

A Performance Test Protocol for Closed System Transfer Devices Used During Pharmacy Compounding and Administration of Hazardous Drugs

DRAFT

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NOTE: Certain sections were left blank intentionally. Once NIOSH completes the protocol testing and finalizes the draft protocol, these sections will be completed.

Authorship

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Introduction

This protocol originates from a collaborative effort between healthcare industry representatives and NIOSH researchers to develop a performance test protocol for closed system transfer devices (CSTDs) [NIOSH 2004]. A CSTD, also known as a closed system drug-transfer device, is used to facilitate the transfer of drug from one reservoir to another, and may be used throughout the drug-handling chain from pharmaceutical compounding to patient dose administration. CSTDs limit the potential for aerosolizing drug contamination and can reduce worker exposure to sharps, thus reducing the likelihood of occupational exposure to hazardous drugs [NIOSH 2004]. By definition, the CSTD mechanically prohibits the transfer of environmental contaminants into the system and the escape of hazardous drug or vapor concentrations outside the system [NIOSH 2004]. CSTD manufacturers utilize one of two approaches to achieve the “...prohibits the transfer...” requirements in this definition: (1) those that use a physical barrier to prevent all mass from crossing the system boundary or (2) those that use air-cleaning or filtration technologies to specifically prohibit environmental contaminants and hazardous drug concentrations from crossing the system.

In 2004, NIOSH released the *NIOSH Alert: Preventing Occupational Exposures to Antineoplastic and Other Hazardous Drugs in Health Care Settings* [NIOSH 2004]. In this Alert, NIOSH identifies CSTDs as supplemental controls that should only be used in combination with primary engineering controls (biological safety cabinets and containment isolators) to further protect against worker exposures to hazardous drugs. At the time of the release of the NIOSH Alert, limited models of CSTDs were available in the market. More recently, the number of marketed CSTD models has increased. Interest in development of a CSTD performance test protocol originated from within the healthcare industry itself,

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with requests for an independently-developed containment test protocol. The intended purpose of this protocol is not to demonstrate that CSTDs are effective in reducing hazardous drug surface contamination, which has already been documented [Vyas 2013]. The protocol's intent is to challenge a CSTD's ability to function as a closed system that restricts drug mass (vapor or liquid) from crossing the system boundary and escaping into the surrounding environment. While CSTD performance standards exist in regards to sterile practice for patient protection, no CSTD performance standards currently apply to drug containment [Douglass et al. 2012]. In the absence of such worker protection standards, the consumers (e.g., healthcare facilities and pharmacies) have no worker-protection performance basis upon which to make their selection of a CSTD, and they may be inclined to select a product based solely upon acquisition costs and uncertain claims of protective performance. Upon publication of this performance protocol, manufacturers of the CSTDs and their consumers will be able to use and refer to this protocol, enabling consumers to conduct meaningful comparisons between products and subsequently choose products based upon their demonstrated ability to perform as closed systems.

The CSTD test protocol is located in Appendix A—Laboratory Performance Test Protocol for CSTDs. The current draft protocol represents the third major iteration of the test protocol. Initially, NIOSH researchers presented their draft test protocol for performance and concept testing to the CSTD focus group, a subgroup of the NIOSH Hazardous Drug Working Group. Pharmacist partners within the focus group identified specific compounding and drug-administering tasks to incorporate into the protocol to ensure that the evaluated tasks represented real world healthcare industry scenarios. The NIOSH researchers and pharmacist partners conducted preliminary test runs using a NIOSH-designed environmental test chamber and data collection protocol. While results of the preliminary test runs

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verified the protocol's concept, additional modifications to the environmental test chamber and performance test protocol were necessary. Subsequently, NIOSH engineers met again with the CSTD focus group to evaluate CSTD vapor containment using an updated performance test protocol and a new environmental test chamber design. Testing of the established protocol used registered pharmacists familiar with CSTDs who performed each of the protocol-prescribed compounding/administration tasks while using multiple manufacturers and types of CSTDs. On September 8, 2015, NIOSH published the draft protocol titled, "A Vapor Containment Performance Protocol for Closed System Transfer Devices Used During Pharmacy Compounding and Administration of Hazardous Drugs," in the Federal Register [NIOSH 2015] for public comment. The September 2015 draft protocol was only applicable to the barrier-type CSTDs. After significant public comment, NIOSH decided to pursue development of an additional test protocol to address air-cleaning type CSTDs [NIOSH 2016]. As the supporting research for the air-cleaning protocol progressed, NIOSH decided to combine the two protocols into one protocol and develop a single test protocol applicable to both barrier and air-cleaning types of CSTDs.

Surrogate Selection

The use of challenge agents as hazardous contaminant substitutes is a valuable practice used to evaluate the performance of engineering control and work practice interventions designed to mitigate occupational exposures [Mead et al. 1999; Nygren et al. 2002; Steil 2011]. The challenge agent selection is based upon a variety of factors, including how the challenge agent interacts with the intervention and whether the challenge agent can be easily and accurately detected when used to evaluate the intervention's ability to control the contaminant. For example, sulfur hexafluoride (SF₆), an inorganic tracer gas, is commonly used to test engineering controls designed to control gases, vapors,

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and very small aerosols that are influenced by prevailing wind currents [NIOSH 1997]. Lactose powder may be used as a challenge agent for controls and equipment intended to handle active pharmaceutical ingredients [Steil 2011]. Fluorescent compounds that are only visible under ultraviolet light, are commonly used to evaluate the effectiveness of engineering control and work practice interventions intended to prevent contact contamination [Jorgenson et al. 2008; Massoomi 2009; Lamerie et al. 2011; Power 2013].

[Note to public: This paragraph will be updated to specifically address the selected drug surrogate(s) once the research and selection process described in this paragraph is completed] In NIOSH's 2015 draft protocol for testing the effectiveness of barrier-type CSTDs, 70% isopropanol (IPA) was chosen as a surrogate compound. However, for CSTDs that utilize organic vapor air filtration, the selected form of IPA is not a suitable surrogate. IPA's high volatility would likely result in vapor breakthrough that is not representative of the behavior expected with the current population of known hazardous drugs, due to their much lower vapor pressures. Therefore, the protocol was modified to use one or more surrogates whose vapor pressures are more representative of currently known hazardous drugs. The surrogate selection strategy involves selection of the drug from the *NIOSH List of Antineoplastics and Other Hazardous Drugs in Healthcare Settings* with the highest known vapor pressure as a worst-case scenario and to use that vapor pressure in the selection of potential surrogates [NIOSH 2014]. The drug with the highest vapor pressure on the NIOSH 2014 Hazardous Drug list (excluding acidic and basic drugs that are used in the form of less-volatile salts) was determined to be thiotepa, with a vapor pressure of 8.00×10^{-3} millimeters of mercury (mm Hg) at 25°C. To build in a safety factor, surrogates are being considered with vapor pressures in the range starting with that of

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thiotepa and going up to approximately 100 times that, or approximately 1.00×10^{-2} mm Hg to 1.00 mm Hg. Other factors guiding initial selection of candidate surrogates include water solubility of at least 0.10%, the surrogate being preferably liquid at room temperature to facilitate evaporation after a leak, and low toxicity. Compounds with structural similarity to hazardous drugs are considered preferable but not critical, as the hazardous drugs are very diverse in chemical structure. Nine surrogate compounds are under current consideration (see Table I). As in the 2015 draft protocol that used IPA as a surrogate, detection of a liquid leak will depend upon evaporation of the surrogate compound. However, direct-reading instrument detection of the leaked surrogate will not be possible for any of the current list of surrogate candidates and escaped airborne surrogate compound will be detected by passing the surrounding air through a thermal desorption tube for subsequent analysis.

Using more than one surrogate compound in a test mix may provide additional information about the leak. In a liquid leak, assuming complete evaporation after leaking, all surrogates will be collected from the air in the same proportion that they existed while in the aqueous test solution. In contrast, in a vapor leak, the relative proportion of the compounds will depend on their relative partitioning from the water into the headspace. So, if complete evaporation of the escaped surrogate can be achieved, the relative proportions of the surrogates in the analyzed sample might then be used to determine if the observed leak was liquid, vapor, or a combination. While this partitioning of the escaped surrogate according to leak type is not a prerequisite for the protocol, if it can be achieved without compromising protocol accuracy or usability, it will be incorporated as an additional informational benefit.

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Table I. Nine Surrogate Compounds under Consideration for Protocol¹

Compound	CAS ² Number	Melting Point (°C)	Boiling Point (°C)	Vapor Pressure (mm Hg)	Water Solubility (mg/L)	Kow ³ , log P	Henry's Constant (atm m ³ /mole) ⁴ 25°C
Dimethyl sulfoxide	67-68-5	19	189	0.61	1.00x10 ⁶	-1.35	1.51x10 ⁻⁹
Trimethyl phosphate	512-56-1	-46	197	0.85	5.00x10 ⁵	-0.65	7.20x10 ⁻⁹
Tetramethylurea	632-22-4	-1.2	176.5	1.16	1.00x10 ⁶	0.19	8.48x10 ⁻⁹
Triacetin	102-76-1	-78	259	0.002	5.80x10 ⁴	0.25	1.23x10 ⁻⁸
Propylene glycol	57-55-6	-60	187.6	0.129	1.00x10 ⁶	-0.92	1.28x10 ⁻⁸
Tetraethylurea	1187-03-7		209	0.208	4.00x10 ⁴	1.76	2.80x10 ⁻⁸
Triethyl phosphate	78-40-0	-56.4	215.5	0.393	5.00x10 ⁵	0.8	3.60x10 ⁻⁸
2-Phenoxyethanol	122-99-6	-2	247	0.007	6.70x10 ⁵	1.16	4.72x10 ⁻⁸
Tripropyl phosphate	513-08-6		252	0.004	6450	1.87	6.80x10 ⁻⁷

¹ Estimated values used where experimental data was unavailable

² Chemical Abstracts Service Registry Number

³ Concentration in octanol phase / Concentration in aqueous phase

⁴ Atmospheres-meter per mole

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Selection of Measurement Methodology

The 2015 draft protocol for testing the effectiveness of barrier-type CSTDs used a direct-reading instrument (i.e., for the NIOSH test a Miran SapphIRe XL Infrared Analyzer model 205B-XL [Thermo Electron Corporation, Franklin, MA] was used) for detection of any leaked 70% IPA drug surrogate. A direct-reading instrument worked well because of the high volatility of IPA and the high concentration of IPA in the test solution. Surrogates of lower volatility used in lower concentrations in the aqueous test solution cannot be adequately monitored in real-time without a much more sensitive detection method. However, collection of a sample over time would enable sufficient surrogate to be collected for measurement of low concentrations. For the new protocol, the airborne surrogate compound is collected by passing the surrounding air through a thermal desorption tube for subsequent analysis. The tube is a single bed of Tenax TA sorbent. The thermal desorption tubes are stainless steel, 0.64-centimeter (cm) (0.25 inch [in.]) diameter, 10.2-cm (4.00 in.) length. The entire sampling apparatus (i.e., tube and pump) would reside within the same or similar environmental test chamber used in the original protocol and discussed later in this section. The tubes will be analyzed by TD-gas chromatography-mass spectrometry (GC-MS). The TD-GC-MS is a very sensitive and selective technique, allowing for definitive identification of very low levels of surrogate compound in the sample. Limits of detection (LOD) will vary from compound to compound, but very low concentrations can be detected because the entire sample collected over a period of time is used in the analysis. The instrumentation used in the development of this procedure is an automatic thermal desorption system with an internal focusing trap packed with adsorbent, intended for C2-C30 range molecules. The thermal desorption unit is interfaced directly to a mass selective detector which operates under electron impact (EI) conditions.

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Background

Healthcare settings use CSTDs to transfer liquid drugs throughout their handling sequence from their primary packaging to dose preparation and even patient administration. NIOSH recommends using CSTDs when transferring hazardous drugs from primary packaging such as vials to dosing equipment such as infusion bags, bottles, or pumps [NIOSH 2004]. CSTDs can protect the compounder during the preparation of the hazardous drug as well as the attending healthcare worker(s) during later administration of the hazardous drug to the patient [ISOPP 2007; Lamerie et al. 2011]. Although, CSTDs may reduce worker exposure to hazardous drugs, they may not entirely eliminate exposure [Sessink and Bos 1999; Nygren et al. 2002; NIOSH 2004; Harrison et al. 2006; Nyman et al. 2007; Yoshida et al. 2009; Sessink et al. 2010; Vyas 2013]. It is also important that any selected CSTD be compatible with the drugs and diluents to which it will come into contact. The use of CSTDs may not be advised if the hazardous drugs are mixed with solvents, such as N,N-dimethylacetamide, that are incompatible with the plastic parts of CSTDs [ICU Medical 2015; ISMP 2015]. Such solvents might dissolve the plastic components within the CSTD and allow the hazardous drug to escape or introduce contaminants into the drug that jeopardize the health of the patient. NIOSH identifies CSTDs as supplemental controls and advises that they are not a substitute for ventilated engineering controls such as biological safety cabinets and containment isolators. During hazardous drug compounding, CSTDs should only be used within ventilated engineering controls [NIOSH 2004; USP 2008]. Appropriate work practices and personal protective equipment should also be used when handling or operating CSTDs [USP 2008].

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Each CSTD system traditionally consists of a syringe adapter (a.k.a. CSTD syringe connector) plus three component adapters: vial adapter, IV port adapter or Y-site adapter, and a bag adapter or infusion adapter. Each of these adapters mates with the syringe adapter. The syringe adapter attaches to the syringe in a manner that eliminates the presence of an exposed needle and thus prevents needle-stick injuries. When used with a mating component adapter, the syringe-component adapter connection allows for a contained (no drug escape or environmental contaminant ingress) transfer of drug between the syringe and the attached component (vial, IV bag, or IV-set). The vial adapter attaches to the vial and prevents leaks due to vacuum and overpressure when diluent or air is injected or withdrawn [Connor et al. 2002; Wick et al. 2003]. For the air cleaning or filtration CSTD, the vial adapter contains a hydrophobic 0.2-micron (μm) filter [Massoomi 2015]. Some air cleaning vial adapters use a double-filter technology with a combination of the 0.2 μm filter and an active carbon filter [Nygren et. al 2008]. The IV port adapter provides a contained connection between the IV administration set and the syringe adapter and is used to transfer drug from the syringe into an IV administration set that is connected to the patient [Wick et al. 2003]. The bag adapter attaches to the IV bag and provides a contained transfer route for the drug into the IV bag [Wick et al. 2003].

CSTD Performance Test Development

The development of the CSTD performance protocol required identification of a functional test environment, challenge agents for manipulation by the CSTD, a detection method for measuring leaked challenge agents, and a list of prescribed tasks. NIOSH researchers developed a strategy to quantitatively evaluate CSTD performance within a custom-built environmental test chamber.

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The test protocol evaluates the CSTD systems during compounding and administration processes, including the connections and disconnections of the CSTD parts during the two tasks:

- Task 1 (compounding)—the pharmacist prepares one 500 mL 0.9% sodium chloride IV bag with 90 mL of the surrogate mixture (Figure 2), using two 45 mL transfers from two 60 mL syringes and two vials (Figure 3). The CSTD components evaluated under this task included one bag adapter, two vial adapters, and two syringe adapters.
- Task 2 (compounding/administration)—the pharmacist prepares a 45 mL dose of the surrogate mixture in each of two 60 mL syringes for the IV push and injected each prepared syringe into the Y-site of the IV tubing (Figures 3, 4a, and 4b). The CSTD components evaluated under this task included two vial adapters, two syringe adapters, one bag adapter, and one IV port adapter.

Environmental Test Chamber

[NOTE: The Environmental Test Chamber section will be finalized when NIOSH completes its testing of the updated protocol with each CSTD.]

The environmental chamber selected for the CSTD vapor containment performance protocol is a customized Secador® Techni-dome® 360 Large Vacuum Desiccator (Bel-Art Products, Pequannock, NJ) (Figure 5). The Secador® Techni-dome® is a sphere of 52.1 cm inner diameter (20.5 in.) that separates at its horizontal equator into equal lower and upper halves. The NIOSH researchers customized the sphere with a 30.0 cm (12.0 in.) extension ring, fitted with 20.0 cm (8.00 in.) glove ports and installed between the lower and upper sphere halves (Custom Part #800260055, Bel-Art Products, Pequannock, NJ). The addition of the extension ring converts the round Techni-dome® sphere into a cylinder with hemispherical ends. This modified enclosure has sufficient interior volume to allow for full pharmacy

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manipulations. Two simultaneously collected thermal desorption tube sampling trains (each sampling train includes a pump, sample hose, desorption tube) are strategically positioned inside the test chamber to collect drug surrogate escaped from the CSTD. The sampling tubes are positioned so as not to interfere with the compounding tasks while sampling from opposite sides inside the test chamber. The sampling pumps will each be calibrated to provide a sample flow rate of XX liters per minute with the sampling train attached.

The environmental test chamber construction and assembly instructions are described in detail in Appendix B—Materials and Assembly of Environmental Test Chamber.

NIOSH Application of the Performance Protocol

Data Analysis

[NOTE: The Data Analysis section will be finalized when NIOSH completes its testing of the updated protocol with each CSTD.]

NIOSH testing of the CSTD performance protocol incorporates an evaluation of each CSTD condition (total number of conditions includes a representative sample from each CSTD under consideration plus one negative control condition without a CSTD) against both Task 1 and Task 2. Each CSTD:Task pairing undergoes four repetitions. A single test run consists of concentration data collection for a single CSTD:Task repetition. Thus, for each CSTD:Task pairing, there will be four test runs representing four repetitions of data.

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Data Interpretation and Discussion

[NOTE: The Data Interpretation and Discussion section will be completed when NIOSH completes its drug surrogate selection and testing of the protocol with each known and available CSTD.]

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Table II. Means and Summary Statistics of the Values for Each CSTD:Task Pairing

Analysis Variable						
Task	CSTD Device	Number of Observations	Mean of Observations (ppm)	Lower 95% Confidence Limit (ppm)	Upper 95% Confidence Limit (ppm)	Standard Deviation (ppm)
1						
2						

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Application of the Performance Protocol

Interested parties may adopt the NIOSH Performance Protocol for CSTDs as described in this document for multiple purposes, including prototype evaluation by manufacturers, comparative product evaluation by potential consumers, training, or even adoption by jurisdictions for use as a performance certification protocol. Depending upon the intended purpose, the declaration of a performance threshold may not be beneficial. Where a performance threshold is desired, it is important that the threshold actually be a value that is measurable by the analytical methodology in use. Values below the method's LOD will not meet this requirement. A calculated LOQ, as used during the NIOSH CSTD testing, may be selected as the performance threshold. Alternatively, some other criterion such as the analytical method's LOD may also be selected. If the protocol is adopted as a performance certification protocol, NIOSH recommends that an independent laboratory perform the certification testing and generate a performance report that certifies the CSTD's performance.

Summary

Healthcare industry representatives and NIOSH researchers collaborated to develop the CSTD performance protocol. Subsequent revisions of the protocol have occurred through the public review process and with the valuable input of industry stakeholders. The purpose of the protocol is to test a CSTD's capability to perform as a closed system transfer device as defined in the NIOSH Alert, *Preventing Occupational Exposure to Antineoplastic and Other Hazardous Drugs in Health Care Settings*. The protocol applies to CSTDs that utilize either barrier or air cleaning technologies. Registered pharmacists, familiar with the use of CSTDs, facilitated in the development and testing of the protocol's prescribed compounding and administration tasks using commercially available CSTDs.

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They also performed the assigned tasks using a negative control condition without a CSTD. Prescribed tasks were performed in an environmental test chamber custom-designed for its compatibility with the protocol. **[NOTE: Analytical details to be added here upon surrogate selection, analytical method refinement, and CSTD testing.]** While an analytical response of zero might represent a 100% containment CSTD, this measurement is not analytically feasible as it is lower than the analytical method's LOD for the surrogates. Thus, if a performance threshold is desired, some alternative value (other than zero) must be chosen. The protocol has multiple applications and can be used by manufacturers to evaluate prototype CSTDs, by consumers to compare CSTD products, or by jurisdictions wishing to adopt the protocol for a performance certification protocol. If a performance pass/fail threshold is desired, users of the protocol may choose to adopt a common analytical practice in occupational safety and health ($3.33 \times$ analytical method LOD) to determine a calculated LOQ value as the pass/fail performance threshold [Burkart 1986; NIOSH 1995].

The application of this CSTD performance protocol can be useful to evaluate the efficacy of CSTDs without creating potential exposures to hazardous drugs. The protocol can be used to provide baseline comparisons between different makes and models of CSTDs and to evaluate CSTD performance for the majority of hazardous drugs for which an analytical method does not yet exist. However, it is important to note that the numerical results could vary from actual results obtained while manipulating materials with different physical properties, and they do not guarantee any resulting exposures with actual hazardous drug compounds will be safe or in compliance with any known occupational exposure limits.

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Figures

[NOTE: Photos will be added/updated when NIOSH completes its testing of the updated protocol with each CSTD.]

Figure 1. GC-MS (Photo Credit: NIOSH)



Figure 2. Photograph showing the injection of one of two 45 mL doses of hazardous drug surrogate into a 500 mL 0.9% sodium chloride IV bag (no CSTD shown). (Photo Credit: NIOSH)

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Figure 3. Photograph showing the transfer of 45 mL of hazardous drug surrogate from a septum-capped vial into one of two 60 mL syringes (no CSTD shown). (Photo Credit: NIOSH)

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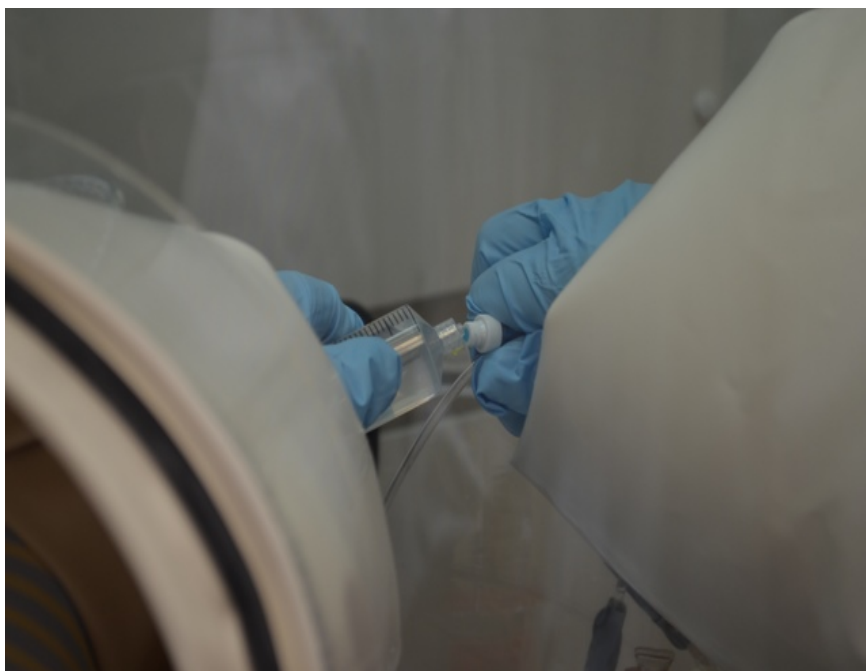


Figure 4a. Photograph showing one of two 60 mL syringes connecting to the Y-site on an IV administration set (no CSTD shown). (Photo Credit: NIOSH)

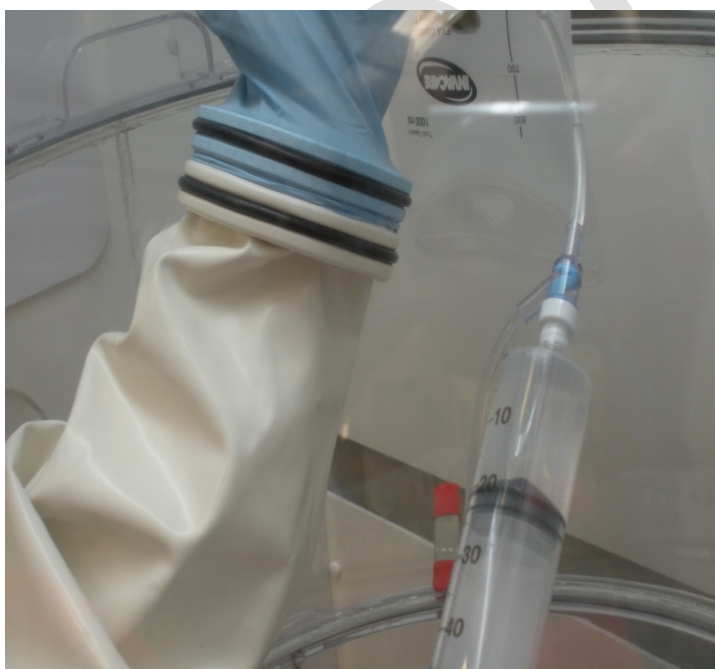


Figure 4b. Photograph showing one of two 60 mL syringes pushing the hazardous drug surrogate into the Y-site on an IV administration set (no CSTD shown). (Photo Credit: NIOSH)

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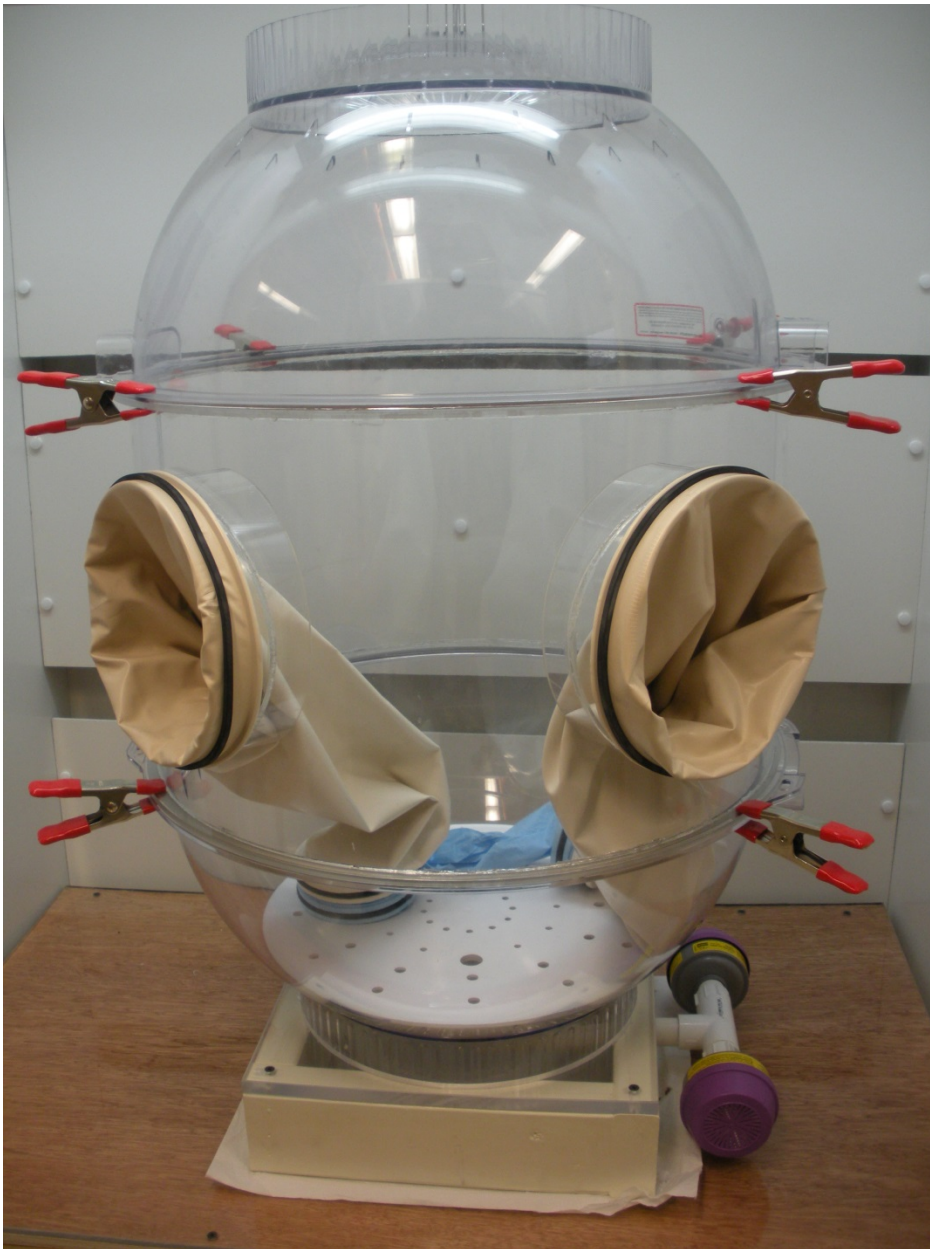


Figure 5. Secador® Techni-dome® 360 Vacuum Desiccator with 30-cm (12-in) extension ring outfitted with glove ports. Note the spring-loaded hand clamps used to keep the environmental test chamber tightly sealed. (Photo Credit: NIOSH)

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Appendix A—Laboratory Performance Test Protocol for Closed System Transfer

Devices (CSTDs)

[NOTE: Appendix A will be finalized when NIOSH completes its testing of the updated protocol with each CSTD.]

Purpose

To quantitatively evaluate the combined liquid, aerosol, and vapor containment performance of commercially-available closed system transfer devices (CSTDs) within a controlled test environment.

Scope of Use

This test protocol provides a methodology for evaluating challenge agent containment performance of CSTDs under the identified compounding and administration tasks. The protocol evaluates the CSTDs using prescribed pharmacy and administration manipulations performed with a known surrogate mixture inside a custom environmental test chamber. **[NOTE: The chosen surrogates may adversely affect the operation of the CSTD parts being tested. Before beginning the protocol tests, verify that there is no adverse effect of the surrogates on the operation of the device.]** If desired, additional compounding and administration procedures may be used to examine various CSTD components within the framework of this test protocol. An analytical method incorporating gas chromatography-mass spectrometry (GC-MS) analysis of air samples is required to evaluate the performance of the CSTDs by measuring the concentrations of hazardous drug surrogate that escape the CSTD into the environmental test chamber. Duplicate sampling trains, incorporating thermal desorption sampling tubes connected to air sampling pumps are placed within the environmental test chamber for collection of the air samples.

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Results of the test protocol may be used to compare containment performance across multiple CSTD models or against a selected maximum leak performance threshold for CSTDs. Based on testing performed within NIOSH laboratories, a maximum leak performance threshold of **[NOTE: performance threshold value will be added after the NIOSH test]** ppm of surrogate vapor was determined to be a feasible performance value when measured in accordance with the procedures spelled out within this protocol. Jurisdictions adopting this protocol may choose a different threshold value to fit their purposes, however it should be above the analytical method's limit of detection (LOD) in order to provide meaningful evaluation of the data. It is important to note that escaped drug surrogate concentration measurements above the method's LOD are representative of liquid, aerosol, and vapor that escaped CSTD containment when handled in accordance with this protocol. Any escaped drug surrogate concentration measurements observed during use of this protocol are useful as a comparative index for CSTD containment performance and have not been correlated with specific exposure reductions expected to occur during actual pharmacy compounding or drug administration manipulations.

Compounding and Administration Materials

Table AI is a list of the supplies needed for the compounding and administration task procedure in this protocol. Table AI only lists the supplies for one complete test run, which includes Task 1 and Task 2. The supplies for each task can be placed into plastic trays (Figure A1). New gloves should be used for each task and repetition. Conduct the test procedures within the NIOSH-designed custom environmental test chamber (see Appendix B for detailed description). If desired, clean the inside of the environmental test chamber with an alcohol-free cleaner prior to test initiation.

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Vial Preparation

Label the four 100 mL Wheaton glass vials one through four. Transfer 50 mL of the surrogate mixture into each of the glass vials using a 60 mL syringe, pipettor, or graduated cylinder. Prepare the vials within an externally exhausted laboratory hood. Place one septum cap on each vial (with the 10 mm center hole face down), place the aluminum crimp seal over the septum cap, and seal each vial using the 20 mm crimping tool.

Test Procedures

Before the start of each task, position two thermal desorption tube sampling trains into opposite sides of the environmental test chamber with the tubes capped and the pumps in the “OFF” condition. Upon loading and sealing of the environmental test chamber prior to a specific task, an air purge will be required to flush the environmental test chamber of unwanted background contaminant concentrations. To conduct the air purge, open the inlet-air valve and activate the high volume sampling pump attached to the top outlet of the chamber and flowing at a minimum of YY liter per minute (lpm) **[NOTE: a minimum flowrate will be added after the NIOSH test]**. Allow the high-volume pump to operate for XX minutes to flush the test chamber’s interior volume with filtered air **[NOTE: the number of minutes will be added after the NIOSH test]**. After XX minutes, simultaneously stop the high volume pump, close the inlet-air valve and proceed towards the conduct of the prescribed task as described below **[NOTE: the number of minutes will be added after the NIOSH test]**. A complete CSTD test evaluation includes four repetitions of paired sequential tasks, identified as Task 1 and Task 2. Within each paired task repetition, conduct Task 1 procedures first, followed by Task 2. **NOTE: It is**

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important to follow CSTD manufacturer's Instruction for Use (IFU) when performing each task (e.g., "draw air into the syringe"). Not following the IFU could give false performance results.

Task 1: Prepare 500 mL 0.9% sodium chloride IV bag with 90 mL of surrogate mixture in the vials using 45 mL transfers

Summary Description of Task 1: To simulate reconstitution, withdraw 45 mL of surrogate mixture from Vial 1 and inject into Vial 2 (for a total volume of 95 mL in Vial 2). Swirl the surrogate mixture in Vial 2 to simulate reconstitution. Withdraw 90 mL of surrogate mixture from Vial 2 in 45 mL increments using the two 60 mL syringes with syringe adapters (or connectors). Inject both the syringes into the 500 mL 0.9% sodium chloride IV bag through the bag adapter. Label the bag and place in a Ziploc bag.

Task 1 Procedures: Assemble the following supplies, and place into small supply trays for each test run:

- 2 × septum-capped vial containing 50 mL of surrogate mixture , labeled 1 and 2
- 2 × 60 mL syringes, labeled 1 and 2
- 1 × 500 mL 0.9% sodium chloride IV bag
- 2 × CSTD vial adapters
- 2 × CSTD syringe adapters
- 1 × CSTD bag adapter

1. Place the trays with the task supplies and two thermal desorption tube sampling trains into the environmental test chamber, close chamber, and position spring-loaded hand clamps onto environmental test chamber to create a tight chamber seal.

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2. Conduct an air-purge of the environmental test chamber as described above.
3. Uncap each desorption tube, activate each sampling pump and note the sample start time.
4. Attach one vial adapter to each of the two vials of the surrogate mixture.
5. Attach one IV bag adapter to the administration port of one 500 mL 0.9% sodium chloride IV bag.
6. Draw 45 mL of air into the 60 mL Syringe 1 (if required by manufacturer's instructions for use).
7. Attach one syringe adapter to 60 mL Syringe 1.
8. Mate the 60 mL Syringe 1 to surrogate mixture Vial 1 using the CSTD connectors.
9. Inject air into Vial 1; withdraw 45 mL of surrogate mixture from Vial 1 and disconnect the syringe adapter from the vial adapter. **BE SURE not to disconnect the syringe from the CSTD syringe adapter!**
10. Set Vial 1 aside; it now contains 5 mL of surrogate mixture.
11. Mate Syringe 1 containing 45 mL of surrogate mixture to Vial 2 using the CSTD connectors.
12. Inject 45 mL of surrogate mixture into Vial 2. Invert the vial and withdraw 45 mL of air from Vial 2 into the Syringe 1 (Syringe 1 now has 45 mL of air in it and there should be 95 mL of surrogate mixture in Vial 2). Leave Syringe 1 connected.
13. Disconnect Syringe 1 from Vial 2.
14. Swirl Vial 2.
15. Reconnect Syringe 1 to Vial 2 and inject the 45 mL of air into Vial 2 and withdraw 45 mL of surrogate mixture; disconnect Syringe 1 with the CSTD attached.
16. Mate the syringe adapter to the IV bag adapter drug injection port; inject the 45 mL of surrogate mixture.

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17. Disconnect at the syringe adapter from the IV bag adapter drug injection port and set the syringe aside. Syringe 1 will now contain no air and no liquid, and it is closed.
18. Select 60 mL Syringe 2, draw 45 mL of air into syringe (if required by manufacturer's instructions for use), and attach the second syringe adapter.
19. Mate Syringe 2 with Vial 2 using the CSTD connectors.
20. Inject air into Vial 2 and withdraw 45 mL of surrogate mixture using Syringe 2.
21. Disconnect syringe adapter from the vial adapter.
22. Mate Syringe 2 with the 500 mL 0.9% sodium chloride IV bag using the CSTD connectors; inject the 45 mL of surrogate mixture. IV bag now contains 90 mL of surrogate mixture and a CSTD adapter (with overfill ~640 mL).
23. Remove Syringe 2 by disconnecting between the adapters (i.e., Syringe 2 and bag adapters).

Task 1 is now complete. Deactivate the two sampling pumps, cap the desorption tubes and note the stop time. Open the environmental test chamber and remove all supplies and trays.

Task 2: Prepare 45 mL surrogate mixture in 60 mL syringes for IV push and Y-site administration

Summary Description of Task 2: Task 2 has two parts, simulating drug reconstitution followed by an IV push of the reconstituted drug. To simulate drug reconstitution, withdraw 45 mL of surrogate mixture from Vial 3 and inject into Vial 4 (95 mL total volume in Vial 4). Swirl the surrogate mixture in Vial 3 to simulate reconstitution then withdraw 90 mL of surrogate mixture from Vial 4 in 45 mL increments

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using two 60 mL syringes with CSTD adapters. For simulating the IV push, inject each syringe dose into the Y-site of the IV tubing.

Task 2 Procedures: Prepare IV setup prior to administering the IV dose to save space inside the environmental test chamber. Close the roller clamp on the IV tubing. Fold the end of the IV tubing and then attach one spring-loaded hand clamp to the end of the IV tubing (shown in Figure A2) to prevent surrogate mixture leakage.

Assemble the following supplies and place into small supply trays for each test run:

- 2 × 50 mL vials of surrogate mixture, labeled 3 and 4
- 2 × 60 mL syringes, labeled 3 and 4
- 2 × CSTD vial adapters
- 2 × CSTD syringe adapters
- 1 × CSTD IV push adapter
- 1 × CSTD bag adapter
- 1 × 500 mL 0.9% sodium chloride IV bag. **Use a new bag; DO NOT use the same bag from**

Task 1.

- IV administration tubing with at least one needleless Y-site
- IV tubing clamp

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1. Place the trays with the task supplies and two thermal desorption tube sampling trains into the environmental test chamber, close chamber, and position spring-loaded hand clamps onto environmental test chamber to create a tight chamber seal.
2. Conduct an air-purge of the environmental test chamber as described above.
3. Uncap each desorption tube, activate each sampling pump and note the sample start time.
4. Attach one vial adapter to each of the two vials of the surrogate mixture.
5. Attach one CSTD IV bag adapter to one 500 mL 0.9% sodium chloride IV bag.
6. Draw 45 mL of air into 60 mL Syringe 3 (if required by manufacturer's instructions for use).
7. Attach one syringe adapter to the 60 mL Syringe 3.
8. Mate the 60 mL Syringe 3 to Vial 3 using the CSTD connectors.
9. Inject air into Vial 3; withdraw 45 mL of surrogate mixture from Vial 3 and disconnect the syringe adapter from the vial adapter. **BE SURE not to disconnect the syringe from the CSTD syringe adapter!**
10. Set Vial 3 aside—it now contains 5 mL of surrogate mixture.
11. Mate Syringe 3 with 45 mL of surrogate mixture to Vial 4 using the CSTD connectors.
12. Inject 45 mL of surrogate mixture into Vial 4. Invert the vial and withdraw 45 mL of air from Vial 4 into Syringe 3 (Syringe 3 now has 45 mL of air in it and there should be 95 mL of surrogate mixture in Vial 4). Leave syringe connected.
13. Disconnect Syringe 3 from Vial 4.
14. Swirl Vial 4.

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15. Reconnect Syringe 3 to Vial 4 and inject the 45 mL of air into Vial 4 and withdraw 45 mL of surrogate mixture; disconnect Syringe 3 with the CSTD attached. This syringe now contains 45 mL of surrogate mixture to administer later into the IV administration set.
16. Draw 45 mL of air into 60 mL Syringe 4 (if required by manufacturer's instructions for use) and attach the syringe adapter.
17. Mate Syringe 4 with Vial 4 using the CSTD connectors.
18. Inject air into Vial 4 and withdraw 45 mL of surrogate mixture using Syringe 4.
19. Disconnect syringe adapter from the vial adapter. Syringe 4 now contains 45 mL of surrogate mixture to administer later into the IV administration set.
20. Check that the roller clamps on IV administration tubing are closed, including the ones to the Y-site and below (the spring clamp should already be attached to the end of the IV tubing—see Task 2 Procedures).
21. Take the cover off the spike of the IV administration tubing and open the infusion port on the bag adapter of the 500 mL 0.9% sodium chloride IV bag.
22. Insert the IV administration tubing spike into the port of the bag adapter affixed to the 500 mL 0.9% sodium chloride IV bag.
23. Gently squeeze the 500 mL 0.9% sodium chloride IV bag to verify there is flow into the drip chamber.
24. Attach the IV push adapter into the Y-Site. Attach Syringe 3 dose (45 mL of surrogate mixture in 60 mL syringe) with syringe adapter already connected (from step 14) to the push adapter.

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25. Open all IV administration tubing roller clamps below the Y-site, and push the first “syringe dose” from Syringe 3 through the IV push adapter and tubing into the 500 mL 0.9% sodium chloride IV bag until Syringe 3 is empty.
26. Remove Syringe 3 by disconnecting between the adapters (i.e., Syringe 3 and IV push adapters).
27. Select Syringe 4 for the second “syringe dose” (45 mL of surrogate mixture in 60 mL syringe) with syringe adapter already connected (from step 18) and attach it to the push adapter.
28. Push the second “syringe dose” from Syringe 4 through the IV push adapter and tubing into the 500 mL 0.9% sodium chloride IV bag until the syringe is empty.
29. Remove Syringe 4 by disconnecting between the adapters (i.e., Syringe 4 and IV push adapters).
30. Close all IV administration tubing roller clamps.

Task 2 is now complete. Deactivate the two sampling pumps, cap the desorption tubes and note the stop time. Open the environmental test chamber and remove all supplies and trays.

Data Analysis

[NOTE: The Data Analysis section will be finalized when NIOSH completes its testing of the updated protocol with each CSTD.]

Table AI. Supplies for Compounding and Administration Procedures for One Complete Test of Task 1 and Task 2

Supply	Quantity
CSTD vial adapter	4
CSTD syringe adapter	4
CSTD IV bag adapter	2
CSTD IV port adapter	1
Spring-loaded hand clamp	1
500 mL 0.9% sodium chloride (NaCl) IV bags	2
IV needleless administration set, split septum injection site, 211 cm (83.0 in)	1
Surrogate mixture	200 mL
100 mL Wheaton clear glass vials, 20 mm neck	4
Septum caps, PTFE/rubber [butyl (Pharma-Fix)], diam. × thickness 20.0 mm × 0.135 in	4
20 mm Aluminum crimp seal	4
60 mL luer lock syringe	4
20 mm crimping tool	1
Ziploc bags (3.79 L or 1.00 gallon)	
Plastic trays 23.0 cm × 15.0 cm × 5.00 cm (9.00 in × 6.00 in × 2.00 in) or similar	4
Labels	
Pen	1

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Figure A1. Supplies for compounding Task 1 loaded into plastic trays (no CSTD shown). (Photo Credit: NIOSH)

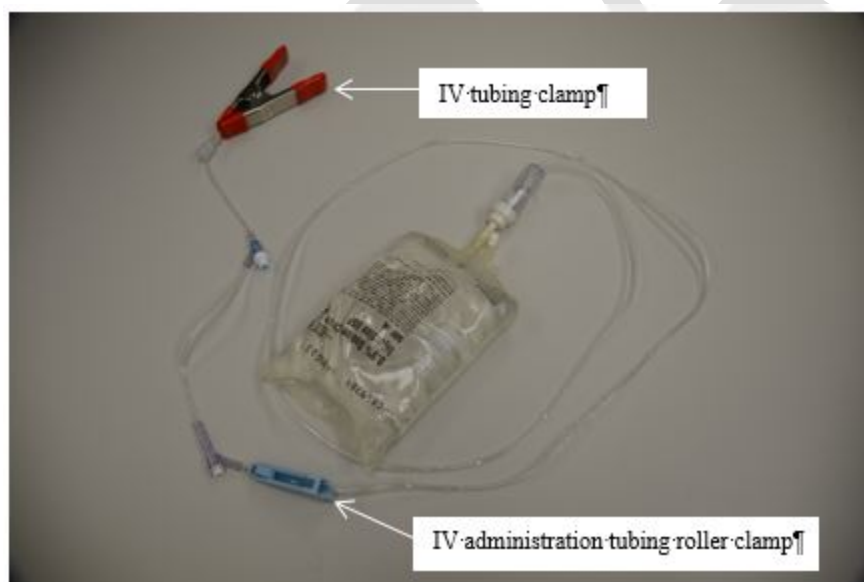


Figure A2. Photograph showing IV administration tubing connected to a 500 mL 0.9% sodium chloride IV bag (no CSTD shown). A spring-loaded hand clamp functions as an IV tubing clamp to prevent the surrogate mixture leakage. (Photo Credit: NIOSH)

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Appendix B—Materials and Assembly of Environmental Test Chamber

[NOTE: Appendix B will be finalized when NIOSH completes its testing of the updated protocol with each CSTD.]

The following modifications apply to a Secador® Techni-dome® 360 vacuum desiccator (or the Environmental Test Chamber) to result in the NIOSH-developed environmental test chamber for the performance protocol. Table BI is a materials list of parts required to make the necessary modifications. Figures B1 and B2 are exploded diagrams of the base and chamber components of the environmental test chamber. For final assembly, use PVC cement to secure all PVC slip-fit connections. The environmental test chamber is modified and assembled in the following order:

1. Drill 2.50 cm (1.00 in.) hole in the center of one of the four 30.0 cm (12.0 in.) wood pieces (Part Number 1 in Table BI) as shown in Figure B1. Use wood screws or nails (Part 25) plus wood glue (Part 26) to assemble all four wood pieces into a square base measuring 34.0 cm x 34.0 cm x 3.90 cm (13.5 in. x 13.5 in. x 3.50 in.).
2. Drill four 0.16 cm (1/16 in.) holes through Part Number 2 and into wood base. Countersink holes in Part Number 2 using a 0.64 cm (1/4 in.) countersink. Using four #8 x 2.54 cm (1.00 in.) drywall screws (Part Number 3), attach Part Number 2 to the wood base. [Figure B1]
3. Drill holes centered into the top and bottom portions of environmental test chamber (Part Numbers 4 and 5, respectively) for airflow. For the top hole, use a 1.11 cm (7/16 in.) drill bit. Tap threads into this hole using a ¼ in.-18 NPT tap. For the bottom, the hole should be 2.50 cm (1.00 in.). **[NOTE: It is very important that you drill slowly using slight pressure** so as not to crack the environmental test chamber. A drill bit designed for acrylic materials may be preferred to reduce the risk of chipping. A backer board is highly advised to reduce chipping potential

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when the bit exits the chamber's polycarbonate material. If a crack does occur, it may be sealed using a polycarbonate-compatible caulk.]

4. Wrap the threads of the threaded male tube adapter (Part Number 6) with PTFE Thread Seal Tape and carefully screw the adaptor into the top of the environmental test chamber using the 1.11 cm (7/16 in.) tapped hole. [Figure B2]
5. Insert 5.00 cm (2.00 in.) long PVC pipe (Part Number 7) into one end of the PVC elbow (Part Number 8). Slide an O-ring (Part Number 9) around the opposite end of the pipe.
6. Place the pipe from Step 5 through the outside opening of the bottom of the environmental test chamber (Part Number 5). Note that the O-ring should rest on the outside of the surface of the chamber.
7. Slide the second O-ring (Part Number 9) around the exposed PVC pipe (Part Number 7) inside the bottom of the test chamber (Part Number 5). Then fasten the PVC adapter (Part Number 10) to the pipe after checking orientation of elbow with respect to the chamber and base. Note that one O-ring is compressed against the interior surface of the chamber, while the other O-ring is compressed against the exterior surface.
8. Connect the 19.0 cm (7.50 in.) long PVC pipe (Part Number 11) to the PVC elbow (Part Number 8). Then lower the completed lower dome assembly (Part Numbers 5, 7-11) into the wooden base (Part Numbers 1-3). Ensure the 19.0 cm (7.50 in.) PVC pipe (Part Number 11) exits the 2.50 cm (1.00 in.) hole in the base.
9. Connect two 5.00 cm (2.00 in.) long PVC pipes (Part Number 7) to opposite ends of the PVC T-connector (Part Number 12). Join the pipes (Part Number 7) to the threaded male adapters (Part Number 13).

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10. Wrap the threads of the threaded male pipe adapters (Part Number 13) with PTFE Thread Seal Tape.
11. Attach filter cartridges (Part Number 14) to threaded male pipe adapters (Part Number 13) to complete T-assembly.
12. Attach gloves (Part Number 15) to sleeves (Part Number 16) using glove cuff (Part Number 17) and transition O-rings (Part Number 18). Attach sleeves to ports in environmental test chamber's extension piece (Part Number 19) using the larger outer retention bands (Part Number 20) to seal them against the outside of the ports. [Steps 11-16, See Figure B2]
13. Remove the clear gasket supplied with the Secador[®] Techni-dome[®] 360 vacuum desiccator sphere (Part Numbers 4 and 5). Apply foam tape seals (Part Number 21) to the flat mating circumference of both top and bottom portions of the environmental test chamber. Make sure the foam tape sits in the groove of environmental test chamber's top and bottom mating surfaces and is secured all the way around the circumference of the seal. Verify there is no gap where the tape ends meet.
14. Place the non-woven filter material (Part Number 22) in the bottom piece of the environmental test chamber (Part Number 5).
15. Place the 38.0 cm (15.0 in.) perforated shelf (Part Number 23) on top of the non-woven filter material.
16. Place the environmental test chamber pieces in the following order: bottom (Part Number 5), extension piece (Part Number 19), and top (Part Number 4) on base. Line up handles of the upper and lower portions ensuring the seal is seated all the way around the lip of the environmental test chamber.

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17. Seal environmental test chamber by placing spring-loaded hand clamps (Part Number 24) on the environmental test chamber extension's lips.

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Table BI. Materials for Environmental Test Chamber

Part Number	Material	Details	Quantity
1	30.0 cm (12.0 in.) wood board	5.00 cm × 10.0 cm (2.00 in. x 4.00 in.)	4
2	Plexiglas square (NOTE: Wood square of same dimensions is also acceptable.)	0.64 cm (0.25 in.) thick, 34.0 cm × 34.0 cm (13.5 in. × 13.5 in.) square, 31.0 cm (12.0 in.) circle cut in center	1
3	Screws	#8 x 2.54 cm (1.00 in.) coarse-thread drywall screws	4
4, 5	Secador® Techni-dome® 360 Vacuum Desiccator	Scienceware, Part F42029-0000 (top and bottom, respectively)	1
6	Male tube adapter	1.30 cm (½ in.) tube OD x 0.64 cm (¼ in.) MNPT, Swagelok, Part SS-8-TA-1-4	1
7	1.90 cm (¾ in.) PVC pipe	5.00 cm (2.00 in.) length	3
8	1.90 cm (¾ in.) PVC 90° elbow	Female slip fit-female slip fit	1
9	O-ring	AS568A-214 size 2.54 cm ID, 3.18 cm OD (1.00 in. ID, 1 ¼ in. OD)	2
10	1.90 cm (¾ in.) PVC adapter	Female slip fit-female slip fit	1
11	1.90 cm (¾ in.) PVC pipe	19.0 cm (7.50 in.) length	1
12	1.90 cm (¾ in.) PVC T-connector	All female slip fit	1
13	1.90 cm (¾ in.) PVC adapter	Female slip fit-male pipe thread	2
14	Organic vapor with particulate prefilter respirator cartridges	Chemical filter for organic vapors with P100 particulate pre-filter, North Safety Products Part No. 7583P100	2
15	Glove	Disposable exam gloves	2
16	Glove sleeve	0.61 m (2.00 ft) long, fits onto 20.0 cm (8.00 in.) diameter glove ports built into environmental test chamber middle section	2
17	Glove cuff	Must be compatible with glove sleeve and accepts O-rings	2
18	Transition O-ring	Used to secure glove cuff to both glove sleeve and gloves	4
19	30.0 cm (12.0 in.) extension piece	Custom made to fit between top/bottom halves of Secador® Techni-dome® 360 Vacuum Desiccator and equipped with 20 cm (8 in.) diameter glove ports. Bel-Art Products, Part# 800260055	1
20	Glove sleeve outer retention band	Square Buna-N O-Ring, AS568A Dash Number 435, 14.5 cm ID, 15.9 OD, and 0.69 cm width (5 ¾ in. ID, 6 ¼ in. OD, and ¼ in. width) Fits 20.0 cm (8.00 in.) opening around glove sleeve	2
21	Foam tape seal	High density foam tape, 0.64 cm (¼ in.) thick, 1.30 cm (½ in.) wide, 171 cm (67.5 in.) long	
22	Nonwoven filter media, polyester fibers bonded	PVC, Fiberbond Corporation, Part 115093, cut into a 38.0 cm (15.0 in.) diameter circle.	1
23	Shelf	Perforated, molded polypropylene shelf, 38.0 cm (15.0 in.) diameter (included with the 360 Vacuum Desiccator)	1
24	Spring-loaded hand clamps		8
25	Wood screws or nails	Used to assemble wood base	4
26	Wood glue		

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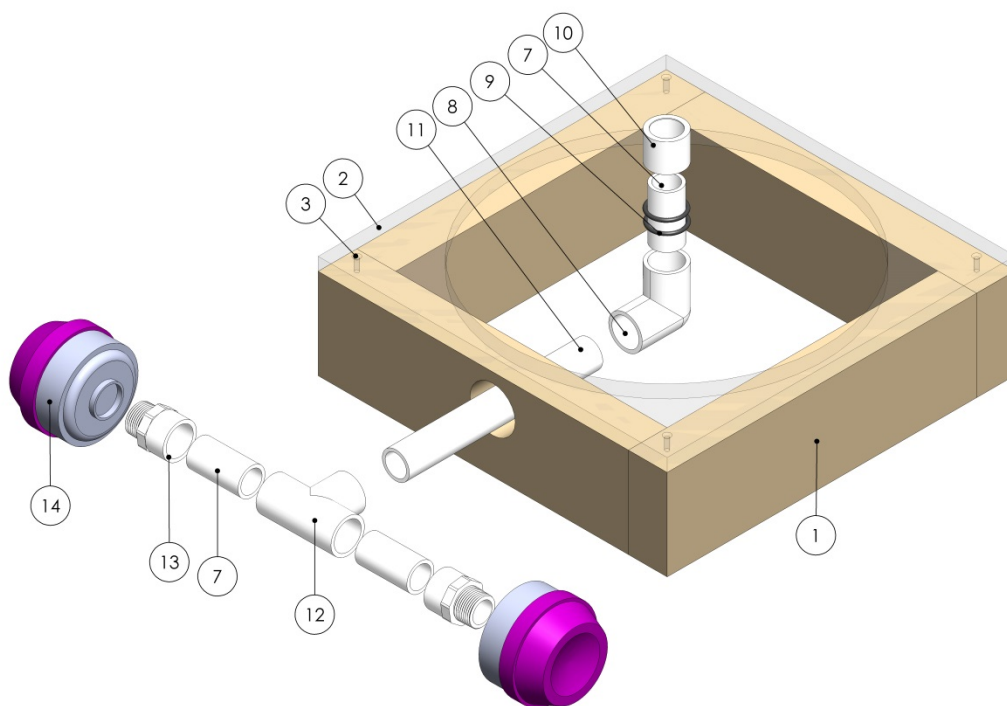


Figure B1. Environmental test chamber parts and assembly—base unit. (Graphic Credit: NIOSH)

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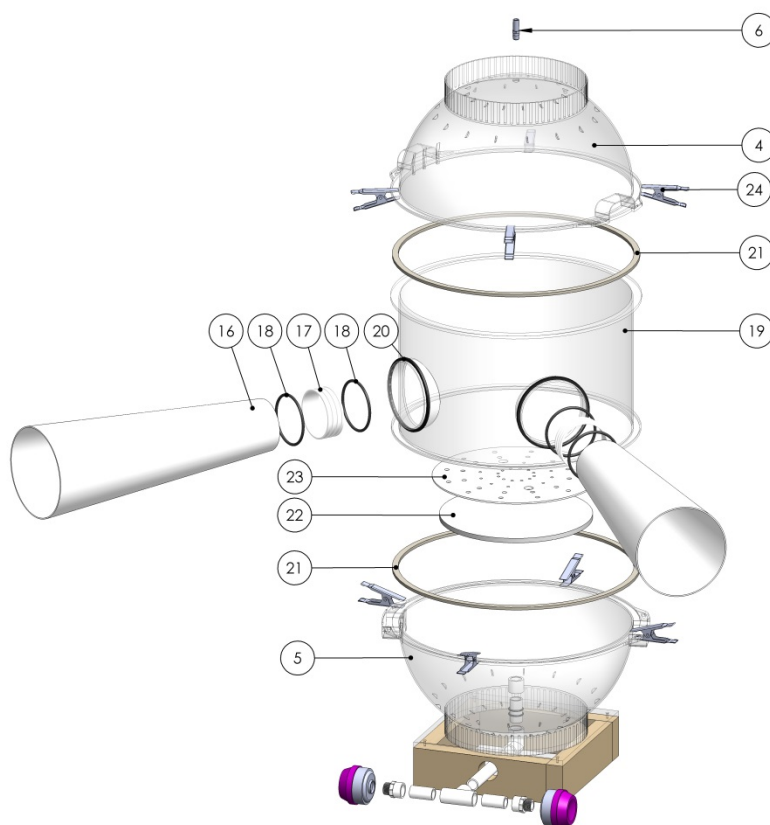


Figure B2. Environmental test chamber parts and assembly (gloves not pictured). (Graphic Credit: NIOSH)

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