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The 10 Activations Challenge

The compounding of cytotoxic medications is recognized today as a hazardous procedure, due to the potential release of drug vapors or droplets to the environment during manipulation. Therefore, the use of Closed System Transfer Devices (CSTDs) for safe handling of such drugs is significantly increasing and the need for supporting data is of importance[1]. An important factor for any CSTD system is the number of connection/disconnections (activations) that can be performed using any pair of CSTD items. This is of high importance due to the fact that after a certain number of activations the functionality of the CSTD's septa may be compromised.
There are two risks associated with compromised septa:

1. A risk to the medical teams: Release of the hazardous drug in the form of droplets, aerosol or vapor through the compromised septa
2. A risk to the sterility of the drug: Penetration of microbial contamination through the compromised septa

According to the Chemfort™ IFU, all components can be used for up to 7 days and 10 activations. This was verified by two experiments that tested the two risks described above.

Risk of Hazardous Drug Release - NIOSH Test with Multiple Activations

The National Institute of Occupational Safety and Health (NIOSH) issued on 2016 a draft protocol called "A Performance Test Protocol for Closed System Transfer Devices Used during Pharmacy Compounding and Administration of Hazardous Drugs"[2]. The protocol's intent was "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". The protocol listed nine molecules that are proposed as drug surrogates, 2-phenoxyethanol being one of them.

Study Outline

Hazardous drug containment was tested during execution of Task 1 (simulating reconstitution and transfer of a hazardous medication to an IV bag) and Task 2 (simulating reconstitution of a drug followed by an IV push), as described in the 2016 NIOSH protocol, using 2.5%w/v 2-phenoxyethanol as a surrogate. The tests were done with intact Chemfort™ products, as well as with product that underwent 6 or 10 activations, prior to the NIOSH test[3].

Results and Conclusion

Table 1. Results of CSTD Performance test according to the 2016 NIOSH protocol

No. of activations	NIOSH task	Mean concentration of 2-POE ± 95% CI (ppb)	Range (ppb) Lower 95% CI – Upper 95% CI (ppb)	LOQ (ppb)
Fresh products: First activation	1	≤LOQ (0.02 ± 0.01)	0.01 – 0.03	0.38
	2	≤LOQ (0.00 ± 0.00)	0.00 – 0.00	0.38
Sixth activation	1	≤LOQ (0.02 ± 0.01)	0.01 – 0.03	0.38
	2	≤LOQ (0.00 ± 0.00)	0.00 – 0.00	0.38
Tenth activation	1	≤LOQ (0.03 ± 0.02)	0.01 – 0.05	0.38
	2	≤LOQ (0.00 ± 0.00)	0.00 – 0.00	0.38
Needle and syringe (open)	1	15.39 ± 10.81	4.57 – 26.20	4.51
	2	113.39 ± 18.88	94.51 – 132.27	14.01

The results (Table 1) clearly show that there is no difference between Chemfort™ components that are used for the first time or components that already underwent 6 or 10 activations - All devices were efficient in preventing release of the drug surrogate solution or vapor. The Syringe-and-Needle technique was used as a positive control, and proved that release of drug actually occurs and can be measured by the NIOSH test protocol when an open system is used.

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Risk of Penetration of Microbial Contamination Through the Compromised Septa

The United States Pharmacopeia (USP) Chapter 797 standards mandates that single-use or non-preserved drugs must be discarded 6 hours after first vial access in ISO class 5 air conditions, otherwise it must be discarded after 1 hour. The purpose of this USP standard is to provide patient protection by limiting the impact potential of any microbial contamination of the drug. However, this guideline creates significant waste of partially used viable drugs, which results in increased financial expenditure. One of the advantages of a CSTD is to prevent the transfer of environmental contaminants into the system (vials), thus enabling an extended use period of the parenteral drug[4].

As a challenge, we tested the ability of the Chemfort™ system to prevent microbial contamination of a parenteral drug for a period of 30 days, during which 10 solution sampling points (septa activations) were performed.

Study Outline

Aim: To perform an extreme-use-conditions test to assess the ability of the Chemfort™ CSTD to prevent the microbial contamination of any parenteral drug vials during 30 days of use, during which 10 activations are performed.
Special challenges:

- Liquid bacterial growth medium was used instead of a drug solution, in order to support proliferation of any bacteria that enters the system
- Duration of testing was 30 days instead of 7 days
- 10 septa activations and sampling points
- Two parallel experiments were performed:
  A. Samplings were performed in ISO Class 5 conditions
  B. Samplings were performed at uncontrolled conditions

Chemfort™ Vial Adaptors (n=40 for each experiment) were applied on sterile glass vials containing 100 mL TSB growth medium (Hylabs, Rehovot, Israel). Five mL aliquots of TSB were sampled from each vial at day "0", and following at days 8, 11, 14, 17, 20, 23, 25, 28 and 30. Growth medium withdrawal was done by attaching a 5mL disposable syringes with male luer connection, connected to Chemfort™ Syringe Adaptor onto the Vial Adaptor. The Syringe/Syringe Adaptors were disconnected from the Vial Adaptors following the 5 mL TSB withdrawal, capped and incubated for 14 days at 30±2°C. Then the TSB in the syringes was visually inspected for signs of microbial growth (turbidity). Following withdrawal of the final sample on day 30, the vial containing the remaining growth medium (50 mL) was incubated for 14 days at 30±2°C and then examined for microbial growth (turbidity, by visual inspection).

Positive control: In order to verify the growth promotion potential of the TSB medium five TSB vials were each inoculated with 10-100 CFUs of one of 5 types of microorganisms. The vials were incubated at 30±2°C until microbial growth (turbidity) was observed.

Results and Conclusion

No signs of microbial growth were observed in any of the samples withdrawn during the 30 day test periods or in the growth media remaining in the vials when samplings were performed either in controlled (ISO Class 5) or uncontrolled environment.

It can be concluded that the results of the present study show the ability of the Chemfort™ system to prevent microbial contamination of a sterile drug during a 30 days use period and 10 sampling procedures, which may be performed either in an ISO Class 5 conditions or even in an uncontrolled environment.

Note: According to the IFU Chemfort™ has been shown to prevent microbial ingress for 7 days and 10 activations.

1. Vyas N., et al., 2014, Occupational exposure to anti-cancer drugs: A review of effects of new technology, J. Oncol. Pharm. Practice, 20(4):278-87
2. Federal Register / Vol. 81, No. 179 / Thursday, September 15, 2016 / Notices
3. Wilkinson A.S., Allwood MC, et al., 2018, Performance testing protocol for closed-system transfer devices used during pharmacy compounding and administration of hazardous drugs. PLoS ONE 13(10) : e0205263.
4. Gilbar PJ et al., 2019, How can the use of closed system transfer devices to facilitate sharing of drug vials be optimized to achieve maximum cost savings?, J. Oncol. Pharm. Practice, 25(1): 205-209