The Role of Litmus Testing with Fluorouracil (5FU) in Analyzing a Closed System Transfer Device's Ability to Prevent External Leaks

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 for hazardous drugs, including the US Pharmacopeia (USP). USP General Chapter ‹800› provides standards that require the use of a closed system transfer device (CSTD) for administration of antineoplastic HDs when the dosage form allows and recommend the use of a CSTD for HD compounding when the dosage form allows.[2,3] Since the development of CSTDs, several options exist for HD compounding and administration, as well as standardized ways to evaluate their efficacy of hazardous drug containment.

Background

One of the more widely accepted methods for evaluating surface leaks is using fluorouracil (5FU), in combination with litmus strips. With a standard pH range of 8.6 to 9.4, 5FU is easily recognizable on litmus strips that are able to detect pH levels greater than 7.[4] 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 use. Alternative nontherapeutic surrogates, such as lemon juice, do not align with the CSTD's intended purpose and may result in an unintended false positive. Any presence of surface 5FU at the connection points of a CSTD would then be easily detected using the litmus strips. 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of published pH litmus studies that represent the current CSTDs on the market, leaving users with a limited number of outdated studies based on products no longer in the market.[4,5]

Objectives

The purpose of this white paper is to provide an analysis of a simulated compounding procedure using 5FU and multiple activations of the third generation and current commercially available version of the ChemoLock™ CSTD to determine its effectiveness in preventing external leaks (i.e., surface fluids) at connection points. A worst-case drug transfer model using 5 repeat transfers, with litmus detection following each activation, was developed to evaluate the ChemoLock injector and port. A litmus test is a simple method to verify that the connection points of a CSTD do not have liquid residuals following a simulated drug transfer procedure with multiple activations.

This testing was conducted at ICU Medical, Inc., San Clemente, CA, in a class IV biological safety cabinet (BSC) as required by USP for the compounding of hazardous drugs. Each CSTD system included a syringe adapter component, a ChemoLock injector, and a vial adapter with an access ChemoLock port.

Withdrawing 5FU with ChemoLock CSTD

Materials

To evaluate how the ChemoLock CSTD performs in its ability to prevent liquid leakage at its connection points, ICU Medical chose fluorouracil as the challenge drug because it is easily detected using standard litmus strips with a pH detection of greater than 7 pH.[4] The pH strips chosen offer a single color match at every 0.5 interval from pH 6.5–13.0 and a large test area making them easy to use.

- 6 vials of fluorouracil (5FU); 2.5 gm / 50 mL, Fresenius Kabi
- Litmus testing strips; Micro Essential #9600, Lot number 203318U
- 10 mL standard luer lock syringes (7 count)
- 18G needle (1 count)
- 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 paper was wetted with sterile water to enhance the uptake of 5FU surface residuals. Before each transfer, the ChemoLock port on the vial spike was disinfected with 70% isopropyl alcohol (IPA) and allowed to dry. The drug was then removed from the vial using a ChemoLock injector assembled to a standard 10 mL syringe. The vial was placed upright on the BSC surface. The CL2000S assembled to the syringe was disconnected, allowing the CL2000S to automatically disconnect from the ChemoLock port on the vial. Following each withdraw, both the ChemoLock injector and ChemoLock port membranes were sampled with the wetted litmus paper and evaluated for 5FU detection.

The selection of 5 total transfers was selected to represent the worst-case scenario. All litmus touches on the CSTD membranes were recorded in the results table and photographed for documentation of results.

All functions were performed wearing nitrile gloves.

Testing ChemoLock port with wet litmus paper

Testing ChemoLock injector with wet litmus paper

Results

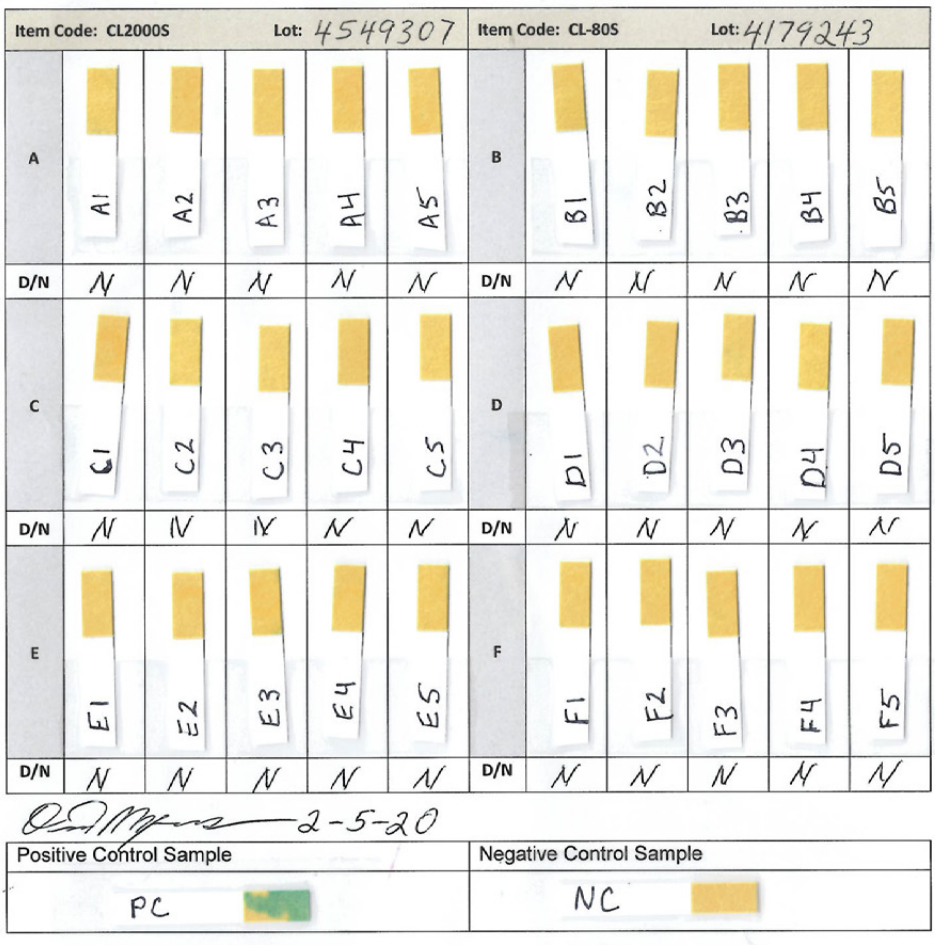
TABLE 1. CL2000S DATA COLLECTION SHEET

Item Code: CL2000S	Result (D, N)	Result (D, N)	Result (D, N)	Result (D, N)	Result (D, N)
A1	N	N	N	N	N
A2	N	N	N	N	N
A3	N	N	N	N	N
A4	N	N	N	N	N
A5	N	N	N	N	N
C1	N	N	N	N	N
C2	N	N	N	N	N
C3	N	N	N	N	N
C4	N	N	N	N	N
C5	N	N	N	N	N
E1	N	N	N	N	N
E2	N	N	N	N	N
E3	N	N	N	N	N
E4	N	N	N	N	N
E5	N	N	N	N	N
Negative Control (NC): N			Positive Control (PC): D		

D= Detection; N= Non-Detect

TABLE 2. CL-80S DATA COLLECTION SHEET

Item Code: CL-80S	Result (D, N)	Result (D, N)	Result (D, N)	Result (D, N)	Result (D, N)
B1	N	N	N	N	N
B2	N	N	N	N	N
B3	N	N	N	N	N
B4	N	N	N	N	N
B5	N	N	N	N	N
D1	N	N	N	N	N
D2	N	N	N	N	N
D3	N	N	N	N	N
D4	N	N	N	N	N
D5	N	N	N	N	N
F1	N	N	N	N	N
F2	N	N	N	N	N
F3	N	N	N	N	N
F4	N	N	N	N	N
F5	N	N	N	N	N
Negative Control (NC): N			Positive Control (PC): D		



Conclusions

The results of the study show the ChemoLock CSTD demonstrated no detection of 5FU hazardous drug presence at the connection points 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 to prevent leaks at the fluid path connection points.

References

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5. UNC Eshelman School of Pharmacy, Connector integrity testing to assess the efficacy of multiple closed system transfer devices; poster presented

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

5FU PIs
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https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=e0794add-67a7-4308-93e9-f889472716cc