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Prevention of Hazardous Drug Vapor Release by the Chemfort™ Vial Adaptor

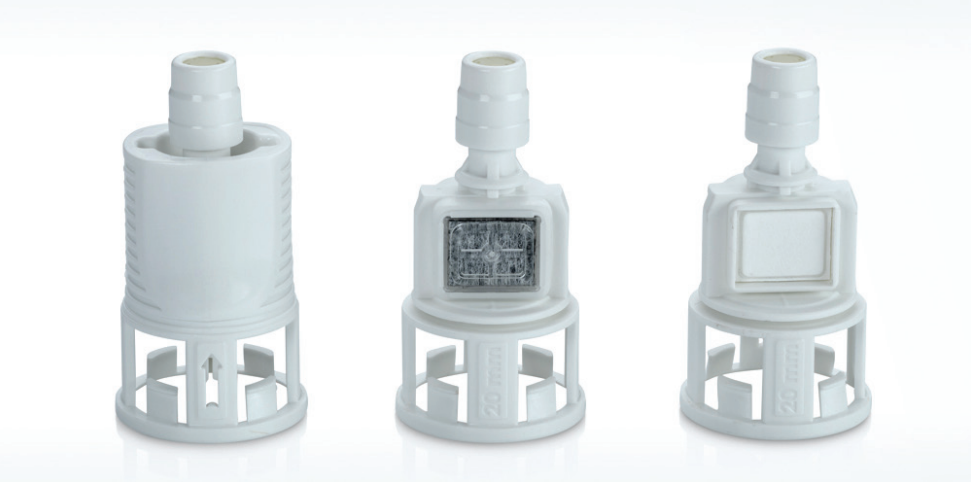


Figure 1. Chemfort™ Vial Adaptor | TOXI-GUARD®'s Charcoal drug adsorbing matrix | TOXI-GUARD®'s 0.2 hydrophobic and oleophobic membrane

TOXI-GUARD®

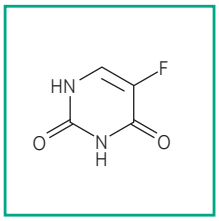
Summary

Chemfort™ is a Closed System Drug Transfer Device (CSTD) designed to prevent the escape of hazardous drug vapors into the environment during drug reconstitution and administration. Drug containment in the Chemfort™ Vial Adaptor is accomplished by the TOXI-GUARD® system, which contains a 100% activated carbon[1] drug binding matrix and 0.2 µm hydrophobic and oleophobic membrane (Figure 1). The activated carbon matrix is highly efficient in adsorption of drug vapors. The 0.2 µm membrane is a sterile barrier preventing microorganisms and particles from entering the system and, due to its hydrophobic and oleophobic properties, preventing aerosols and liquids from being released from the system. Together, they serve as an effective sterile, particulate and toxic drug vapor barrier.

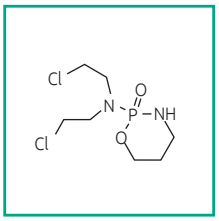
The TOXI-GUARD® system ensures that the Chemfort™ air pathway only allows particulate and bacteria-free air to enter the drug vial during drug reconstitution and preparation. It also ensures that the air exiting the drug vial is free of hazardous drugs' vapor.

Several studies were performed, challenging the efficacy of the Chemfort™ Vial Adaptor to prevent the escape of drug vapors[2]. A model system was designed to induce drug vapors within the drug vial. Since under normal usage conditions, the drug vapors that are generated are minimal, extreme conditions were employed to significantly increase vapor quantity. Vapors released from the Chemfort™ Vial Adaptor were trapped within a closed test chamber. The trapped drug was collected and then analyzed by highly sensitive LC/MS/MS methods.
The Chemfort™ Vial Adaptor was challenged with three commonly used antineoplastic drugs: Cyclophosphamide, 5-Fluorouracil and Doxorubicin (Figure 2). With Cyclophosphamide and 5-Fluorouracil, vapors were consistently detected in control samples in which the TOXI-GUARD® system had been removed from the Chemfort™ Vial Adaptor. In test samples containing an intact TOXI-GUARD® system, **no drug vapors were detected**. With Doxorubicin no drug vapors were detected in either the positive control or test sample.
These results support the validity of the Chemfort™ Vial Adaptor to prevent release of hazardous drug vapors.

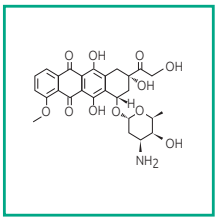
Figure 2. Chemical structures of the anti-neoplastic drugs used for challenging the Chemfort™ Vial Adaptor and the TOXI-GUARD® system. Figure shows the range of the drugs tested in terms of their size (molecular weight) and structural complexity.



5-Fluorouracil
$C_4H_3FN_2O_2$
MW = 130 g/mol



Cyclophosphamide
$C_7H_{15}Cl_2N_2O_2P$
MW = 261.1 g/mol



Doxorubicin
$C_{27}H_{29}NO_{11}$
MW = 543.5 g/mol

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Introduction

The Chemfort™ Vial Adaptor, once connected to a Chemfort™ Syringe Adaptor/Syringe Adaptor Lock, equalizes the pressure inside the vial without any need of action or activity by the user, thereby saving time and preventing potential errors. The Vial Adaptor spike contains two channels. One channel serves as the air pathway (see Figure 3, item 3) and the second channel as the liquid pathway (see Figure 3, item 4). The TOXI-GUARD® system has a sterile 0.2 µm hydrophobic and oleophobic membrane (Figure 3, item 2) on the interior side of the air channel and a 100% activated carbon drug binding matrix on its exterior side (Figure 2, item 1). The hydrophobic membrane blocks passage of aqueous liquids out of the air channel, while maintaining high air permeability. The manufacturing process for the activated carbon matrix results in a woven carbon cloth with a highly microporous structure and strong electrostatic forces (Figure 4). This matrix is highly efficient in adsorbing active molecules that may pass through the 0.2 µm filter, preventing their release into the environment[1].

Figure 3. Left. Cross-cut of the Tevadaptor® Vial Adaptor. (1) TOXI-GUARD® active carbon matrix, (2) 0.2 µm hydrophobic and oleophobic membrane, (3) air path and (4) liquid path.

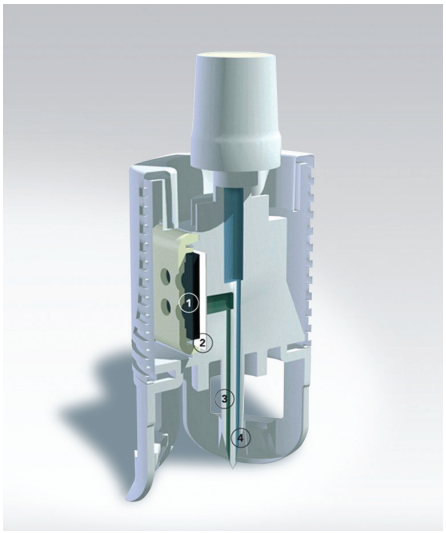
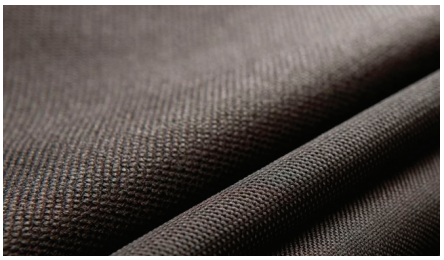


Figure 3. Right. Activated Carbon Cloth Matrix (Flexzorb™) in the TOXI-GUARD® system. Top panel, unmagnified picture. Bottom panel, magnified picture of the active carbon cloth, showing the tight weave of the carbon cloth matrix.



About Flexzorb™

Protection against toxic gases is one of the oldest applications of activated carbon, dating back to its use in World War I for protection against chlorine and other gases. Today it is used for a variety of industrial, military and medical applications. This includes removal of toxic and volatile gases in chemical manufacturing plants, in water purification systems, in industrial and military respirators, as protective clothing against chemical, biological or nuclear agents, and as wound dressings for protection against microbial infection.

The Flexzorb™ 100% activated carbon cloth is manufactured by Chemviron Carbon. Their special manufacturing process results in the cloth having a micro-porous matrix, with an extremely large surface area (1000-2000 m2/g). The surface area of one gram of activated carbon cloth is over half the size of a football pitch. The microporous structure and cloth weave, gives the cloth a very high air permeability. The large surface area of the cloth, combined with the strong electrostatic forces that are induced in the cloth as part of the manufacturing process, and its high air permeability, result in the carbon cloth having very rapid adsorption kinetics. In addition, the active carbon cloth is suitable for use in applications where there is high humidity as its adsorption capacity is less adversely affected by moisture[1].

Test Method

The efficacy of TOXI-GUARD® system to prevent release of hazardous drug vapors was evaluated by employing a closed test chamber for capture of released drug vapors. Since the quantity of drug vapors that may be generated under normal use conditions is extremely low, and typically below analytical limits of detection, a model system was developed using extreme laboratory conditions to induce and generate drug vapors to a much larger extent than what would be found in typical working environment in hospitals and pharmacies. This entailed heating the drug vial and its solution to elevated temperatures (50-60˚C) and having a constant stream of nitrogen gas flow into the vial via the Chemfort™ Vial Adaptor fluid pathway. Vapors released from the Chemfort™ Vial Adaptor were trapped and then recovered by dissolving in the appropriate diluent. LC/MS/MS methods developed and validated specifically for each test drug, were employed to detect and quantify the amount of drug recovered. In order to verify that the test conditions resulted in drug vaporization, parallel testing was performed using Chemfort™ Vial Adaptors in which the TOXI-GUARD® system had been removed (positive control). For each drug tested, the quantity of drug recovered from the sealed test chamber when intact Vial Adaptors were challenged, was compared to the quantity of drug recovered in the Positive Control sample.

Test Results

Study parameters and results are listed in Table 1. Testing was performed at Nextar (Ness Ziona, Israel). The limit of quantitation (LOQ) in the LC/MS/MS systems ranged between 0.1-0.5 ng/ml, which represents a LOQ of 1-5 ng of recovered drug after compensating for the volume of diluent used to recover drug from the closed vapor trap chamber (10 ml).
Drug vaporization was performed using 75 L nitrogen gas at a 50ºC drug incubation temperature. With Cyclophosphamide and 5-Flourouracil, drug was consistently recovered in the positive control samples which had Chemfort™ Vial Adaptors without the TOXI-GUARD® system, **and not found in the test samples which had Chemfort™ Vial Adaptors with the TOXI-GUARD® system.** With Doxorubicin, even under the extreme conditions that were employed, no drug was recovered in either the positive control or test sample.

Table 1. Quantity of Drug Recovered following Vaporization

Drug Tested	System LOQ[1]	Liters N2 Gas[2]	Quantity Drug Recovered from Outside of the Vial Adaptor	
			Positive Control (TOXI-GUARD® Removed)	Test Sample (TOXI-GUARD® Present)
Cyclophosphamide	1 ng	75	69 ng	Below LOQ
5 Fluorouracil	5 ng	75	35 ng	Below LOQ
Doxorubicin	5 ng	75	Below LOQ	Below LOQ

1. 10 fold the LC/MS/MS Limit of Quantitation
2. Liters of nitrogen gas used to induce the drug vapors

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Study Conclusions

Extreme conditions were employed to challenge the efficacy of the Chemfort™ Vial Adaptor's TOXI-GUARD® system to trap hazardous drug vapors. Three different anti-neoplastic drugs were utilized in the study.
These drugs differ in size, physical properties and chemical formulation. With two of the three antineoplastic drugs tested, drug was recovered from the positive control samples in which the TOXI-GUARD® system was removed from the Chemfort™ Vial Adaptor. Drug levels recovered in these positive control samples ranged between 35-69 ng. In contrast to these levels, in the test samples which had an intact TOXI-GUARD® system, drug levels were consistently below the level of quantitation.

The absence of recovered drug vapor in the test samples confirms the efficacy of the TOXI-GUARD® system present in the Chemfort™ Vial Adaptor to stop hazardous drug vapors' release.

With Doxorubicin no drug was detected in either the positive control samples or the test samples. This is most likely due to low vapor pressure as a result of the large size of the molecule.

The ability of the TOXI-GUARD® system to prevent vapor release with the different drugs that were tested, attests to the efficacy of the Chemfort™ Vial Adaptor to meet the challenge of different drugs.

References

1. Flexzorb™ Activated Carbon Cloth Product Brochure published by Chemviron Carbon, Cloth Division, United Kingdom http://www.chemvironcarbon.com
2. Tevadaptor Data on file, Nextar Report, 2018, 2019