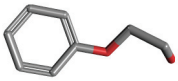
A Performance Test Protocol for Closed System Transfer Devices by NIOSH

NIOSH test being replicated at BSTL
Environmental chamber described in the NIOSH protocol

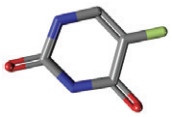
- NIOSH (National Institute for Occupational Safety and Health), US, recognized the importance of having a universal protocol for evaluating the performance of CSTDs (Closed System Transfer Devices). [1]
- NIOSH's initial protocol (September 2015) utilized 70% isopropanol as an agent to mimic hazardous drugs, thereby excluding the possibility of using the protocol with CSTDs that are based on air cleaning technology such as Tevadaptor® (OnGuard®). [2, 3]
- NIOSH issued a **revised draft protocol in September 2016,** excluding isopropanol as a surrogate candidate, due to its poor similarity to hazardous drugs. The new protocol listed nine proposed surrogates that are chemically and physically more similar to hazardous drug molecules. [1]
- BioPharma Stability Testing Laboratory (BSTL, UK), replicated the NIOSH environmental test chamber using one of the listed surrogates, 2-phenoxyethanol (2-POE), to evaluate CSTDs' mechanical barrier and air cleaning technologies. [4, 5]
- BSTL partnered with the Health and safety Laboratory (HSL) of the UK, who are the equivalent to the NIOSH in the US, to analyze the test performance of different CSTDs using their proposed surrogate, 2-Phenoxyethanol (2-POE), in the draft NIOSH protocol.

TDPT-IL-00126

Why use 2-Phenoxyethanol and not Isopropanol as a surrogate?



2-Phenoxyethanol
Molecular Weight: 138 g/mole
Formula: $C_3H_{10}O_2$
Henry's constant: 4.72 x 10^{-8} atm x m^3/ mol



5-Fluorouracil
Molecular Weight: 130 g/mole
Formula: $C_4H_3FN_2O_2$
Henry's constant: 1.66 x 10^{-10} atm x m^3/ mol

Isopropanol
Molecular Weight: 60.1 g/mole
Formula: C_3H_7O
Henry's constant: 7.90 x 10^{-6} atm x m^3/mol

Left panel shows the molecular structure and chemical active groups for 2-phenoxyethanol, 5-fluorouracil and isopropanol. As can be seen, 2-phenoxyethanol is structurally more similar to a hazardous drug such as 5-fluorouracil, as compared to isopropanol. Moreover, Henry's constant, defining the volatility of molecules dissolved in water, is similar for 2-POE and 5-FU, the most volatile cytotoxic drug diluted in water, whereas Henry's constant for Isopropanol is 100 fold greater. [6]

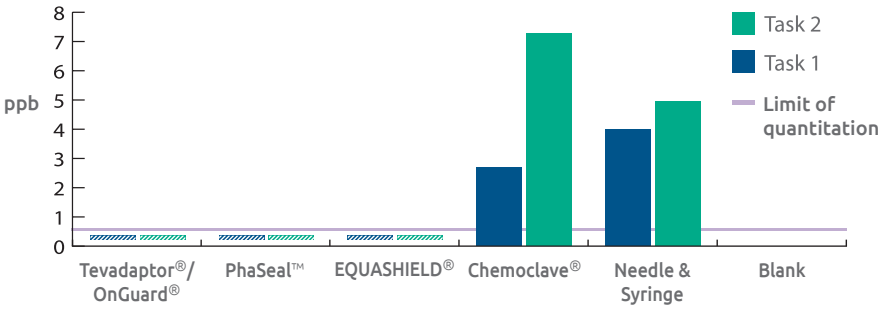
Vapor containment was tested during execution of Task 1 (reconstitution and transfer to an IV bag) and Task 2 (reconstitution followed by an IV push), as described in the NIOSH protocol.

Samples Tested

CSTDs:	Tevadaptor® (Teva)/ OnGuard® (BBraun), PhaSeal™ (BD), EQUASHIELD® (EQUASHIELD) and Chemoclave® (ICU medical)
Positive Control:	Needle and Syringe
Negative Control:	Water for injection instead of 2-Phenoxyethanol
Blank:	Sampling of chamber air before the start of each test session

Test Results as analyzed by HSL

The quantity of 2-POE vapors detected with Tevadaptor®/ OnGuard®, PhaSeal™ and EQUASHIELD® was consistently below the limit of quantitation (<0.71 ppb - Parts per billion). Vapors detected with Chemoclave® ranged between 1.3-5.4 ppb, with a peak at 24 ppb and an average of 2.70 ppb for Task 1 and 7.30 ppb for Task 2. Vapors detected with a needle and syringe had an average of 4.00 ppb for Task 1 and 4.97 ppb for Task 2.



Test Conclusions

- The test results for the needle and syringe show the potential risk of drug vapor release when a CSTD is not used for drug compounding and transfer.
- Tevadaptor®/ OnGuard®, PhaSeal™ and EQUASHIELD® reduced the quantity of vapors between 5 to 20 fold, relative to the needle and syringe.
- Chemoclave® results were inconsistent. In some instances, drug vapors were reduced approximately 2 fold, relative to the needle and syringe. However, during the execution of task 2, one of the replicates showed 5-6 fold more drug vapors than those released with a needle and syringe.

Tevadaptor® showed equal performance to PhaSeal™ and EQUASHIELD® when tested under the NIOSH draft test protocol, therefore demonstrating that Tevadaptor®'s air-cleaning technology is as effective as physical barrier in preventing vapor release.

It is of high importance to have a universal test that compares the safety and efficacy of all CSTDs and includes tasks that challenge different CSTD components in relevant clinical procedures.
The NIOSH test protocol, when using a 2-POE solution as a surrogate, efficaciously tests the design of CSTDs and their components and the capacity of each component to prevent drug vapor, aerosol or droplet release.

1. Federal Register / Vol. 81, No. 179 / Thursday, September 15, 2016 / Notices
2. https://www.federalregister.gov/documents/2016/09/15/2016-22132/a-performance-test-protocol-for-closed-system-transfer-devices-used-during-pharmacy-compounding-and
3. http://www.cdc.gov/niosh/docket/review/docket288a/default.html
4. Wilkinson A.S., Allwood MC, et al. Performance testing protocol for closed-system transfer devices used during pharmacy compounding and administration of hazardous drugs. PLoS ONE 13(10), 2018: e0205263.
5. Wilkinson A.S. et al. Assessment of vapour containment performance for closed system drug transfer devices (CSTDs) that either employ a mechanically closed physical barrier or air filtration technology – a harmonised approach to NIOSH. ASHP 2016, Poster session 4-173
6. Atmos. Chem. Phys., vol. 15, 4399–4981, 2015