

New Drug Vial Optimization Processes Help Maintain Drug Stability: Why the ICU Medical ChemoClave™ system can help reduce drug waste

INTRODUCTION

Antineoplastic drugs are common agents used for the intravenous treatment of many cancers. These hazardous agents are very expensive for facilities to procure and dispense. However, facilities often remove only part of the drug from the vial during preparation based on the scheduling of patients, resulting in the premature disposal of the vial and subsequent loss of the valuable drug. A recent study by Vandenbroucke and Robays found that at the Ghent University Hospital in Belgium, where approximately 28,000 cytotoxic preparations are done yearly, as much as \$900,000 (USD) was being wasted on early drug disposal.³ Their model allowed drugs to be used in a multi-dose format in accordance with their physical and chemical stability expiry dates.

The preferred method of accessing antineoplastic drug vials for preparation is through the use of a closed system transfer device (CSTD). These systems provide a means for accessing the drug vial with a needlefree or protected needle design. The CSTD will also equalize pressure within the vial while medication is being withdrawn, thus preventing unwanted leaks and aerosols that result from traditional needle access. Organizations such as the National Institute for Occupational Safety and Health (NIOSH) and the United States Pharmacopeia USP <797> have recommended the use of CSTDs to help protect the healthcare worker from exposure to hazardous agents and to protect the sterility and integrity of the drug itself.^{1,2}

New research into the use of a CSTD to maintain both the sterility and the stability of an antineoplastic drug for its useful life is necessary to determine the appropriateness of an extended-use, multi-dose model. ICU Medical has conducted a series of studies to measure the physical and chemical properties of cytotoxic drugs when used in connection with the ICU Medical ChemoClave CSTD.

These studies investigate the CSTD from a microbiological standpoint to verify that the CSTD will maintain the physical sterility of the vial over an extended time period and a simulated-use model. Secondly, the studies have investigated the drug itself from an integrity standpoint to ensure the interaction of the drug with the CSTD does not affect the drug's stability or composition over time.

Results show that the early disposal of drugs may not be necessary and facilities may be able to save more on drug costs by using a CSTD in a multi-dose application.

EXTENDED-USE MICROBIOLOGICAL INTEGRITY STUDY

De Prijk et al. recently conducted a study involving CSTDs and microbial ingress; however, the study design is not consistent with how vials and CSTD are handled in the clinical environment.⁴ In De Prijk et al.'s study, the investigators contaminated the drug vial stoppers with a series of bacterium at various concentrations in a process called the "dopping step." The study used 3



Closed System Transfer Devices (CSTD) like ICU Medical's ChemoClave™ system help protect healthcare workers from exposure to hazardous agents while protecting the sterility and integrity of the drug itself.

different CSTD systems to access the vials by means of “spiking” the vials with the CSTD, which was intended to be permanently affixed to the vial.

The investigators then measured the amount of bacterial transfer into the vials for each CSTD. In the discussion, the investigators note how the “thinnest” spike allowed for the least amount for bacterial transfer, while the “thickest” spike caused the most. The problem with this study design is that the manufacturers sterilize drug vials in the manufacturing process so that under the protective cap the stopper is isolated from any type of handling contamination. Pharmacists then prepare the drug vials using a sterile technique in a biological safety cabinet in accordance with pharmacy standards, so that when the protective cap is removed and the drug vial accessed, there should be no bacterial contamination.

De Prijk then goes on to study the effects of multiple accesses to a vial through the access point on the CSTD in a process called the “coupling step.” In this process, the investigators contaminated the access point of each of the CSTD, which over

time is probable in an extended-use model. However, De Prijk failed to follow the CSTD instructions and standard hospital protocol of disinfecting the access point before each access. Therefore, it would be expected that if no disinfection occurred before accessing the CSTD that bacteria would most certainly be transferred into the vial.

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To properly answer the question of whether or not a specific CSTD would pose a risk of bacterial transfer in a typical handling environment, ICU Medical developed an extended-use model. The ICU Medical Clave® Connector has been shown in patient populations to reduce the risk of bacterial colonization in central venous catheters and to reduce bloodstream infections.^{5,6}

The Clave is also an integral component to the CSTD manufactured by ICU Medical and serves as the “access point” for all vial manipulations in the same manner it serves as the access point for all patient catheters. In the ICU CSTD extended-use model, the Clave Needlefree Vial Access Device was studied to demonstrate microbiological integrity for 30 days in a laboratory setting.⁷ The investigators of this study aseptically attached the Clave vial access device to a 50 mL vial in accordance with the vial manufacturer’s instructions.

When connected to a vial, the Clave plastic spike creates a seal through the vial stopper, thus preventing any migration of bacteria or escape of the drug. This connection is intended for the life of the vial as is explicitly stated in the product instructions. The Clave thereafter serves as the entry point for the vial to infuse diluents or aspirate medication using a standard ISO Luer Lock™ syringe or ISO compliant CSTD luer such as the Spiros® Closed Male Luer.

For the study, the investigators changed the vial-Clave assembly to an extended-use model that included 30 accesses to the vial through the Clave access point for the removal of fluid over a 30-day period. The study tested a total of 20 vial-Clave assemblies, resulting in a total of 600 independent accesses to the vials. Prior to each access, the investigators disinfected the Clave with a 70% Isopropyl alcohol (IPA) swab using an aggressive circular motion for 3 seconds, which is in accordance with the Clave instructions. They then aspirated 1 mL of fluid from the vial at each access and transferred it to a filter funnel unit for bacterial capture. Next, they transferred the filters to Soybean Casein Digest Broth (SCDB) plates, allowed them to incubate for 7 days, and characterized them for bacterial growth. All vials were stored on the laboratory bench in an uncontrolled environment at room temperature.

At the time of study termination on day 30, the investigators characterized the filters for microbial growth. Results showed that none of the filters exhibited forms of bacterial growth, confirming that the Clave allowed for 30 repeat accesses to the vial, while effectively maintaining the vial sterility for a 30 day period.

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EXTENDED-USE DRUG STABILITY STUDY

To evaluate the chemical and physical interaction between the ChemoClave system preparation products and a series of antineoplastic drugs that are

known to react with plastics, an Italian Research Facility, STUDIO AMBIENTE S.r.l. (VR) Italy, developed protocols.^{8,9} This study prepared and stored antineoplastic drugs in a variety of methods and conducted investigational work to determine an extended-use model that would demonstrate that the integrity of the drug was not compromised when stored using ChemoClave system devices for a minimum of 30 days. The study researched and selected specific drugs to represent various therapeutic classes and chemical compositions.

Each series of devices was exposed by the study to three different antineoplastic drugs in their undiluted forms: etoposide, fluorouracil, and cisplatin. To prepare test samples, investigators infused each drug through independent test samples, agitated them, and then subjected them to a storage protocol. The investigators placed the samples in refrigeration for a 30-day period and then removed them and allowed them to sit at room temperature for 1 day. The investigators visually inspected the devices during the storage period at various time points and then leak tested them to verify functional integrity. Following the storage period, the investigators removed the drug from each sample and tested it for stability using the High-Performance Liquid Chromatography (HPLC) method.

Results showed that all ChemoClave devices, including the Clave, Genie[®] and the Spiros, maintained acceptable limits of drug concentrations for the 30-day extended-use model. Stability measurements are reported in the table below.

Test Device	Etoposide ^a	Fluorouracil ^a	Cisplatin ^a
Genie Vial Access Device (Includes Clave)	99.2	99.2	99.6
Spiros Closed Male Luer	99.6	99.6	99.6

^aPercent of drug measured in respect to original concentration following 30 days of refrigeration and 1 day at room temperature.

CONCLUSIONS

The ChemoClave system will maintain the sterility of a drug vial for a maximum of 30 days when used in accordance with its instructions. Stability studies demonstrated that the chemical integrity of 3 drugs, Etoposide, Fluorouracil, and Cisplatin, were within acceptable limits when exposed to the ICU Medical ChemoClave CSTD system for a 30 day period.

DISCUSSION

The use of multi-dose vials can have substantial cost savings when facilities use them in connection with the ChemoClave CSTD under an extended-use model. ICU Medical does not support extending the life of a drug that is otherwise explicitly indicated on the drug package insert unless independent stability studies are completed.

References

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