Evaluating the containment performance of CSTDs

This study was performed as an independent assessment of the draft protocol devised by NIOSH for evaluating the performance of CSTDs that employ a physical barrier, as intended by NIOSH. The study applied the same test protocol to include an assessment of one example of a CSTD system that uses air filtration technology

Alan-Shaun Wilkinson PhD
Biopharma Stability Testing Laboratory Ltd (BSTL), BioCity Nottingham, UK;
University of Derby, College of Life and Natural Sciences, Derby, UK
Michael Charles Allwood PhD
Andrew Wallace PhD
Rebecca Finnis BSc
Colin Patrick Morris HNC
Joe Miller
Biopharma Stability Testing Laboratory Ltd (BSTL), BioCity Nottingham, UK
Ian Pengelly BSc
Michael Hemmingway PhD
John Saunders BSc
Dominic Pocock BSc
Health and Safety Laboratory (HSL) Harpur Hill, Buxton, UK
Email: alan@biopharmatesting.co.uk

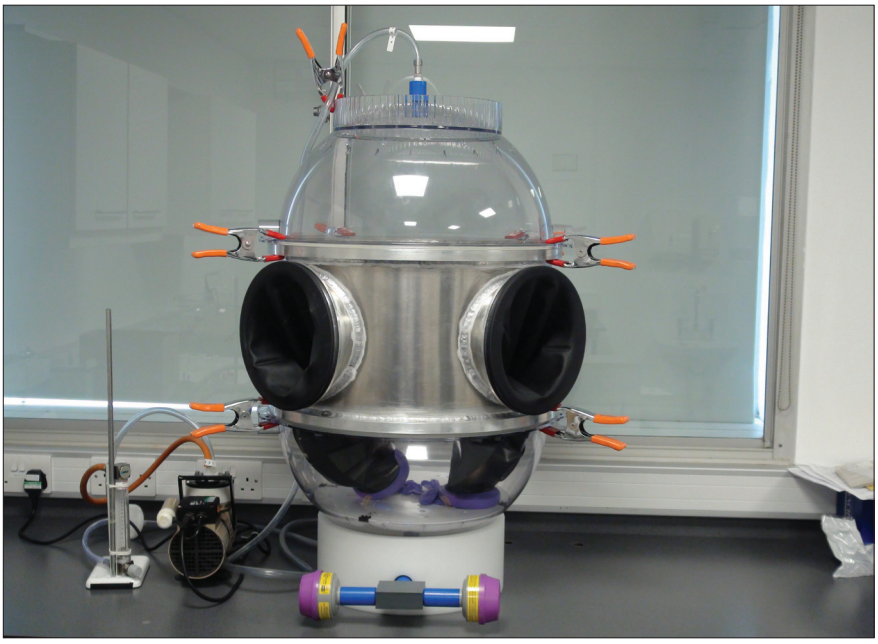

Figure 1: The BSTL environmental test chamber as used to replicate the NIOSH test protocol for assessment of CSTD systems.

The National Institute for Occupational Safety and Health (NIOSH) in the US has developed a performance testing protocol for use with mechanically closed system transfer devices (CSTDs).[1] CSTDs are devices used to facilitate drug transfer and reduce the likelihood of exposure to hazardous drug materials. The concept of a CSTD is that is should "prohibit the transfer" of environmental contaminants into the system and also prevent escape of hazardous drug material or vapour concentrations from the containment system. In order to achieve this, CSTD manufacturers use one of the following two approaches:

1. Use of a physical/mechanical barrier to prevent loss of any material (including air) from the system;
2. Use of air filtration technology to specifically prevent loss of hazardous drug vapours from the system.

The purpose of the test protocol drafted by NIOSH was to test the containment performance of CSTDs of the physical barrier type. Five commercially available CSTDs that employ a mechanical barrier to the environmental were tested during an evaluation of the protocol. Testing at NIOSH was performed by registered pharmacists in the US who were familiar with the use of CSTD systems. The testing was composed of two distinct set of manipulations: task 1, which mimics the drug reconstitution process and preparation of an IV bag; and task 2, which mimics the delivery of an IV bolus injection or 'push'.

NIOSH also performed the assigned tasks 1 and 2 using a control set of equipment that employed a standard needle and syringe approach without the use of a CSTD. All of the tasks that were performed at NIOSH involved the use of a 70%:30% isopropyl alcohol (IPA) : water mixture as the hazardous drug surrogate. The choice of surrogate was partly to challenge the CSTD systems with a highly volatile material and partly due to the availability of a highly specific gas analyser, the Thermo Scientific SapphIRe 205B XL (MIRAN), which has a measurement capability specific to IPA with a limit of detection (LOD) of 0.3ppm when operated at a wavelength of 8.9 microns.[2] In the present study, we adopted an additional portable real time detector, a ppbRAE that operates using photonionisation detection (PID) and has a limit of detection of 50ppb. This provided an

Change Item Number	Table 1: Changes made by BSTL to original NIOSH CSTD test protocol and or equipment
1	The extension ring used in the chamber (see item 19 in Table B1 of the NIOSH test protocol (1)) was constructed from high grade aluminium instead of clear plastic, but is otherwise of the same dimensions. The use of this alternative material does not have any detrimental effect on the performance of the test chamber and, if anything, will be more resistant to ingress of organic material, and thus easier to decontaminate after a test run. In addition, BSTL noted that the weight of the aluminium extension ring results in a better seal in the lower section of the chamber.
2	The test chamber has been constructed with two alternative lower sections allowing the equipment to be used in one of two configurations: open, as used in the NIOSH protocol, and closed. The open configuration (see Figure 2) has a chamber capacity of approximately 125 litres and was used for the majority of testing of the CSTD devices. The closed configuration (see Figure 3) also has a chamber capacity of approximately 125 litres but incorporates a syringe injection port to allow introduction of known volumes of isopropanol (IPA). The closed configuration was used to check the performance of the IPA detection devices used and calibrate the system for IPA.
3	The foam seal tape used in the NIOSH protocol (see Piece 21 in Table B1 of the NIOSH test protocol (1)) was replaced with a ring of silicone (polymethylsiloxane) material. HSL considers that the use of this alternative material would not have any detrimental effect on the performance of the test chamber and, if anything, would be more resistant to mechanical deformation than the foam seal tape, which should result in a longer lasting and more leak resistant gas tight seal.
4	A MIRAN SapphIRe 205B XL Infrared Analyser, (2) hereafter referred to as the MIRAN analyser, was used for detection of IPA. However, the device was used with an external pump and was connected to the test chamber using clear flexible polyvinyl chloride (PVC) tubing and metal barbed connectors in place of the standard black plastic flexible tubing. The Swagelock connector shown in the NIOSH protocol was used as described. The external pump delivered air from the test chamber to the MIRAN analyser at a flow rate of 15 litres per minute, with the flow rate being monitored using a flow-through rotameter. The external pump was used following discussions with HSL as the flow rate of the internal pump used in the MIRAN analyser can vary if used in a situation where it is pulling against a slight back pressure, as would be the case with the test chamber specified in the NIOSH protocol. Following discussions with HSL, the MIRAN analyser was u sed with the device laid horizontally, rather than the vertical orientation shown in Figure 1 of the NIOSH test protocol; (1) HSL have found performance to be more consistent if the instrument is used in this way.
5	In addition to the MIRAN analyser, a ppbRAE detector (3) was also used to measure IPA concentration. The ppbRAE device uses a photoionisation detector (PID), which is not specific to IPA, but has a limit of detection which is better than that of the MIRAN analyser. Also, the ppbRAE device is sufficiently compact to be placed inside the chamber during testing. As with the infra-red detector used in the MIRAN analyser, the PID in the ppbRAE is a non-destructive detector. The ppbRAE device samples at a flow rate of approximately 500ml per minute, with the sampled gas passing into the device, through the detector and then back into the chamber. The ppbRAE LOD was 50ppb.
6	All commercially off the shelf (COTS) closed system transfer devices (CSTDs) were used originally according to the NIOSH instructions for performing task 1 and task 2 and then according to the original device manufacturer's instructions for use (IFU). The levels of IPA release were significantly different when operating all but one of the medical devices under the two separate conditions for use. The IFU conditions produced the most consistent data with the lowest IPA vapour release and consequently this operation condition was followed in all subsequent testing in the study and is recommended for all future CSTD evaluations. IFU also ensured that the CSTD devices were nor compromised in terms of their operation under the test conditions.
7	All tested CSTDs were manipulated using 100% water for infusion as a negative control for both task 1 and task 2 to provide a representative blank data set for that CSTD. In the data presented, however, the blank correction approach suggested by NIOSH was performed to allow comparison of the data sets with the original research.

orthogonal detector that could be placed inside the test chamber closer to the source of IPA release.[3]

NIOSH stipulated clearly that the draft test protocol issued was not intended for CSTDs designed to operate using air-cleaning technologies. On 19 January 2016, NIOSH issued a request for information (RFI) concerning draft protocols for the assessment of the vapour containment performance of CSTDs that employ air filtration technology. NIOSH also extended the initial comment period for the draft protocol, and this has enabled independent scientific investigation of the protocol, such as the study described here to be conducted. The extended comment period closed for comment on 8 March 2016.

Biopharma Stability Testing Laboratory Ltd (BSTL) undertook an independent evaluation and review of the test protocol published by NIOSH by testing four of the same commercially available CSTD systems as described in the test protocol to compare the data with that published by NIOSH. The assessment was extended to include one example of an air filtration CSTD (Tevadaptor®; marketed as OnGuard™ in the US).[4] BSTL also studied the effect of using a lower percentage IPA surrogate solution that more closely represents a clinically useful concentration of a hazardous drug. Thus a 1% v/v solution of IPA: water was used with the selected air filtration technology system under the conditions of the original NIOSH protocol, modified to account for the manufacturer's instructions for use (IFU). The decision to undertake this work was based on some initial concerns over the approach taken by NIOSH in the draft protocol and the overall experimental design, including that of the environmental test chamber used to perform the pharmacy manipulations. As part of the due diligence, BSTL enlisted the assistance and collaboration of the Health and Safety Laboratory (HSL) located in Buxton, UK to provide expert opinion and to audit the equipment and facilities of BSTL based at BioCity Nottingham in the UK. The lead analyst and scientific group from HSL have published several papers on the detection of volatile organic vapours using both real time and time weighted average (TWA) chemical vapour detection approaches.[5–7]

"Data obtained in this study supports manipulating CSTDs according to the manufacturer's instructions for use rather than NIOSH when assessing the vapour containment performance to avoid compromising the CSTD"

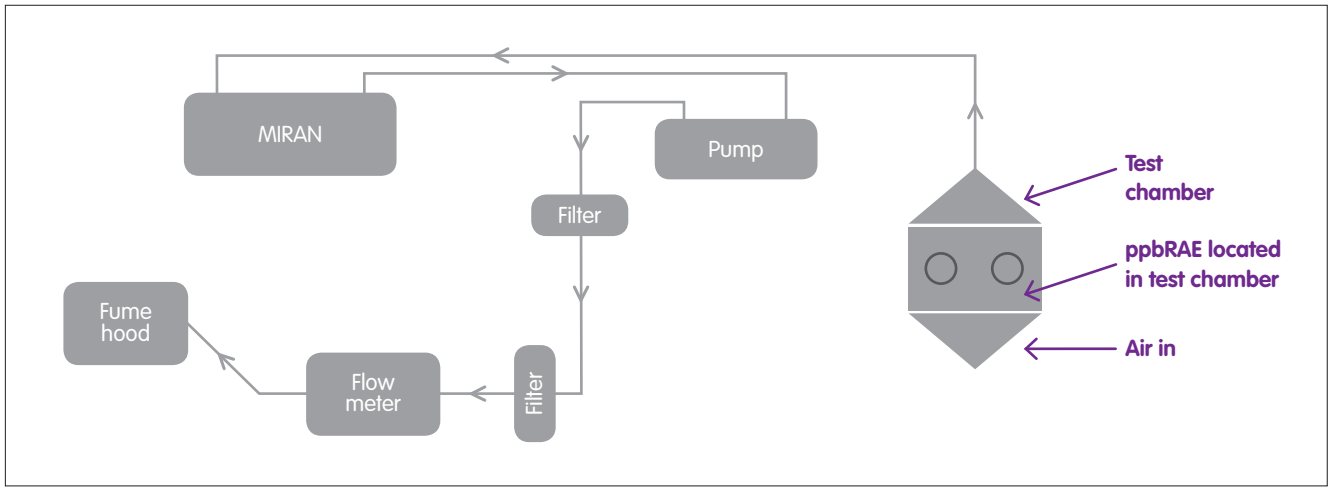

Figure 2: Test chamber in the open configuration.

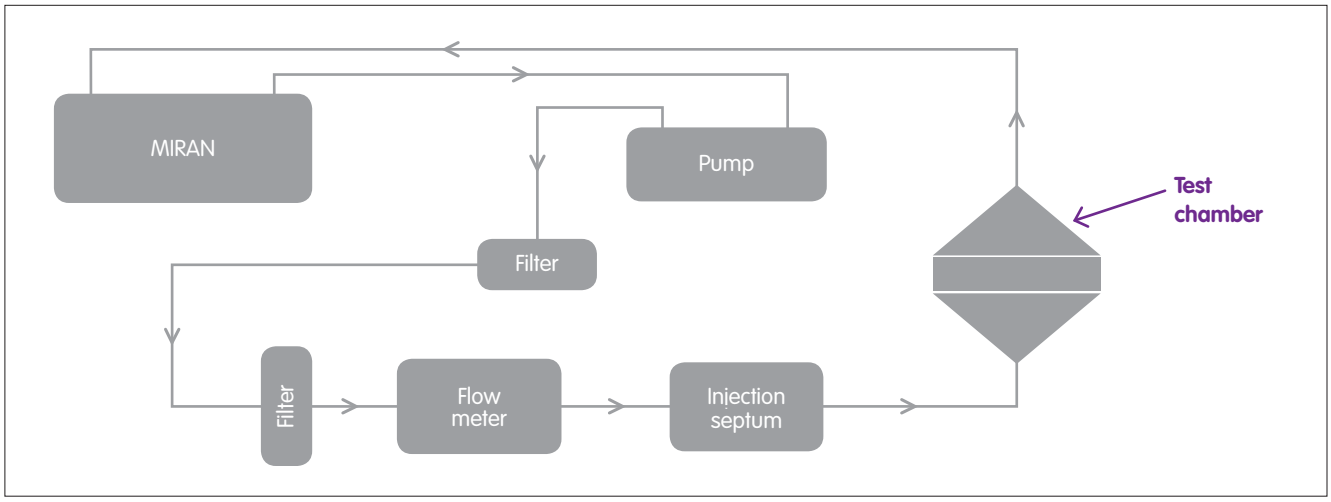

Figure 3: Test chamber in the closed configuration.

Main findings

As regards modifications to the test protocol, BSTL and HSL have identified possible areas for consideration including how the CSTD is tested, methods of detection, blank correction of data, the challenge agent used and testing the effectiveness of the filtration system used in CSTDs employing air cleaning technology.[5]

As a result of this work, BSTL and HSL have identified some areas where we believe the existing protocol for mechanically closed CSTDs could be improved, as a basis for assessment of air filtration technology CSTD systems. We would therefore like to recommend that these ideas are considered for incorporation into any proposed protocol for the assessment of air filtration CSTD systems. The recommendations and amendments, which include changes to how the device is used, the methods of detection and how the data are blank corrected, would be applicable to all CSTDs and not just those employing one of the closed system technologies: physical barrier or air cleaning technology. Given the specialised nature of this type of testing, we would also recommend considering whether testing and certification of these devices would be better done by specialised testing companies or organisations rather than individual pharmacists or hospitals.

Methods

Prior to undertaking any testing, BSTL made specific improvements and modifications to the original NIOSH experimental apparatus and design. The chamber constructed by BSTL is shown in Figure 1 and the changes from the original NIOSH design and operation are summarised in Table 1.

With the above modifications, each commercial CSTD system was tested both according to the original NIOSH instructions for performing task 1 and task 2 and under the device manufacturer's IFU, and these data are presented in Tables 2 and 3. A representative example of the resultant data obtained from operating one CSTD system under the original NIOSH protocol (not IFU) is presented in Figure 4. In our study, the use of an external pump allowed a constant flow rate of 15 litres per minute to be achieved during the testing. According to NIOSH, the flow rate achievable using the internal MIRAN pump was 10 litres per minute although no measurement of the flow rate was made and the internal pump operation is not designed to perform connected to external laboratory equipment, being more suited to operation at atmospheric pressure using the wand attachment supplied. Higher flow rates will improve the operation of the system and help to move the IPA released from the chamber to the MIRAN detector in a reduced amount of time. All other parameters were kept and followed as per the NIOSH

protocol.[1] One further additional check that BSTL performed was a quality control (QC) check on all drug vials produced with the 70% IPA mixture to ensure that there was no IPA vapour leakage from the drug vial septa prior to testing. Any prepared vials of 70% IPA that were not sealed correctly were placed in quarantine and not used in the study. The QC release test of IPA drug vials was achieved using the ppbRAE detector due to its superior sensitivity of detection. Finally, testing was also performed using a 1% v/v solution of IPA under identical conditions to the 70% IPA mixture testing but with the lower concentration of IPA to better mimic a reconstituted hazardous drug substance at clinically relevant concentration. All other conditions were kept identical to those employed by NIOSH.

Results

A complete capture of IPA release data is shown below from testing of one of the CSTD systems selected in accordance with the NIOSH protocol but using the manufacturer's IFU. Data are presented from both the MIRAN and ppbRAE detectors with a LOD of 0.3ppm and 50ppb, respectively. Five replicate measurements were performed; however, a typical result is displayed for one test from each of the measurement detectors. The data shown are for the manipulations according to task 1. Each experiment provides a different output, but they follow the same general trend in output IPA values throughout the operation with the highest IPA release (instantaneous release) showing in the range of 4–5ppm with both real time detectors. The results shown were obtained from using the CSTD with the open configuration (Figure 2) as employed in the original NIOSH protocol but under IFU conditions. It can be seen that with this CSTD device (ICU Medical ChemoClave™), the IPA vapour release values are higher than those found when operating other CSTD systems according to task 1 under the IFU (see Tables 2 and 3). The question is, whether this slight increase in IPA vapour release is significant or meaningful in the context of hazardous drug vapour containment. In addition to performing testing according to the original NIOSH and IFU conditions, the CSTD systems were also tested according to an alternative closed configuration shown above in Figure 3 (data for all CSTDs not shown), which provided a quantitative value for the total IPA vapour released from the CSTD. An example plot illustrating what would be a typical readout from operating the closed system is shown again for the ICU Medical ChemoClave™ CSTD system in Figure 5. The data shows an increasing IPA concentration as this builds up during the execution of NIOSH task 1. At the end of the manipulations the IPA concentration levels off to provide a final IPA concentration of approximately 8.3 ppm that represents the total amount of IPA vapour release from the system under the conditions of performing NIOSH task 1 (devices manipulated according to the IFU). The sharp decrease in IPA (purple line) is from opening the environmental test chamber at the end of the testing. The readouts for IPA concentration from the ppbRAE and MIRAN show good agreement. This measurements under the closed loop conditions is a more reliable value for IPA vapour release and although twice the amount recorded under the NIOSH open flow path configuration is still a very low value for vapour release given the extremely high vapour pressure of IPA.

Comparison of the replicate (n=5) tests shows that for this particular task (task 1), with this particular CSTD (ICU Medical ChemoClave™), we observe a few short duration transient peak IPA concentrations when the CSTD is

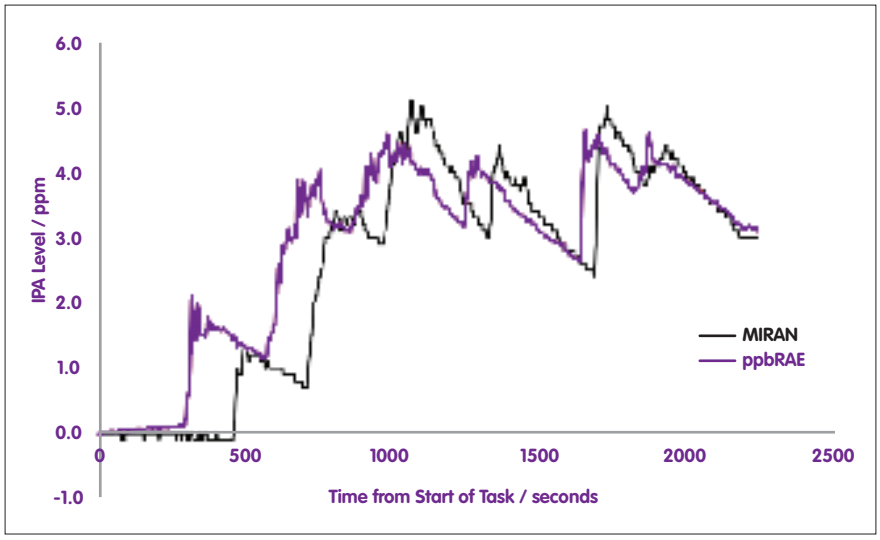

Figure 4: Figure showing the IPA vapour release output as recorded in ppm using the MIRAN and ppbRAE detectors when a 70% IPA mixture is manipulated in drug vials according to IFU for task 1 using the ICU Medical ChemoClave™ CSTD system. The data shown was obtained using the open flow path NIOSH system.

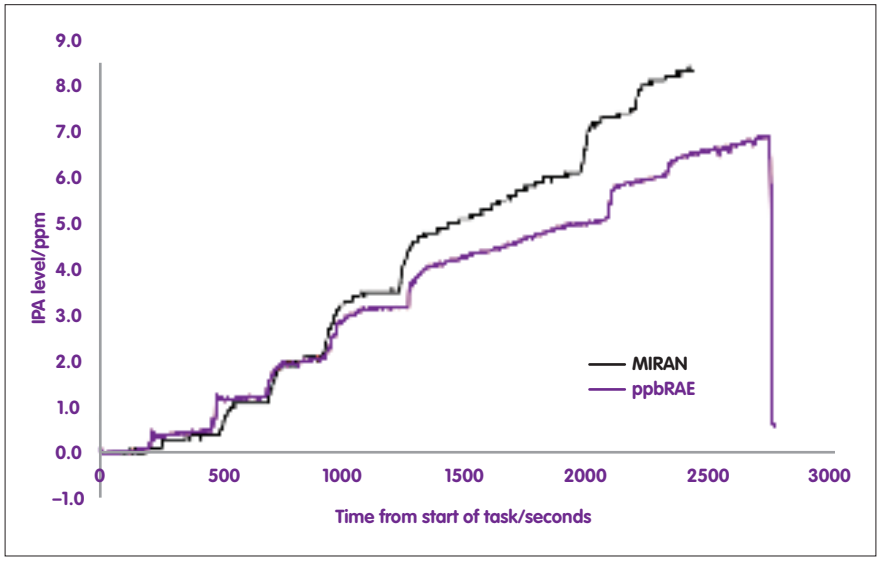

Figure 5: IPA vapour release output as recorded in ppm using the MIRAN and ppbRAE detectors when a 70% IPA mixture is manipulated in drug vials according to IFU for task 1 using the ICU Medical ChemoClave™ CSTD system. The data shown were obtained using the closed loop system.

Table 2: Analysis variable: BG-0_{max}

Task	CSTD device	Number of BG-0max observations (*n*)	Mean of BG-0max observations (ppm)	Lower 95% confidence limit (ppm)	Upper 95% confidence limit (ppm)	Standard deviation (ppm)
1	Carefusion Smartsite®/Texium®	5	1.4	1.1	1.6	0.1
	ICU Medical ChemoClave™	5	4.0	2.9	5.1	0.9
	BD Phaseal™	5	0.4	0.3	0.4	0.0
	Tevadaptor®	5	7.2	6.7	7.7	0.4
2	Carefusion Smartsite®/Texium®	5	1.1	1.0	1.2	0.0
	ICU Medical ChemoClave™	5	3.0	2.6	3.5	0.4
	BD Phaseal™	5	0.6	0.5	0.8	0.1
	Tevadaptor®	5	8.6	6.2	11.0	1.9
2	†Tevadaptor® 1% IPA	5	0.6	0.5	0.6	0.1

** = 70% IPA : 30% water for infusion was used as the test mixture for all testing unless stated.*
† = 1% solution of IPA in water for infusion was used to mimic clinically relevant drug concentrations.

Table 2: Performance data recorded using the ppbRAE for CSTD systems evaluated according to the amended NIOSH (IFU) vapour test protocol using mixture of 70% IPA : 30% water*.

Table 3: Analysis variable: BG-0_{max}

Task	CSTD Device	Number of BG-0max observations (*n*)	Mean of BG-0max observations (ppm)	Lower 95% confidence limit (ppm)	Upper 95% confidence limit (ppm)	Standard deviation (ppm)
1	Carefusion Smartsite®/Texium®	5	1.5	0.0	2.9	0.9
	ICU Medical ChemoClave™	5	3.8	1.5	6.1	1.8
	BD Phaseal™	5	0.4	0.3	0.4	0.1
	Tevadaptor®	5	7.4	6.2	8.6	1.0
2	Carefusion Smartsite®/Texium®	5	1.1	0.6	1.6	0.3
	ICU Medical ChemoClave™	5	2.7	2.2	3.1	0.4
	BD Phaseal™	5	0.5	0.5	0.5	0.0
	Tevadaptor®	5	9.0	8.9	9.0	0.1
2	†Tevadaptor® 1% IPA	5	0.2	0.1	0.2	0.1

** = 70% IPA : 30% water for infusion was used as the test mixture for all testing unless stated.*
† = 1% solution of IPA in water for infusion was used to mimic clinically relevant drug concentrations.

Table 3: Performance data recorded using the MIRAN detector for CSTD systems evaluated according to the amended NIOSH (IFU) vapour test protocol using mixture of 70% IPA : 30% water*.

manipulated. The IPA concentration then returns to a lower value until the next stage of the manipulations. The transient fluctuations in IPA concentration can vary from one test run to another, suggesting that performing a statistical analysis of a number of replicate tests is less meaningful as the distribution will not be normally distributed about the calculated mean value. Consequently, the reporting of IPA release values might be more meaningful if quoted for each separate replicate rather than as an aggregated IPA release value. In the testing under IFU conditions, the IPA release values were significantly improved compared to those observed using the NIOSH conditions. It is clear that the NIOSH protocol compromises the integrity of the CSTD operation and results in a higher IPA release for some CSTD devices including the one device tested from ICU medical. All future testing, we recommend, should be performed according to the manufacturer's specific instructions for use to avoid compromising the CSTD device being assessed. We also suggest that it might be the case that a TWA IPA concentration covering the task as a whole may result in a more reproducible exposure value (if required this could be done with the collected data). Data collected from the closed loop configuration showed an increasing trend in IPA values that plateaued at the end of the test, as would be expected. The final IPA reading represents the maximum IPA concentration, and hence release of IPA vapour, during operation of the specific CSTD system. The approach of a closed test system allowed a quantitative determination of the system performance of respective CSTDs for vapour containment. The use of a closed system allows a valid comparison to be made between CSTD systems for vapour containment performance. This mode of testing the CSTD systems also enabled a rapid system verification to be performed using the whole test system, through the injection of known aliquots of pure IPA liquid via a septum. Data from daily system checks yielded correlation R values between known IPA additions (providing known IPA concentrations) to the chamber and the MIRAN detector response for IPA of >0.9995. Similar values were also obtained for the ppbRAE detector platform located inside the test chamber.

For the complete CSTD performance data under IFU conditions from the MIRAN detector, see Table 2. The ppbRAE detector values from the same IFU tests are presented in Table 3. Data are presented in the same format as that of NIOSH for ease of comparison.

A representative plot from the work undertaken using a CSTD employing air filtration technology (Tevadaptor® systems) is shown below in Figure 6 for NIOSH task 1 (IFU). The data presented are for manipulations performed with 1% IPA solution under NIOSH (IFU) conditions and shown for the ppbRAE and MIRAN detectors (only one experimental run shown) (n=5).

The above data shows a marked improvement in performance when a 1% v/v solution of IPA is employed as opposed to the 70% IPA mixture. The vapour pressure for the 1% v/v IPA

solution is estimated to be around 44 Pa at 20°C, which is still three orders of magnitude higher than that of the most volatile hazarous drug molecule, an example of which would be carmustine (19 mPa, 20°C). Given the NIOSH determined acceptance criteria of <1.0ppm, this would suggest that the air filtration technology CSTD would achieve a PASS rating according to NIOSH for a 1% v/v IPA solution. This data supports the use of air filtration technology as an alternative to a physical barrier type CSTD in preventing healthworker exposure to hazardous materials. Moreover it also lends support for a combined CSTD test protocol that is able to assess the vapour containment performance of either type of device using a single unified test system. This would simplify the testing demands for the pharmacy budget holders and allow comparisons of CSTD systems to be made under the same identical test conditions.

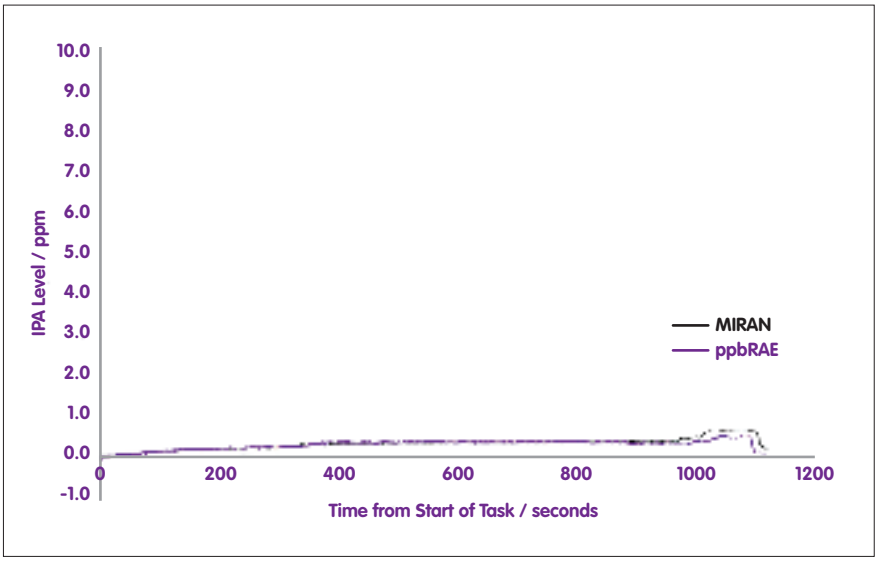

Figure 6: Figure showing the IPA release when a 1 % v/v solution of IPA is manipulated using an air filtration technology CSTD (Tevadaptor® systems) according to NIOSH (IFU) task 1. Data presented from both MIRAN and ppbRAE detectors from one experimental run.

Discussion and conclusions

Following on from our study, it is recommended that the protocol, for both types of CSTD system, should be amended to allow tasks 1 and 2 to be carried out following the manufacturer's IFU rather than the current instruction provided in the NIOSH protocol that appear to suit just one CSTD system. The tasks themselves would not change, but the way in which they are carried out would, with the procedure following the IFU for the particular medical device to be employed rather than the current generic protocol for all CSTD operations. For example, if vial 1 does not require flushing with air (for example to pre-fill an expansion chamber) before removal of the first 45ml aliquot of liquid, this need not be done. To ensure transparency, it is essential that any deviations from the standard procedure, and the reasons for these modifications, are fully documented by the testing laboratory within the final test report.

Our study data also suggests[5] that the environmental test chamber designed by NIOSH operates quite effectively as a mixing chamber although it does not support plugged flow as suggested in the original NIOSH document. This is actually helpful in quickly establishing a steady state IPA concentration inside the chamber. A real-time PID instrument placed inside the test chamber was able to measure concentrations of IPA that matched the values of IPA vapour release recorded using the MIRAN which is located downstream of the test chamber. This observation lends further support to the hypothesis that complete mixing of IPA 'drug' vapour released during the manipulation of the CSTD is achieved on a very short time scale. The data obtained from the ppbRAE provides a confirmatory check that the MIRAN detector was working correctly throughout the test because it uses an alternate orthogonal chemical detection method (PID) to the MIRAN (infrared). Moreover, the ppbRAE (PID) instrument used in this study provided a lower limit of detection (LOD) and quantitation (LLOQ), allowing data to be reported for values for IPA release down to 50ppb, significantly below the lowest IPA concentration that the MIRAN can detect and quantify (LLOQ 1.0ppm). Another advantage of using the ppbRAE detector was that if directed towards specific areas of the CSTD during manipulations, the source of the release of IPA vapours could be located. We suggest that this information could be useful to manufacturers of CSTDs. In this way, we were able to report a small transient release of IPA vapour on insertion of the CSTD spike from each connection of the vial adaptor on to the drug vial with some CSTDs. Only a true real-time detector with an appropriate sensitivity and temporal response such as the ppbRAE could be used to detect such specific events from the manipulation of the CSTD systems.

> "Recommendations made by HSL to the existing NIOSH protocol could allow assessment of CSTDs that employ both air filtration and physical barrier technologies in a single unified test protocol"

We also recommend that the airflow system be separated from the detection system by the use of an external pump, as used in the testing carried out in this study by BSTL, or a mass flow controller to control the flow of air through the test chamber and detector. Indeed, we would also recommend that consideration be given to using the system under a closed loop configuration that would not dilute any releases of the chemical surrogate (in this case IPA) with additional 'clean' air entering the chamber during the test. The closed loop operation would therefore provide more accurate quantitation for IPA vapour release and improve detection of the IPA release by ensuring no dilution of IPA vapour can occur.

BSTL recommends that the MIRAN

detector should be coupled to the environmental test chamber using gas tight tubing and connectors rather than the non-gas tight connection described in the NIOSH protocol. NIOSH describe 'pushing on' the rigid tube wand device supplied with the MIRAN to the external side of the Swagelock fitting at the top of the test chamber. The wand is, however, only intended to be used for sampling of environmental air in a portable field-based measurement system where it is open at the distal end (and hence at atmospheric pressure). A wand accessory is not intended to be used as part of a laboratory test system, which, may present significant resistance to flow (and produce backpressure). As such, the wand attachment is not designed to be attached at the distal end or be used to make a gas tight connection. To obtain accurate IPA vapour release data, a gas-tight connection must be made at each and every joint within the test system. This is prerequisite to prevent any losses of IPA vapour from the measurement system and improve accuracy of the measurement. Furthermore, if air can gain access to the inside of the chamber and test system, it follows that the IPA vapour released will be diluted by an unknown amount of 'non-clean' air. With the current NIOSH presented configuration for connecting the MIRAN detector to the chamber introduction of external 'non-clean' air is unavoidable and will effect the accuracy of all IPA vapour release measurements.

The findings from performing smoke testing of the BSTL test chamber[5] demonstrate that although the chamber does not operate as suggested by NIOSH in the test protocol, the function of the chamber is fit for purpose for this type of testing and should be considered for future adoption in any updated test protocol. Consideration may be given to the selection of materials for the test chamber fabrication, including the use of less permeable materials, or a perfluoro polymer coating may be employed to reduce vapour adsorption on to internal surfaces and to assist with decontamination of the internal chamber surfaces between experiments.

In addition to real-time detection, it is recommended that consideration be given to the use of TWA sampling methods, such as sorbent collection tubes, which form the basis of the test method 109 issued by OSHA for quantitation of IPA in vapour.[8] While the TWA approach would not give real-time information, the limits of detection for this type of sample are significantly lower than devices such as the MIRAN analyser (ppm) or even the ppbRAE (ppb). Furthermore, the study reported here shows that using the test chamber as described by NIOSH with an internal volume of 125 litres, does not support real-time detection using the MIRAN detector. With a suggested flow rate of 10 litres per minute (NIOSH) for the MIRAN, a simple calculation shows that it would take 12.5 minutes to perform a single exchange of the air inside the test chamber with this system and hence transit time for any IPA release to the MIRAN for detection. Operating the system at the higher flow rate of 15 litres per minute as performed in the present study, reduced the transit time

"NIOSH states that vapour containment performance protocol is not intended for CSTDs that employ air filtration technology"

for IPA to reach the detector following release. By increasing the flow rate to 15 litres per minute, which is what the MIRAN is designed to operate at, we were able to improve the temporal response of the system to 8.3 minutes from 12.5 minutes. The inclusion of the ppbRAE detector within the environmental chamber, however, supports a close to real time detection readout. This is because the ppbRAE has a smaller internal sample gas flow cell and can sample and detect the IPA vapour within a few seconds. The small foot print of the hand held ppbRAE detector makes it possible for the IPA vapour to be detected close to the point of actual release from the CSTD system inside the chamber.

For sorbent tubes analysed by thermal desorption and gas chromatography, limits of detection of 1–2ng are entirely possible, which, for a sample volume of around 2 litres, would equate to an average airborne concentration of around 0.5–1µg/m^3, which is equivalent to around 0.2–0.4 ppb IPA. This is a superior performance to the ppbRAE detector, which has a LOD of 50ppb. Chromatographic methods of analysis also offer much improved selectivity as well as sensitivity, particularly those employing mass spectrometry detection systems.

In the tests carried out by BSTL as part of this study, all devices tested showed evidence of release of IPA vapour at concentrations around the NIOSH 'PASS'criteria of 1 ppm; for both task 1 (drug preparation) and task 2 (IV administration) and one device provided a PASS based on the average release data. For the complete set of CSTD performance data, please see Tables 2 and 3. Data are presented in the same format as that of NIOSH for ease of comparison, although operations for the data presented were performed according to IFU. As can be seen from the data, there is a good correlation between our test data and that obtained by the original researchers, although for some CSTDs, the IPA values are lower when IFU conditions are used. The data follow the same trends for similar devices. In contrast to NIOSH, we have published the names of the CSTD devices tested.

However, in our study, only one of the four CSTDs tested by BSTL appears to meet the criteria required by the draft NIOSH protocol to achieve a PASS rating. This is not unsurprising given that most plastic or polymer materials are generally porous to gas/vapour down at the low levels being measured in the study. This is further supported by the measurements made using the higher sensitivity ppbRAE detector, which was not available to the researchers from NIOSH. The ppbRAE detector reveals levels of IPA vapour which would otherwise sit beneath the level of detection of the MIRAN detector and be assigned a 'below detection limit' reading. When using a more sensitive detector such as the ppbRAE, we have demonstrated that there is clear evidence of IPA vapour release from even the best performing CSTD systems. Effectively all CSTD systems tested leaked IPA vapour albeit at IPA vapour concentration readings of sub ppm levels. Good agreement is shown consistently in our study between the ppbRAE IPA readings and those obtained from using the MIRAN

detector. This further increases our confidence in the data for IPA vapour release obtained throughout the testing of CSTD systems.

Further studies (full set of CSTD performance data not shown) revealed that when the surrogate was changed to a 1% v/v solution of IPA in water for infusion (which is more representative of an actual clinically relevant hazardous drug concentration), the air filtration CSTD system tested (Tevadaptor®) was able to satisfy the PASS criteria as set by NIOSH of <1ppm release of IPA vapour. The testing was again performed under IFU conditions rather than the generic NIOSH conditions for use of the medical devices. We would however, recommend adoption of a different chemical surrogate to better represent the hazardous drugs for evaluating closed system devices, and consideration should be given to a compound that is much less volatile than IPA (vapour pressure of 4400 Pa at room temperature) and more representative of an actual drug substance. Possible candidates are plentiful and some that show promise include: benzoic acid; glycerol, cinnamaldehyde and 2-Phenoxyethanol (POE). All of these materials have suitable vapour pressures, for example POE has a vapour pressure of 1.0 Pa at room temperature. This vapour pressure is three orders of magnitude higher than that of the most volatile hazardous drug, an example of which is carmustine, and so measurements made with these substances provide a degree of safety. Very little empirical data has been obtained and published on the vapour pressures of actual hazardous drugs, but what does exist shows values that are in the range of 1.4 mPa to 19 mPa (carmustine) recorded at 20°C.[10] For comparison, pure IPA liquid has a vapour pressure roughly six orders of magnitude higher than that of carmustine which is one of the more volatile hazardous drug substances.

A full disclosure of experimental details and results from the studies described above and performed by BSTL under both the original NIOSH and NIOSH IFU conditions can be found in a HSL report submitted through the docket web portal for invitation to comment set up by NIOSH as part of the discussion process for the test protocol for mechanically closed CSTDs.[5,11]

The work presented here was the subject of an invited presentation given to the United Kingdom National Health Service (NHS) Quality Assurance Committee Research and Development Group in April 2016.[12] ●

Key Points

- A revised protocol is proposed for assessment of both mechanically closed and air filtration based closed system transfer devices.
- It is proposed that the chemical surrogate selected to represent a hazardous drug (HD) should be used at a clinically relevant concentration and be representative of a HD in terms of vapour pressure, and ideally something not ubiquitous in the environment to avoid cross contamination.
- We recommend that a closed loop system should be considered as an alternative method of operating the test system. This could enable a quantitative assessment of total IPA vapour release from the CSTD under test.
- It is recommended that an approved test laboratory should undertake the testing of CSTD systems rather than this be performed in house within a hospital pharmacy setting.
- We suggest that, wherever possible the individual medical device manufacturer's instructions for use (IFU) should be followed when manipulating the CSTD system. This is based on the findings that by following the generic instructions for use issued by NIOSH in the draft protocol, the CSTD operation may be compromised leading to false positive results.
- All CSTD systems that were tested in this study appear to leak IPA vapour to some extent when operated under the NIOSH conditions according to tasks 1 and 2.

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11. Comment on the Centers for Disease Control and Prevention (CDC) Notice: Request for information on development of a performance test protocol for closed system transfer devices that incorporate air-cleaning technology to provide worker protection during pharmacy compounding and administration of hazardous drugs. Regulations.Gov portal Docket for 030816 Docket No. CDC-2015-0075 NIOSH-Teva response to request for information. www.regulations.gov/#!documentDetail;D=CDC-2015-0075-0028 (accessed May 2016).
12. The United Kingdom National Health Service (NHS) Quality Assurance Committee Research and Development Group invited BSTL to presents its findings on the assessment of CSTD systems for vapour containment in April 2016. This was a private closed meeting.