

The role of Litmus testing using 5FU to evaluate Syringe Barrel plunger contamination when using with a CSTD for preparation of hazardous drugs

Data on File at ICU Medical, Inc.

Introduction

The risks associated with the compounding and administration of hazardous drugs (HD) have been evaluated and documented in several studies.¹ The Occupational Safety and Health Administration (OSHA) and professional organizations began promoting the adoption of safe handling guidelines starting in the mid-1980s. Several organizations and government agencies in the US have published safe handling guidelines and standards for hazardous drugs, including the US Pharmacopeia (USP).^{2,3} USP General Chapter <800> provides standards that require the use of a closed system transfer device (CSTD) for antineoplastic HDs when the dosage form allows administration and recommend the use of a CSTD for HD compounding when the dosage form allows.

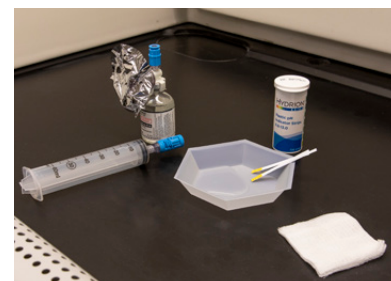
Since the development of CSTDs, several options exist for HD preparation and administration, as well as standardized ways to evaluate their efficacy of hazardous drug containment. Some are being promoted today for their effectiveness by “closing all routes of exposure,” indicating multiple routes of clinician exposure to hazardous drugs.⁴ These routes include at the connection point and the posterior (barrel) end of the syringe. It’s been suggested that having a proprietary syringe design that closes off the syringe barrel (posterior end) ensures that all routes of exposure are closed, thereby providing a safer CSTD compared to others on the market.

USP <800> requires the use of a closed system transfer device (CSTD) for HD administration and recommend the use of a CSTD for HD preparation.

Background

One of the more widely accepted methods for evaluating surface leaks is using Fluorouracil (5FU), in combination with litmus strips.⁵ With a standard pH range of 8.6 to 9.4, 5FU is easily recognizable on litmus strips that can detect pH levels greater than 7. Using 5FU is preferred over other surrogate options because it is a common hazardous drug that can be compounded in accordance with both the drug’s instructions for use (IFU) and the CSTD’s intended purpose. There are currently a limited number of published pH litmus studies that represent the current CSTDs on the market, leaving users with a limited number of outdated studies based on products no longer in the market.

While the primary focus of litmus testing has been at the connection points of the CSTD, further evaluation of the syringe component is warranted.



ChemoLock™ CSTD on 5FU vial and BD syringe, sterile water for wetting litmus

Objectives

The purpose of this white paper is to provide an analysis of the presence of residual hazardous drug on the inner syringe barrel after multiple activations in a simulated compounding environment. A worst-case drug transfer model using 5 repeat transfers for 3 separate syringe, for a total of 15 each, with litmus detection following each activation, was developed to evaluate the ChemoLock CSTD. A litmus test is also a simple method to verify that the posterior (barrel) end of the syringe of a CSTD does not have liquid residuals following a simulated drug transfer procedure with multiple activations.

Testing was conducted at ICU Medical, Inc., San Clemente, CA, in Class IV Biological Safety Cabinet as required by USP for the compounding of hazardous drugs. Each CSTD system included a syringe adapter component ChemoLock™ injector and a vial adapter with an access ChemoLock port.

Materials

To evaluate the risk of contamination associated with hazardous drug transfers using a standard syringe barrel, ICU Medical chose Fluorouracil (5FU) as the challenge drug. Fluorouracil (5FU) is easily detected using standard litmus strips with a pH detection of greater than 7 pH.⁵ The pH strips chosen to offer a single-color match at every 0.5 intervals from pH 6.5–13.0 and a large test area making them easy to use.

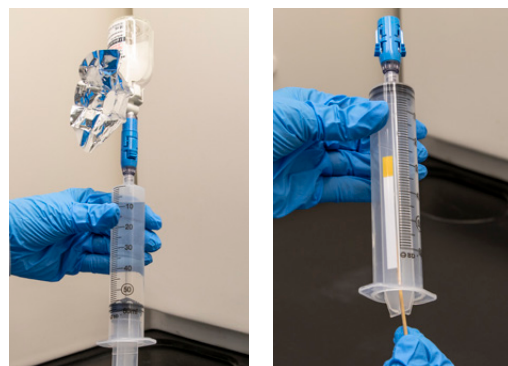
- › 1 vial of Fluorouracil (5FU); 2.5 gm / 50 mL, Fresenius Kabi
- › Litmus testing strips; Micro Essential #9600, Lot number 203318U
- › 30 mL standard BD luer lock syringes (3 count)
- › 20 mL standard Monoject™ luer lock syringe (3 count)
- › One 18G needle attached to 5mL luer lock syringe
- › Sterile water
- › ChemoLock injectors (6 count); CL2000S, Lot number 4549307
- › ChemoLock vial spikes (6 count); CL-80S, Lot number 4179243

Methods

In this model, the litmus testing strips were wetted with sterile water to enhance the uptake of 5FU surface residuals.

First, to process a positive control, 1 mL of the drug was removed from the vial using an 18G needle attached to a 5 mL luer lock syringe. Wet litmus paper was rubbed against the needle in which a bead of 5FU was exposed.

A ChemoLock vial spike with the port was then attached to the 5FU vial. A ChemoLock injector was attached to the vial spike, and 20 mL of 5FU was withdrawn from the vial. The vial was stood upright on the BCS surface, and the 20 mL of 5FU was re-infused into the vial. The ChemoLock injector was disconnected from the syringe.



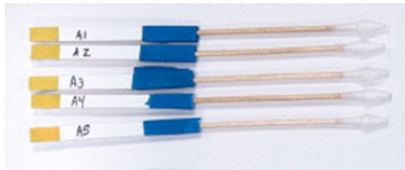
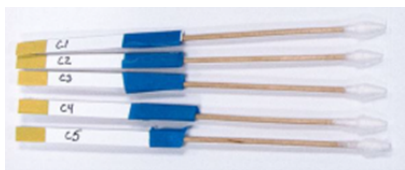
Left: ChemoLock vial adaptor and syringe adaptor withdrawing 5FU. Right: Litmus testing inside syringe barrel

The litmus paper was inserted into each syringe barrel, and the sidewalls of the syringe barrel were firmly swabbed to ensure the litmus paper contacted the 5FU. The selection of 5 transfers were selected to represent the worst-case scenario. All litmus touches within the syringe barrels were recorded in the results table and photographed for documentation of results.

All functions were performed wearing nitrile gloves.

Results

Results of the syringe barrel litmus testing show no detectable residual hazardous drug on the inside barrel of common syringes used in the pharmacy, suggesting that the syringe piston clears the inner barrel of the syringe of residual hazardous drug during use.

BD 30 mL Syringe Study Results	Swab	D/ND
	A1	ND
	A2	ND
	A3	ND
	A4	ND
	A5	ND
	B1	ND
	B2	ND
	B3	ND
	B4	ND
	B5	ND
	C1	ND
	C2	ND
	C3	ND
	C4	ND
	C5	ND

Monoject 20 mL Syringe Study Results	Swab	D/ND
	D1	ND
	D2	ND
	D3	ND
	D4	ND
	D5	ND
	E1	ND
	E2	ND
	E3	ND
	E4	ND
	E5	ND
	F1	ND
	F2	ND
	F3	ND
	F4	ND
	F5	ND

Conclusions

The results of the study show that the use of the ChemoLock CSTD with standard BD and Monoject syringes demonstrated no detection of 5FU hazardous drug presence within the syringe barrel following a worst-case simulated use model. The use of wet litmus paper and a high pH drug, such as 5FU, is a simple and effective way to analyze the ability of a CSTD syringe combination to detect presence of residual drug inside the barrel of a syringe.

References

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2. American Society of Health System Pharmacists Council on Professional Affairs. ASHP Guidelines on Handling Hazardous Drugs. *Am J Health-Syst Pharm.* 2006;63:1172-1193
3. USP General Chapter <800>: Hazardous Drugs—Handling in Healthcare Settings. The United States Pharmacopeial Convention Pharmacopeial Forum (PF). December 2019
4. Comparative Study of Syringe Contamination by Hazardous Drug
5. Centers for Disease Control (CDC). Regulations.gov Comments from Firouzan Massoomi, Comparative Research Report Assessment of Closed System Transfer Devices 5-FU Drug Leakage: <https://www.regulations.gov/documentd?D=CDC-2015-0075-0027>

Micro Essential Laboratory, pH Strips
<https://microessentiallab.com/ProductInfo>

5FU Pls
<https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=55dbd7b2-f9f1-4863-82b5-d4d85bd5d28b>
<https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=e0794add-67a7-4308-93e9-f889472716cc>