Vapor Containment Efficacy of Air-Cleaning CSTDs with 3 NIOSH Surrogates

Final Report

Device and surrogate Names:	ChemoClave by ICU Medical ChemoLock by ICU Medical Texium/SmartSite by BD OnGuard/Tevadaptor by B. Braun Chemfort by Simplivia Tetramethylurea Tetraethylurea Propylene Glycol
Short Title:	Efficacy of Air-Cleaning CSTDs With NIOSH Surrogates
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Date of Report:	September 20, 2021

2. Table of Contents

3. Summary

Study Title: Vapor Containment Efficacy of Air-Cleaning CSTDs with 3 NIOSH Surrogates

Purpose:

The primary objective of this study was to determine the effectiveness of three hazardous drug surrogates suggested by NIOSH with 5 vented CSTDs and thereby help to exclude ineffective surrogates from the NIOSH surrogates list, as ineffective surrogates may lead to a false sense of security from the use of CSTDs, thereby putting the well-being of healthcare workers at risk.

Methods:

The continuously updated NIOSH list of hazardous drugs contains a large variety of molecules and compounds. NIOSH states that "… air-cleaning technologies can have varying efficiencies based upon the chemical and physical make-up of the contaminant." The current study was intended to assess the varying efficiencies of air-cleaning CSTDS and the appropriateness of 3 out of 9 HD surrogates (tetramethylurea, tetraethylurea, and propylene glycol) suggested by NIOSH for use in testing of air-cleaning CSTDs.

This study was designed to evaluate straightforward the vapor containment efficacy of the air-cleaning technology (air filter test) in 5 commercially available air-cleaning CSTDs during simulated hazardous drug reconstitution using 3 of the 9 NIOSH-proposed surrogates and the Gasmet DX4040 FTIR analyzer which is also utilized by NIOSH for the development of its CSTD performance protocols. The DX4040 analyzer is designed to detect over 300 various gases at low concentrations, including 5 of the 9 NIOSH surrogates.

The analyzer's air sampling funnel was placed externally next to the vent opening of an air-cleaning CSTD vial adapter during the injection of 60ml of diluent (water) into a vial containing 3ml of undiluted surrogate. The analyzer was run on continuous mode to collect the vented air from the CSTDs and any escaped surrogate vapor concentrations were detected, quantified and displayed in real-time.

The surrogate concentration selected for this study was intended to correspond to the real-world condition of a 3-gram dose of ifosfamide free of excipients (eg, 3mL surrogate) and the required injection of 60ml of diluent (water) during the reconstitution process.

In this study, 10 replications of testing for each of the CSTDs was conducted with each surrogate, yielding a total of 150 measurements.

72-hours after testing, a compatibility assessment was performed to exclude CSTD incompatibility with the surrogates. The compatibility study assessed whether the functionality and integrity of the tested CSTDs are affected.

Conclusions:

The tested air-cleaning CSTDs failed to contain vapor, and significant concentrations were released into the environment, which were detected and quantified; Tetramethylurea concentrations were the highest, followed by Tetraethylurea. Propylene Glycol was proven to be an inappropriate and ineffective surrogate since minimal detectable concentrations of Propylene Glycol were released into the environment from CSTDs that utilize carbon filters with additional hydrophobic filters. The study provided evidence and data to confirm that air-cleaning technologies can have varying efficiencies based upon the chemical and physical make-up of the contaminant. The tested surrogates were found compatible under the tested conditions with the tested CSTDs.

4. Introduction

By definition, Closed System Transfer Devices (CSTDs) are devices designed to specifically prevent the escape of hazardous drug or vapor concentrations outside the system to protect healthcare workers from exposure to hazardous drugs (NIOSH 2015). Two CSTD designs are currently used: (1) either a physical barrier in a self-contained closed system that prevents any transfer across the system boundary, the "Barrier CSTD" or (2) an air filtration technology in a vented system that cleans the air that passes between the hazardous drug vial and the environment, the "Air-Cleaning CSTD." The relative success of each CSTD in preventing exposure remains uncertain due to a lack of performance standards and uniform testing procedures that would allow robust comparison of the various devices. In 2012, the US Food and Drug Administration (FDA) began issuing 510(k) clearances under the product code ''ONB'' that was specific to CSTDs. However, companies have no set performance standards to follow to obtain these 510(k) clearances. The selection of a product for use in a particular institution relies primarily on cost and manufacturer claims of protection performance.

In order to address these concerns, NIOSH began the development of a CSTD testing protocol, which is still pending. The first 2015 draft NIOSH protocol was designed to test the CSTDs' effectiveness in containing drug vapor and preventing release into the surrounding environment within a glove chamber during simulation of common compounding and administration tasks performed by healthcare workers (NIOSH 2015). However, the protocol was applicable only to barrier-type CSTDs and employed a 70% isopropyl alcohol (IPA) solution as the surrogate due to its safety, ease of manipulation, and detectability.

Following public and stakeholder comments to this protocol, it was concluded that IPA solvent may not be a suitable surrogate representative of hazardous drugs for testing Air-Cleaning CSTDs because it generates high vapor concentration. The observed vapor breakthrough with Air-Cleaning CSTDs is not representative of the behavior expected with the current population of known hazardous drugs, due to their lower vapor pressures (NIOSH 2016, Gonzalez 2016; Wilkinson 2018, Forshay 2019).

Subsequently, NIOSH proposed an alternative unified draft protocol that is applicable to both barrier type and air-cleaning CSTDs (NIOSH 2016). The modified protocol proposed 9* non-hazardous surrogates that are potentially more representative for hazardous drugs in terms of vapor pressure, water solubility and physicochemical behavior (NIOSH 2016, Wilkinson 2018). These surrogates are: *Dimethyl sulfoxide, Trimethyl phosphate, Tetramethylurea, Triacetin, Propylene glycol, Tetraethylurea, Triethyl phosphate, 2-Phenoxyethanol, Tripropyl phosphate.*

In the 2019 meeting, NIOSH presented its status update on the CSTD Testing Protocols (NIOSH 2019). NIOSH announced that separate protocols are in development, one based on ethanol using the Gasmet DX4040 FTIR analyzer and one protocol based on the 9* surrogates. The protocol for Air-Cleaning CSTDs is based on using one or more of the 9* surrogates and includes a two-stage approach to testing: *"In stage 1 the "air filter test": The CSTD vial adapter of an air-cleaning CSTD was to first be evaluated. In stage 2: testing of all CSTDs."*

The continuously updated NIOSH list of hazardous drugs contains a large variety of molecules and compounds. NIOSH also says that "… air-cleaning technologies can have varying efficiencies based upon the chemical and physical make-up of the contaminant." (NIOSH

2015). The current study was intended to assess the varying efficiencies of air-cleaning CSTDS and the appropriateness of 3 out of 9 HD surrogates (tetramethylurea, tetraethylurea, and propylene glycol) suggested by NIOSH for use in testing of air-cleaning CSTDs, thereby helping to exclude ineffective surrogates from the NIOSH surrogates list. The 3 surrogates were chosen based on preliminary testing to represent various behavior of surrogates.

This study was designed to evaluate the vapor containment efficacy of the air-cleaning technology (air filter test) in 5 commercially available air-cleaning CSTDs, during a simulation of reconstitution of a hazardous drug. The vented air from air-cleaning CSTDs was sampled directly next to the vent opening, using the Gasmet DX4040 FTIR analyzer, and any escaped surrogate vapor was detected and quantified in real-time.

It is also imperative that any selected CSTD be compatible with the surrogates when interacting under the testing conditions. Thus, the included compatibility study assessed the functionality and integrity of the tested CSTDs following storage of 72 hours after the testing. (NIOSH 2019)

Note: *- NIOSH continued with the development and modification of the testing protocols, and another two surrogates were added to the list.

5. Study Methods

5.1. *Background*

Three NIOSH-proposed surrogates were utilized to evaluate the vapor containment efficacy of each air-cleaning CSTD using the Gasmet DX4040 FTIR analyzer that is also used by NIOSH for the development of its CSTD performance protocols (NIOSH 2016, NIOSH 2019).

5.2. *Study Objectives*

The primary objective of this study was to determine the effectiveness of each of the three surrogates with each of the 5 CSTDs and thereby help to exclude ineffective surrogates from the NIOSH surrogates list, as ineffective surrogates may lead to a false sense of security from the use of CSTDs, thereby putting the well-being of healthcare workers at risk.

The secondary objectives of this study were to determine the compatibility of the three surrogates under the testing conditions with materials of the CSTDs for a duration of at least 72 hours.

5.3. *Overview of Study Procedures*

The vapor containment performance of 5 commercially available air-cleaning CSTDs to prevent vapor release during simulated hazardous drug reconstitution was assessed using 3 of the 9 NIOSH-proposed surrogates. The 3 surrogates were chosen based on preliminary testing to represent various behavior of surrogates. The surrogate concentration selected for this study was intended to correspond to the real-world condition of a 3-gram dose of ifosfamide (eg, 3mL surrogate) and the required injection of 60ml of diluent (water) during the reconstitution process (IFEX Package Insert). An air sampling funnel was placed externally and in proximity to the vent opening of an air-cleaning CSTD vial adapter during the reconstitution (injection). The Gasmet DX4040 FTIR analyzer was utilized for sampling and analyzing in real-time the vented air to establish the maximum concentration values (in ppm) observed during each test run (the "air filter test"). Ten replications of testing were conducted for each CSTD with each surrogate.

For testing of each CSTD/surrogate pair, 100mL vials were filled with 3mL of the NIOSH surrogate. CSTD syringe adapters and syringes were prepared and filled with 60mL of Water For Injection (WFI) from bags, in accordance with the individual instructions for use (IFU) of each CSTD manufacturer. The CSTD vial adapter was attached to a vial containing a surrogate, and the CSTD syringe was attached to the vial adapter. The analyzer was run on continuous mode to collect the vented air from the CSTDs in real-time. The results were displayed every second in ppm and indicated whether the air-cleaning system was able to filter out the surrogate gas and vapor component from the vented air following injection of 60mL of water, which allowed for monitoring and collection of data in real-time. The injection was completed within 15 seconds into the vial.

In this study, 10 replications of testing for each of the CSTDs (5) was conducted with each surrogate (3), yielding a total of 150 measurements. The goal of this study was not to provide absolute vapor quantities; rather, the performance metric of interest was the maximum concentration value (in ppm) observed during each test run (NIOSH 2015). As recommended by NIOSH: "Within the environmental sciences, where environmental data are evaluated to estimate true exposures, the rules for handling below LOD data can be complex and labor-intensive. For purposes of the CSTD evaluation protocol, the performance metric of interest is the maximum value observed during the test run."

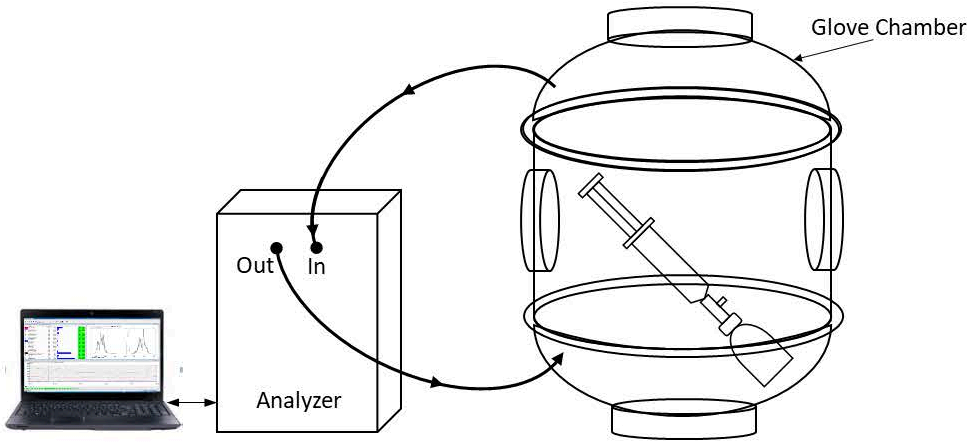

Figure 5.3-1: NIOSH suggested testing configuration with the Gasmet DX4040 Analyzer

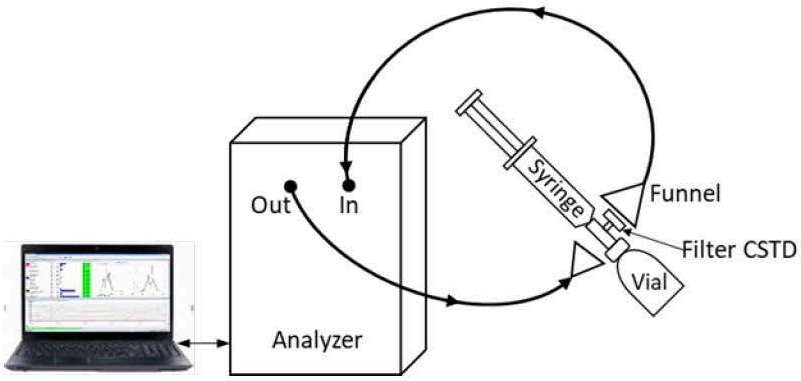

Figure 5.3-2: Actual testing configuration with the Gasmet DX4040 Analyzer

5.3.1. Analyzer

NIOSH suggested use of the Gasmet DX4040 FTIR Analyzer for full testing of barrier-type CSTDs with ethanol (NIOSH 2019). The DX4040 analyzer is universally available and is designed to detect over 300 various gases at low concentrations, including 5 of the 9 NIOSH

surrogates. It is ideal for straightforward testing of the vapor containment efficacy of the air-cleaning feature of vented CSTDs.

The method of testing was based on the NIOSH approach but was simplified. The Gasmet FTIR Analyzer has a flexible air sampling tube with a 60-mm-diameter funnel attached at its end. This funnel allows efficient air sample collection because vented gases from CSTDs tend to spread in all directions.

The analyzer was further attached to its air outlet via another flexible tube with a 50-mm funnel at its end. To create a loop and significantly increase the efficiency of sample collection, the openings of both funnels were brought into proximity to face each other and fixed to a stand. For best results, the CSTD with syringe and vial assembly is 45 degrees inclined with vent/ facing up.

5.3.2. Surrogate Selection and Dosage

This study was based on ifosfamide and similar drugs that require reconstitution. Ifosfamide is a common hazardous antineoplastic drug listed in the NIOSH List of Hazardous Drugs (2020 Hazardous Drug List). Each 3-gram dosage strength vial contains 3 grams of ifosfamide without any excipients. Injection of 60mL of water for injection (WFI) or alternative diluent into the ifosfamide vial was required for reconstitution with a final concentration of 50mg per mL (IFEX Package Insert).

NIOSH selected its surrogates to represent undiluted Active Pharmaceutical Ingredients (NIOSH 2016). thus, the surrogate concentration selected for this study is intended to correspond to a 3-gram dose of ifosfamide (e.g., the 3-gram dose of ifosfamide approximately translated to the equivalent of 3mL surrogate/60mL water). In all terms, the testing represented absolute real usage of drugs and CSTDs.

5.3.3. Compatibility

After injection of 60mL of water and removal of the syringe with vial and syringe from the testing assembly, a 72-hour-long compatibility assessment was performed to exclude CSTD incompatibility with the surrogate. The compatibility study assessed whether the functionality and integrity of the tested CSTDs are affected.

6. Investigational Products

6.1. *CSTD Products*

The 5 CSTD products assessed in this study are listed in Table 6.1-1. All are commercially available and utilize air-cleaning technology.

Table 6.1-1: CSTD Products

Device	Manufacturer	Air-Cleaning Technology
ChemoClave	ICU Medical	Hydrophobic filter

Table 6.1-1: CSTD Products

ChemoLock	ICU Medical	Hydrophobic filter
OnGuard/Tevadaptor	B. Braun/Simplivia	Hydrophobic + carbon filters
Chemfort	Simplivia	Hydrophobic + carbon filters
Texium/SmartSite	BD (CareFusion)	Hydrophobic filter
BD Plastipak 60 ml syringes	BD	Luer Lock tip

6.2. *Surrogates*

3 NIOSH-suggested surrogates were used.

Table 6.2-1: Surrogates for Hazardous Drugs

Surrogate	**Abbreviation**	**Supplier**	**Purity** ≥	**Dosage**	**Identification**
Tetramethylurea	TMU	SIGMA - ALDRICH	99%	3ml	CAS: 632-22-4
Tetraethylurea	TEU	CHEM-IMPEX INC	99.7%	3ml	CAS: 1187-03-7
Propylene glycol	PG	SIGMA - ALDRICH	99.5%	3ml	CAS: 57-55-6
Sterile water for injection USP	WFI	BBraun		60ml	Bag

7. Testing Methods

7.1. *Testing Conditions*

1. Room temperature 72°F-77°F (22°C-25°C).
2. Testing environment (room) free of items that may contain the surrogates, such as markers, disinfection gels, makeup, hand creams and more.
3. Means for air refreshment (i.e., window).
4. All materials and equipment must have been at room temperature before testing.
5. Normal clean environment free of dust and air disturbances.

7.2. *Study Preparation: Filling Vials*

1. The pipettor was set to 3mL and 3mL of the surrogate was transferred into an empty 100mL glass vial (Duran-Wheathon-Kimble, 100ml serum bottle, glass clear, type-1). Transfer was directly from the original surrogate container (if practical) or the surrogate was poured first into a glass flask, then transferred from the flask.

2. Drips on the vial exterior of the vial neck and spills were to be avoided, and the use of absorbent tissues as the working surface was required. Although the pipettor should have ensured clean transfers without drips, the sealed vial was carefully washed in water if in doubt.

3. The rubber stopper and the 20mm aluminum cap were placed (Duran-Wheathon-Kimble, 20mm stopper, st plug, ultra pure, and 20mm aluminum seal, Flip-Cap, unlined) and the vial was sealed using a crimper device.

   Throughout the study, the surrogate was prevented from coming in contact with the rubber stopper. Vials were stored in upward manner.

4. The vial was labeled to identify the surrogate.

5. The filling process was repeated with the same surrogate for all vials required for the study.

6. The pipette was discarded, a new pipette was installed on the pipettor for each surrogate and the filling process was repeated for each of the remaining surrogates.

7.3. *Study Preparation: Filling Syringes*

1. The CSTD syringe connectors were attached and CSTD bag adaptors were connected to the WFI bags. The syringes were filled with 60mL of water in accordance with the manufacturer's instructions for use; any air bubbles were removed.

2. The filling process was repeated with all syringes and CSTDs required for the study.

7.4. *Analyzer Setup*

1. The analyzer was installed along with the tubing, laptop, and cables.

2. The laptop was turned on and the Calcmet Pro software was opened with the licensing key plugged in.

3. Tubing was connected to the analyzer's IN port and the analyzer was set to Cable Mode.

4. The analyzer was warmed up for at least 45 minutes.

5. Zero/background calibration was performed at the beginning of each testing day using nitrogen gas 99.999% purity (nitrogen gas tank with regulator) in accordance with the analyzer manufacturer's instructions.

6. The analysis time in the Calcmet Pro software was set to "Continuous 1 second measuring time (pump enabled)". It should be noted, that for measurement of constant vapor concentration (which doesn't change rapidly), the longer measuring time cycles, such as 60 or 20 seconds are more adequate; however, for short concentration changes that occur during the 15 seconds of water injection, the 1 second cycle setup provides higher resolution and better captures the peak concentration value.

7. The testing stand was set up with its clamps and funnels.

8. The tubing with funnels was connected to the analyzer with the sampling tube to the IN port and the return/exhaust tube to the OUT port.

7.5. *Testing Procedures*

All materials and equipment were to be at room temperature before testing.

1. To coat the inner glass walls of the vial with the surrogate (simulation of real-world drug powder coating the inner walls of the vial), the technician was instructed to:

    a. Lay and roll the vial slowly on the table surface to coat the side walls.
    b. To coat the vial neck, lift the vial and begin to invert the vial while rolling while keeping a safe distance between the rubber stopper and the surrogate.

2. The Flip-Cap was removed from the vial, and the CSTD vial adapter was attached to the vial in accordance with the manufacturer's instructions for use (IFU).

3. For CSTDs with a hidden vent opening (i.e., OnGuard/Tevadaptor and Chemfort), the side on which the vent is installed was to be identified and visibly mark that side externally using a pencil.

4. The syringe (filled with 60mL of water) was connected with its CSTD connector to the surrogate vial CSTD adapter.

5. The CSTD with syringe and vial assembly was fixed and clamped at a 45-degree angle in the testing stand, ensuring that the vent opening was facing up (using the marking for OnGuard/Tevadaptor and Chemfort CSTDs).

6. The upper glass funnel was brought to the closest position for covering the vent opening area of the CSTD vial adapter.

7. The lower glass funnel (Buchner type) was brought to the closest position in front of the upper funnel (the CSTD is placed between the funnels).

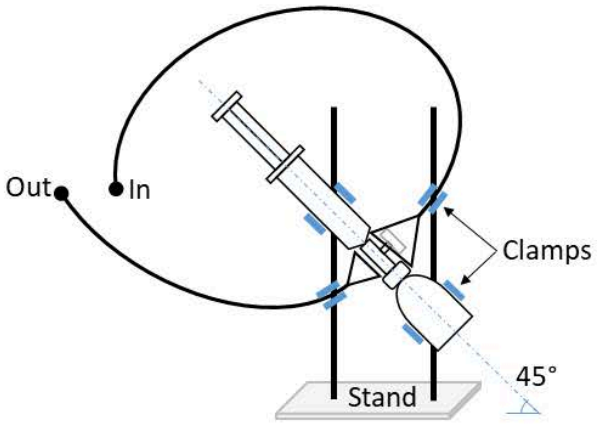

Figure 7.5-1: Fixed and clamped at a 45-degree angle in the testing stand.

8. To prepare for injection and measuring, the plunger and syringe were held with both hands in a way that was convenient for injection.

9. The analysis on the laptop was monitored; the background surrogate vapor concentration was displayed in ppm every second (typically zero or close to zero).

10. Before the start of each test run, the background (BG) concentrations were observed for at least 5 seconds and the maximal concentration value was recorded on the data collection form.

    Later, for data analysis, this maximal BG concentration was subtracted from the maximal concentration data point collected during the test run to create the BG-adjusted test data. If BG was zero, there was no need for BG adjustment.

11. The testing began with water being injected into the vial. The plunger was pushed at a steady pace, and the injection finished within 15 seconds (after a few standarization repetitions, injection time can easily be kept within a tolerance of 2 seconds).

12. After a short delay of analysis, the monitored concentration values increased if the surrogate released vapor. After waiting for the highest value, it was recorded on the data collection form. After the highest value is reached, values begin to decrease. If no vapor was detected, values would remain at BG levels or zero.

13. Additionally, the ambient temperature and the analyzer's cell temperature were recorded on the data collection form.

The Calcmet Pro software automatically saves all data and spectra in the background. These data could be used for deeper analysis of the results and for troubleshooting.

14. The lower funnel was moved away to allow for the system to be clean (purged) with fresh air and the monitored concentration values decreased until they reached BG levels or zero.

15. The syringe and vial were unclamped from the stand, and the vial was kept upright.

16. The syringe with its CSTD connector was disconnected from the vial CSTD adapter.

17. Both the syringe and the vial with their respective CSTD were stored for 72 hours to perform compatibility assessment following the storage period (see **Section 9**, Compatibility Assessment, for details).

18. After the analyzer reading dropped to BG levels or zero the next test was started.

19. The testing procedure was repeated a total of 10 times with the same CSTD type and the same surrogate (10 x 1 = 10 replicates), with each of the 5 CSTD types using the same surrogate (10 x 5 = 50 replicates), and with each of the 3 surrogates (50 x 3 = 150 replicates), for a total of 150 replicates tested for the study.

8. Study Controls

8.1.1. Negative Control Procedure

A negative control procedure was automatically conducted with every tested 150 replicates. The Calcmet software displays simultaneously all 3 surrogate concentrations continuously on the monitor; whenever one surrogate is tested and detected during injection, the other surrogates showed no change in their concentration values, which means the surrogate identification by the analyzer is correct and that the other two surrogate values are not affected and confirming the negative control.

8.1.2. Positive Control Procedure

The positive control test was performed by bypassing the CSTD vent filter.

1. A representative CSTD with a disk-shaped filter and a hole in the middle was chosen (ChemoClave). To bypass the filter, a G19 needle was used to puncture the filter through the vent hole. The needle was entered approx. ¼″ into the device.

2. The regular test procedure was performed with each of the surrogates, the results of the unfiltered stream of vapor were recorded.

9. Compatibility Assessment

After injection of 60mL of water and removal of the CSTD with syringe and vial from the testing assembly, a 72-hour-long compatibility assessment was performed to exclude CSTD incompatibility with the surrogate under the testing conditions.

1. The tested syringe (with its CSTD connector attached) was disconnected from the vial CSTD adapter, and both (syringe and vial with their respective CSTDs attached) were stored for at least 72 hours at room temperature. Vials always remained in an upright position, and no surrogate contact with the vial's rubber stopper or vial adapter was allowed.

2. After at least 72 hours:

    a. The syringe was connected to the vial and the plunger pulled back to draw 60mL of air (vial upright).
    b. The plunger was pushed entirely in at a normal injection pace (vial upright).
    c. The syringe was disconnected from the vial.
    d. During the above steps (a, b, and c), the mechanical integrity of the devices was monitored for leaks, and blockage of filters, as a blocked vent filter may stop the plunger from moving.
    e. Each set of CSTD with syringe and vial was inspected visually for damage to the CSTD.
    f. The filter was visually inspected for damage.
        i. Disk filters are visible through their transparent covers.
        ii. To inspect the OnGuard/Tevadaptor and Chemfort filters, the vial adapter cover that is held by a simple snap connection was removed with an adequate tool. The carbon filter that is loosely seated was removed and the hydrophobic and carbon filters were inspected for damage.

3. Assessments were recorded on the data collection forms.

10. Data Collection and Analysis

For vapor containment efficacy, the performance metric of interest was the maximum value observed during each test run (NIOSH 2015).

Maximal background (BG) concentration data was observed and recorded for at least 5 seconds before the start of each test data collection. As part of the data analysis, the maximal observed BG concentration was subtracted from the maximal concentration value observed during the test run to create BG adjusted test data. The final test result was equal to the BG adjusted maximal concentration (NIOSH 2015).

11. Results

11.1. *Study Date*

Study procedures were conducted on Dec 3, 2020 and Dec 4, 2020.

Compatibility assessment procedures were conducted on Dec 7, 2020

11.2. *Temperature and Humidity*

Ambient room temperatures were within the pre-specified range for all tests and replications (22-25°C). The analyzer cell temperature was recorded as 29-31°C for all tests.

Humidity was recorded as 10%.

11.3. *Analyzer calibration*

Zero/background calibration data on Dec 3, 2020 was recorded as 93.04% and on Dec 4, 2020 as 92.86%. Spectra within normal parameters and both the hardware status and calibration statuses were displayed as OK.

11.4. *Results*

Positive Controls: The maximum BG-adjusted values obtained for the unfiltered stream of vapor were 23.84 ppm for TMU, 3.71 ppm for TEU, and 5.93 ppm for PG.

Background adjusted values for each test repetition with each CSTD and surrogate combination are presented in **Table 11.4-1**.

Table 11.4-1: Background Adjusted Vapor Concentrations

	Surrogate Concentration (ppm)		
CSTD	**TMU**	**TEU**	**PG**
OnGuard/Tevadaptor			
1	0.81	0.15	0.17
2	0.59	0.32	0.18
3	1.53	0.08	0.10
4	3.87	0.23	0.08
5	1.45	0.20	0.08
6	3.17	0.42	0.36
7	6.02	0.57	0.22
8	0.63	0.33	0.12
9	1.67	0.08	0.13
10	1.57	0.11	0.10
Chemfort			
1	1.16	0.49	0.14
2	1.45	0.59	0.12
3	0.21	0.75	0.14
4	1.43	0.55	0.14
5	0.85	0.48	0.10
6	1.40	0.74	0.08
7	0.82	0.65	0.18
8	2.84	0.69	0.09
9	0.33	0.36	0.05
10	0.84	0.39	0.08
Chemoclave			
1	35.84	5.18	5.50
2	37.52	3.54	5.28
3	34.93	4.59	5.14
4	34.61	4.47	5.45
5	28.39	4.99	6.27
6	34.79	6.24	6.33
7	30.20	4.92	5.81
8	33.43	3.76	6.83
9	35.91	4.71	6.31
10	31.48	3.13	5.97

Table 11.4-1: Background Adjusted Vapor Concentrations

	Surrogate Concentration (ppm)		
CSTD	**TMU**	**TEU**	**PG**
Chemolock			
1	26.53	3.73	4.83
2	24.13	3.47	4.70
3	24.67	3.10	5.60
4	25.85	3.77	5.46
5	24.02	3.13	5.14
6	25.99	3.27	5.72
7	28.21	3.25	7.00
8	29.97	3.92	5.47
9	25.80	3.08	6/05
10	27.93	3.34	6.00
Smartsite			
1	10.67	4.63	3.19
2	18.55	3.82	2.66
3	7.62	4.95	2.49
4	14.53	4.18	3.04
5	9.55	4.68	1.41
6	17.34	3.24	1.44
7	9.59	3.12	1.61
8	14.87	4.50	1.91
9	19.11	2.85	1.75
10	16.90	3.87	1.44

The maximum concentration value (in ppm) observed during each test run for each device/surrogate combination is shaded gray.
Note: Chemoclave, Chemolock, and SmartSite/Texium were tested on day 1; Onguard and Chemofort were tested on day 2.
Abbreviations: PG=propylene glycol; ppm=parts per million; TEU=tetraethyurea; TMU=tetramethyurea.

11.5. *Compatibility Testing Results*

Following at least 72 hours of storage at room after the testing procedures all CSTDs were inspected.

1. All CSTDs were found to be fully functional.

2. All CSTDs fully maintained their mechanical integrity.
3. All CSTDs and their filters successfully passed visual inspections; however, ChemoLock and ChemoClave CSTDs underwent in addition a filter leak testing after suspicious visible deformations were detected on and around their filters. Following an investigation, it was determined that the same deformations exist as well on new unused products from various manufacturing lots. To exclude the possibility of filter leaks, the spikes of original ChemoLock and ChemoClave vial adapters that were tested in this study, were attached to 3.5' long infusion sets and the drip chambers were filled with approx. 6ml of blue colored water and were left hanging for at least 4 hours. The blue water filled the whole space on the inner side of each filter, thereby applying breakthrough pressure on the filter. Result: none of the tested ChemoLock and ChemoClave adapters leaked.

11.6. *Results Analysis*

11.7. *Study Endpoint Analyses*

Table 11.4-1: Max., Mean, Range and Standard Deviation of Vapor Detected for each CSTD/Surrogate Combination

CSTD	Value (ppm)	Surrogate		
		TMU	TEU	PG
OnGuard/Tevadaptor	Maximum	6.02	0.57	0.36
	Mean	2.13	0.25	0.15
	Range	(0.59-6.02)	(0.08-0.57)	(0.08-0.36)
	Standard Deviation	1.64	0.15	0.08
Chemfort	Maximum	2.84	0.75	0.18
	Mean	1.13	0.57	0.11
	Range	(0.21-2.84)	(0.36-0.75)	(0.05-0.18)
	Standard Deviation	0.70	0.13	0.04
Chemoclave	Maximum	37.52	6.24	6.83
	Mean	33.71	4.55	5.89
	Range	(28.39-37.52)	(3.13-6.24)	(5.14-6.83)
	Standard Deviation	2.70	0.85	0.52
Chemolock	Maximum	29.97	3.77	7.00
	Mean	26.31	3.41	5.60
	Range	(24.02-29.97)	(3.08-3.77)	(4.70-7.00)

Table 11.4-1: Max., Mean, Range and Standard Deviation of Vapor Detected for each CSTD/Surrogate Combination

	Standard Deviation	1.81	0.29	1,52
SmartSite/Texium	Maximum	19.11	4.95	3.19
	Mean	13.87	3.98	2.09
	Range	(7.62-19.11)	(2.85-4.95)	(1.41-3.19)
	Standard Deviation	3.98	0.69	0.65

Maximum is the highest value out of 10 repetitions; Mean value of 10 repetitions for each CSTD/surrogate; range is the high to low values of 10 repetitions; Standard deviation of 10 repetitions for each CSTD/surrogate.
Abbreviations: PG= propylene glycol; ppm=parts per million; TEU=tetraethyurea; TMU=tetramethyurea

12. Conclusions

1. All tested air-cleaning CSTDs failed to contain vapor, and significant concentrations were released to the environment, detected and quantified.
2. Escaped Tetramethylurea concentrations were the highest, followed by Tetraethylurea.
3. Significant concentrations of Propylene Glycol were released to the environment from air-cleaning CSTDs that utilize hydrophobic filters only.
4. Propylene Glycol was proven to be an inappropriate and ineffective surrogate since insignificant or hardly detectable concentrations of Propylene Glycol were released to the environment from air-cleaning CSTDs that utilize carbon filters in addition to hydrophobic filters. Propylene Glycol should be excluded from the NIOSH surrogates list, as ineffective surrogates may lead to a false sense of security from the use of CSTDs, thereby putting the well-being of healthcare workers at risk.
5. The current study provided evidence and data to confirm that "… air-cleaning technologies can have varying efficiencies based upon the chemical and physical make-up of the contaminant." (NIOSH 2015)
6. The current study provided scientific evidence and data to prevent further misrepresentations.
7. All 3 surrogates were found compatible under the tested conditions with the tested CSTDs.

13. Bibliography/Publications

13.1. *References*

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14. Abbreviated Terms

API	active pharmaceutical ingredient
BG	background concentration
CSTD	closed system transfer device
FDA	Food and Drug Administration
HD	hazardous drug
IFU	instructions for use
LOD	limit of detection
NIOSH	National Institute for Occupational Safety and Health
PG	propylene glycol
TEU	tetraethylurea
TMU	tetramethylurea
WFI	water for injection

15. Signature Page

15.1. *Signature of the Investigator*

Study Title:
Vapor containment Efficacy of Air-Cleaning CSTDs with 3 NIOSH Surrogates

Sponsor:
Equashield

I have reviewed this report and confirm that to the best of my knowledge, it accurately describes the conduct and results of the study.

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