Dispelling the myth of plunger rod contamination during hazardous drug preparation

BD Plastipak™ Syringes and portfolio of BD PhaSeal™ Closed System Drug Transfer Devices help ensure a leakproof and airtight transfer of hazardous drugs without syringe plunger-rod contamination

Working with antineoplastic drugs poses a risk for healthcare workers because of the potential for hazardous chemical exposure or contamination of the work surface, according to the National Institute for Occupational Safety and Health (NIOSH).[1] Drug exposure can occur by inhalation, ingestion or dermal absorption when compounding or administering drugs or when cleaning up spills. NIOSH also warns that serious health effects from hazardous drug (HD) exposure include infertility, miscarriage, birth defects and even cancer.[1] Therefore, using closed system drug transfer devices (CSTDs) to reduce contamination of work environments and potential exposure has become the recommended practice during preparation and is required for administration of HDs.[2]

Studies

According to a number of studies[3-8] the BD PhaSeal™ Portfolio of CSTDs has been shown to reduce surface contamination by HDs (e.g., cyclophosphamide, ifosfamide, and 5-fluorouracil) when compared with standard drug preparation techniques without the use of CSTDs. The BD PhaSeal™ Optima System, built on the foundation of the BD PhaSeal™ System, retains the architecture of the BD PhaSeal™ System and utilizes the same physical barrier technology to prevent exposure — a vapor-capturing mechanism in the protector component that is assembled to the vial, and membrane-to-membrane connections that self-seal upon disconnect to enable airtight, leakproof transfers.[3-8]

In 2015, NIOSH developed a draft laboratory vapor containment performance test protocol to test whether CSTDs adequately restrict drugs from crossing the boundary of the system and escaping into the surrounding environment.[9] Most CSTD systems in use in the U.S. require a syringe for HD preparation.[10] The draft NIOSH vapor containment protocol tested CSTDs that use standard syringes and detected no contamination released from the system.[9] In contrast to results from the draft NIOSH vapor containment protocol, Smith and Szlaczky published a study in which they have presented that the use of a syringe (e.g., BD Plastipak™) is not safe and that its plunger rod can become contaminated during HD transfer.[11] The questions raised by their methods are outlined in the next paragraph, and independent experimental evidence demonstrating no detectable contamination of the syringe plunger rods is provided. In addition, the design of the BD Plastipak™ Syringe to prevent plunger-rod contamination is reviewed.[12-15]

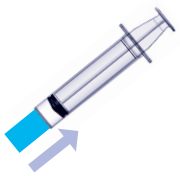
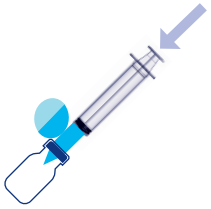
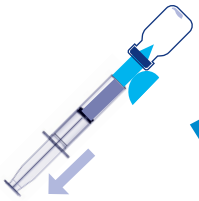
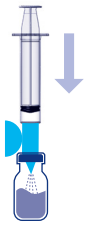
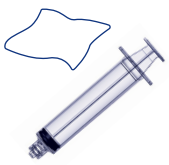
Flawed statistical analysis and assumptions

Smith and Szlaczky published their report on plunger-rod contamination before an independent and scientifically sound protocol for detecting contamination from CSTDs had been released by NIOSH. The study design used by Smith and Szlaczky is inconsistent with clinical practice and does not contain the typical level of scientific rigor for this type of evaluation. First, they used a "pump-action" protocol, in which 50 mL of substance was drawn into the syringe and injected back into the vial 2 to 8 times. This pump-action method is not common practice because the repetition of pumping could lead to compromised aseptic technique, ultimately causing the syringe to fail and increasing the risk for plunger-rod contamination.[12] The Smith and Szlaczky study also did not contain the expected positive or negative controls or positive recovery controls, which prevented the study design from determining whether laboratory errors were made.[13] Also, the likelihood that 1 of the 12 syringes would have no contamination, while 11 of the 12 had an average of 1622 ng, calls into question their results.[13] There is a 1-in-10-million probability that the results presented would be found, which suggests that their statistical analyses, as well as their methods, were flawed.

The small sample size has been called into question, along with the unequal distribution of test devices (n=12 for BD; n=11 for comparator), with no explanation for this difference offered.[13]

Figure 1. Experimental design replicated by BD and The Ohio State University. The protocol used by The Ohio State University was a slight modification of that developed by Smith and Szlaczky and included positive and negative controls to add scientific rigor to the protocol.

Cyclophosphamide vials were reconstituted by using 0.9% NaCl.[15]

1	Air was drawn into BD Plastipak™ Syringes (n=12). Injectors[a] were connected.	
2	Vial protectors[b] were placed on the drug vials by using a BD PhaSeal™ Assembly Press.	
3	Syringes were connected to the protector, and air was injected into the vials (expansion chamber inflation).	
4	A 50 mL aliquot of cyclophosphamide was *withdrawn* from each vial. Air bubbles were removed.	
5	With the syringe and vial in a vertical position (upright on the table), the entire aliquot of the drug was *returned* to each vial.	
6	The plunger rods were wiped for drug contamination by using a wipe kit and analyzed by a ChemoGLO™ reference laboratory.	

Experimental evidence

Two separate replicate studies, one by BD and one by an independent third party, investigated whether the BD Plastipak™ Syringe plunger rods would become contaminated during HD preparation.[14,15] The protocol used in the BD replicate study[14] was identical to that of the Smith and Szlaczky protocol.[13] The design of the independent Ohio State University Wexner Medical Center study was modified slightly by including positive and negative controls to improve study reliability (**Fig. 1**).[15]

In brief, twelve syringes were divided into three groups of four each, and each group underwent either two, four or eight withdrawal-return cycles of 50-mL aliquots of cyclophosphamide (*NDC 10019-0956-01; Baxter International Inc; Deerfield, Illinois*) in 0.9% NaCl. After each syringe went through the cycle, the plunger was wiped by using a wipe kit (*ChemoGLO™; ChemoGLO, LLC; Chapel Hill, North Carolina*). Wipes were evaluated for drug contamination by using liquid chromatography tandem mass spectrometry (LC-MS/MS).

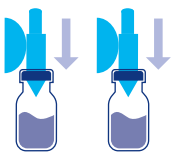
These replication studies demonstrate that the syringe plunger rods would not be contaminated by an HD such as cyclophosphamide, even under the harsh and unrealistic testing conditions.

TWO
withdrawal-return cycles per syringe

(n=4 syringes per vial)

FOUR
withdrawal-return cycles per syringe

(n=4 syringes per vial)



EIGHT
withdrawal-return cycles per syringe

(n=4 syringes per vial)

[a]BD PhaSeal™ N35 Injector, [b]PhaSeal™ P50 Protector (*BD; Franklin Lakes, New Jersey*)

Table 1: Replication studies: amounts of cyclophosphamide found on syringe plungers, work surface, vials and controls[14,15]

Cyclophosphamide concentration in nanograms per square foot (*nanograms per square centimeter*)		
Location	**BD replicate study**	**The Ohio State University study**
Positive control[a]	N/A	>4,000 (*>4.31*)
Negative control[b] Additional controls: wipes from the work surface before and after (n=2) experiment; cyclophosphamide vials (n=4)	N/A	 Nondetectable on all syringes, work surfaces, vials and negative controls
Syringes: two withdrawal-return cycles (n=4 syringes)	 Nondetectable on all syringes	
Syringes: four withdrawal-return cycles (n=4 syringes)		
Syringes: eight withdrawal-return cycles (n=4 syringes)		

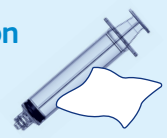
[a]Use of one wipe saturated with drug. [b]Use of one unadulterated wipe. N/A = not applicable

Neither the BD replicate study nor The Ohio State University study found syringe plunger-rod contamination (**Table 1**).[14,15]

In The Ohio State University study, the positive control flooded the analyzer and caused false-positive results. As a result, samples were reanalyzed, and the limit of quantification (LOQ) was increased (from 10 ng/ft^2 in the Smith and Szlaczky study to 150 ng/ft^2). At this LOQ, no samples had a detectable level of contaminant.

Figure 2: Amount of 5-fluorouracil or cyclophosphamide found on syringe plungers.[16]

	BD Plastipak™ Syringe + BD PhaSeal™ System	BD Plastipak™ Syringe + BD PhaSeal™ System
Drugs	5-fluorouracil (2.5 g/50 mL)	Cyclophosphamide (1 g/50 mL)
Number of vials[a]	10 	10 
No. of replicate procedures and wipe tests[a]	10 	10 

No contamination detected in any of 20 wipe tests 

[a]A separate syringe and wipe was used for each replicate.

Even at the increased LOQ, if the contamination reported by Smith and Szlaczky had been present, it would have been detected. Furthermore, the multiple withdrawal-return cycles simulating reuse of the syringe in both studies would have resulted in a higher likelihood of contamination, as compared with the real-life practice of using syringes a single time.

It is also important to note that all manipulations in these studies were performed by technicians with training who used appropriate aseptic technique. To minimize error and potential cross-contamination, gloves were changed between each step of the studies.[14,15] These replication studies demonstrate that the syringe plunger rods would not be contaminated by an HD such as cyclophosphamide, even under the harsh and unrealistic testing conditions.

In an additional BD multi-drug study similar to those just described, BD Plastipak™ Syringe plunger rods were evaluated for contamination during HD transfer.[16] Simulations were conducted on preparations of cyclophosphamide and 5-fluorouracil in which syringes were used in conjunction with the BD PhaSeal™ System as a representative CSTD.

In brief, the entire (50-mL) content of a single vial was withdrawn from each syringe to maximize the surface area of internal barrel and plunger-rod exposure to simulate the worst-case scenario (**Fig. 2**).

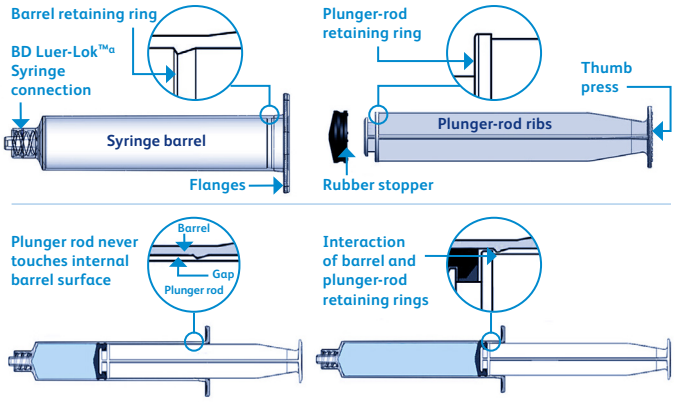
After withdrawal, liquid was returned to the vial, withdrawn again and then wiped by using a wipe kit. Samples were analyzed by a ChemoGLO™ reference laboratory. The lack of detectable contamination by either 5-fluorouracil or cyclophosphamide further supports the established safety and reliability of BD Plastipak™ Syringes and BD PhaSeal™ device.

Anatomy of the BD Plastipak™ Syringe

The design of the BD Plastipak™ Syringe (**Fig. 3**) plays an important role in syringe performance with or without the BD PhaSeal™ System. The BD Plastipak™ Syringe contains a retaining ring in the internal barrel surface that by design prevents contact of the plunger rod with the syringe's internal barrel surface to prevent drug transfer or contamination.[13,14]

On the basis of the syringe design, shown in Figure 3, the design minimizes risk of the plunger rod being pulled out beyond the syringe's normal volume marking and also minimizes the risk of the ribs of the plunger rod touching the internal barrel surface during the withdrawal. Thus, the features of the ring design should mechanically assist in prohibiting contamination in the Smith and Szlaczky study. This design supports the findings that the BD Plastipak™ Syringe continues to be an effective solution when working when working with HDs.

Figure 3: *Top:* magnification of the barrel and plunger-rod retaining rings, the key parts of the BD Plastipak™ Syringe. *Bottom left:* cross-section magnification of the retaining ring. *Bottom right:* cross-section magnification of the barrel and plunger-rod retaining rings during maximum withdrawal.[16]



[a]BD Luer-Lok™ 1-mL Syringe *(BD; Franklin Lakes, New Jersey)*.

Conclusion

Working with HDs is dangerous, the BD Plastipak™ Syringe and BD PhaSeal™ Optima System by design, helps prevent contamination thereby protecting healthcare workers from risks of hazardous drug exposure.[14] The methods used in the refuted study that claims that the syringe is unsafe because the exposed plunger rod can become contaminated with HDs have been found to be flawed.[12]

No contamination of syringe plunger rods was found when replicating the Smith and Szlaczky study[14,15] by using proper controls and aseptic technique. The BD multi-drug study involving the transfer of HDs 5-fluorouracil and cyclophosphamide by using the syringe with the CSTD also found no plunger-rod contamination.[16]

Independent of these findings, it must be noted that the performance and effectiveness of a CSTD do not rely exclusively on protection from plunger-rod contamination. NIOSH developed a draft protocol using 70% isopropyl alcohol (IPA) vapor to test the effectiveness of a CSTD in vapor containment. The BD PhaSeal™ System was one of the two systems (of six tested) that adequately contained vapors and remained closed during both compounding and administration with IPA.[17,18] Therefore, the myth of plunger-rod contamination during HD preparation is a distraction from the true performance of CSTDs.

In summary, the specific design of the BD Plastipak™ Syringe helps prevent contamination of the plunger rod[14] and further supports the evidence that the syringe is an effective solution when working with HDs. The BD Plastipak™ Syringe and BD PhaSeal™ Optima System are important tools for safe handling of HDs and may help reduce potential exposure to potentially harmful chemical substances.

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