------------------------|------------------|--------------------------------|
| <i>Staphylococcus aureus</i>      | 0                         | 0                | 3.2                            |
| <i>Staphylococcus epidermidis</i> | 0                         | 0                | 3.7                            |
| <i>Klebsiella pneumoniae</i>      | 0                         | 0                | 2.4                            |
| <i>Pseudomonas aeruginosa</i>     | 0                         | 0                | 3.2                            |

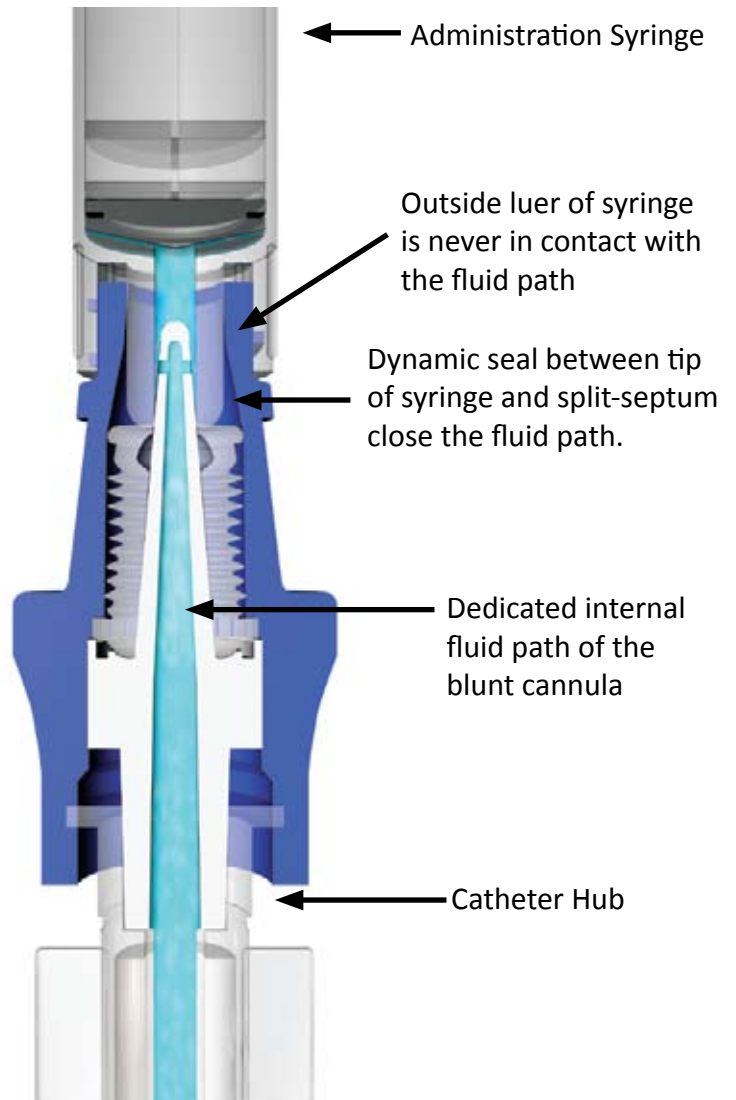
## The CLAVE Connector

The CLAVE was developed in the early 90s as a Microbiologically and Mechanically Closed Connector. Its primary intent at the time was to serve as a fail-safe closing device that would protect the patient from bleed out, or air ingress during an accidental disconnect of the IV tubing to the catheter. The CLAVE was a simplified version of the Click Lock<sup>®</sup>, which was the first device to replace needles and tape for connecting IV lines.

The CLAVE is a reversed, split-septum technology which incorporates an internal blunt cannula and a pre-slit silicone septum to seal off the fluid path. The internal blunt cannula creates a unique dedicated internal fluid path such that at no time the housing, outside of the silicone seal or outside of the administration device luer comes in contact with the fluid path.

The CLAVE is the most widely used and published Needleless Connector on the market today. Various studies have demonstrated that the CLAVE is a more effective component compared to other devices in the infection control regimen. Other studies have shown that the CLAVE will independently reduce catheter hub colonization on central venous catheters. Additionally, a large comparative in vitro study found that the CLAVE was the least likely of nine other commercially available Needleless Connectors to allow for the transfer of bacteria into the fluid path. The heart of the CLAVE design is founded in the reversed, split-septum technology which provides the dedicated internal fluid path and is incorporated in all variations of the CLAVE including the MicroCLAVE, the Y-site CLAVE and the Antimicrobial CLAVE devices.

## CLAVE Internal Fluid Path Operation



## References

- <sup>1</sup> Kluger DM, Maki DG. The relative risk of intravascular device related bloodstream infections in adults. Abstract of the 39th Interscience Conference on Antimicrobial Agents and Chemotherapy. ASM 199:514.
- <sup>2</sup> Guidance for Industry and FDA Staff: Intravascular Administration Sets Premarket Notification Submission [510(K)]. 2005.
- <sup>3</sup> Guidelines for the Prevention of Intravascular-Related Device Infections. MMWR, 2002. Vol.51 No.RR-10.