

ChemoClave[®] Closed System Transfer Device (CSTD) Compatibility With Hazardous Drugs

INTRODUCTION

Hazardous drugs used in the therapeutic treatment of many cancers are most commonly delivered to a patient intravenously. Unfortunately, traditional IV equipment, including tubing and plastic components used to deliver medications, can be degraded by exposure to hazardous drugs, damaging the plastic and releasing chemicals into the fluid path that can ultimately be delivered to the patient.

Furthermore, the health risks posed by exposure to these agents for healthcare workers has prompted organizations such as the United States Pharmacopeia (USP <797> and <800>) to recommend the use of specialized closed system transfer devices (CSTDs) to reduce clinician exposure to these hazardous drugs.^{1,2}

This paper describes the ways in which certain drugs interact with the ChemoClave system during compounding and administration. It also describes the compatibility validation process used by ICU Medical to prove that the ChemoClave CSTD system meets standards required for hazardous drug preparation and administration.

PLASTIC INTEGRITY FOLLOWING DRUG INTERACTION

Solid plastic components used in the manufacture of intravenous sets and preparation devices can be damaged by interaction with solvent agents such as alcohol. Hazardous drugs, such as the etoposide and paclitaxel classes, contain undiluted organic solvents at 33 and 50 percent respectively.^{3,4} Plastic devices made of acrylic or ABS (a polymer composed of acrylonitrile, butadiene, and styrene) have been reported to crack and leak when exposed to these agents.⁵ The degree of damage caused to ABS or acrylic by etoposide and paclitaxel agents is dependent on several factors, including the design of the component and how much stress is applied into the part. Cracks can occur in the component as the solvent acts as a stress reliever and can potentially result in drug leakage.

CHEMICAL LEACHING AND SORPTION

In the United States, one fourth of all plastic medical products are made of polyvinyl chloride (PVC), including most IV bags and tubing.⁶ The chemical composition of PVC resins produces a brittle plastic. Therefore, many PVC components contain diethylhexyl phthalate (DEHP), a plasticizer that lends flexibility, strength, and optical clarity to the plastic. The PVC used in medical devices often contains a relatively high percentage (20–40 percent) of DEHP, which has been identified by the United States Environmental Protection Agency (EPA) as a probable human carcinogen.⁷

Because DEHP is not chemically bound to PVC, it can migrate or leach from the medical device into lipid emulsions.^{8,9,10} In the case of intravenous infusion of hazardous drugs, chemicals can leach from IV tubing and bags when exposed to hazardous drugs. Data collected for the presence of DEHP show that levels increase with time and concentration when dilutions are prepared in PVC containers.

ChemoClave Closed System Transfer Device



All ChemoClave components are non-DEHP and have been proven to resist sorption and support drug stability.

Consequently, the use of plasticized PVC containers and administration sets that contain DEHP is not recommended. None of the components in ICU Medical's ChemoClave product line contain DEHP.

Drug sorption describes the process by which drug components stick to or are absorbed into the plastic devices.¹¹ Drug sorption impacts the agent's chemical makeup and can result in a loss of stability when hazardous drugs are exposed to the plastic for long periods of time or infused through lengthy expanses of tubing. Careful selection of plastics used to manufacture infusion devices can improve resistance to drug sorption and the devices' ability to support drug stability. The plastics used to manufacture ICU Medical's ChemoClave product line are chosen for their resistance to drug sorption and their ability to support drug stability.

ICU MEDICAL PRODUCT EVALUATION

Recognizing the potential for plastic components to negatively impact the intended use of hazardous drug therapies, ICU Medical developed a stringent compatibility protocol for testing plastic components.

HAZARDOUS DRUG COMPATIBILITY PROTOCOL

To evaluate the interaction between the ChemoClave product line and the series of hazardous drugs that are known to react with plastics, protocols were developed at Studio Ambiente S.r.l. (VR) in Italy that were derived from investigational work in which the researchers studied worst-case exposure and storage procedures for a number of preparation and storage methods.

METHOD

Specific drugs were researched and selected to represent various therapeutic classes and chemical compositions. ChemoClave system components, including the Spiros® closed male luer, along with CSTD vial spikes, were each exposed to the twelve selected hazardous drugs in their undiluted form. Drugs were diluted to three times their therapeutic value for testing with IV sets to represent the worst-case exposure for the administration equipment. Three separate tests were completed, including a functional integrity test, a drug stability test, and a plastic migration test, to verify drug compatibility with the chemotherapy devices.

To prepare test samples, each drug was infused through independent test samples, agitated, and then subjected to a storage protocol as noted in the table on the following page. Samples were placed in refrigeration for a specified time period and then stored at room temperature for a specified time period. Devices were visually inspected during the storage period at various times and then leak tested to verify functional integrity.

Following the storage period using cisplatin, etoposide, fluorouracil, and Herceptin®, the drug was removed from each sample and tested for stability using the high-performance liquid chromatography (HPLC) method. Using gas chromatography with mass detector, the drug samples were then evaluated for plastic migration, including concentrations of phthalate and vinyl chloride. The standard used for phthalate concentration was based on the European Directive 2005/84/EC with an acceptance level of 0.1 percent of mass. The standard used for vinyl chloride concentration was based on the European Pharmacopeia, which requires < 1ppm. All results are available in Table 1.

RESULTS

All ICU Medical chemotherapy preparation and delivery devices evaluated per the protocol reached acceptable limits for all phases of testing.

CONCLUSION

Known effects of drug interaction, including cracking of plastic devices, reduced stability due to drug sorption, and leaching of chemicals such as DEHP, can be eliminated with proper product design and validation. Ongoing evaluation of all plastic components developed for use in the ChemoClave product line follows the aforementioned hazardous drug compatibility protocol. In addition, ICU Medical components are non-DEHP and are proven to resist sorption and support drug stability. Complete test reports are kept on file at ICU Medical, San Clemente, CA.^{12,13}

TABLE 1

Spiros Closed Male Luer
120 Days of Refrigeration, and 7 Days at Room Temperature

Hazardous Drug	Functional Failure	Drug Stability - 120 Days	Plastic Migration per Device
Bevacizumab	0/10	NT	NT
Cetuximab	0/10	NT	NT
Cisplatin	0/10	99.60%	P = .25µg; VC = < .08µg
Cyclophosphamide	0/10	NT	NT
Doxorubicin	0/10	NT	NT
Etoposide	0/10	99.60%	P = .05µg; VC = < .05µg
Fluorouracil	0/10	99.60%	P = .58µg; VC = < .07µg
Herceptin	0/10	97.30%	P = < 5µg; VC = < .2µg
Methotrexate	0/10	NT	NT
Paclitaxel	0/10	NT	NT
Vincristine	0/10	NT	NT

Vial Spikes*
30 Days of Refrigeration, and 7 Days at Room Temperature

Hazardous Drug	Functional Failure	Drug Stability - 30 Days	Plastic Migration per Device
Bevacizumab	0/10	NT	NT
Cetuximab	0/10	NT	NT
Cisplatin	0/10	99.96%	P = .125µg; VC = < .05µg
Cyclophosphamide	0/10	NT	NT
Doxorubicin	0/10	NT	NT
Etoposide	0/10	99.66%	P = .014µg; VC = < .05µg
Fluorouracil	0/10	99.52%	P = .014µg; VC = < .05µg
Herceptin	0/10	97.30%	P = < 5µg; VC = < .2µg
Methotrexate	0/10	NT	NT
Paclitaxel	0/10	NT	NT
Vincristine	0/10	NT	NT

Administration Sets*
24 Hours at Room Temperature Diluted to 3x Therapeutic Level

Hazardous Drug	Functional Failure	Drug Stability - 24 Hours	Plastic Migration per Device
Bevacizumab	0/10	NT	NT
Cetuximab	0/10	NT	NT
Cisplatin	0/10	99.93%	P = .07µg; VC = .07µg
Cyclophosphamide	0/10	NT	NT
Doxorubicin	0/10	NT	NT
Etoposide	0/10	99.73%	P = .25µg; VC = .09µg
Fluorouracil	0/10	99.73%	P = .60µg; VC = .05µg
Herceptin	NT	NT	NT
Methotrexate	0/10	NT	NT
Paclitaxel	0/10	NT	NT
Vincristine	0/10	NT	NT

*Includes Clave® Needlefree Connector in evaluation
NT = Not Tested

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