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Special Topic Commentary

Challenges of Using Closed System Transfer Devices With Biological Drug Products: An Industry Perspective



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ABSTRACT

Hazardous drug is a common term used by the National Institute of Occupational Health and Safety (NIOSH) to classify medications that may induce adverse mutagenic and reproductive responses in health care personnel. NIOSH publishes a list of drugs it defines as hazardous where it may be appropriate for health care workers to take protective measures to reduce the potential for occupational exposure. Recent updates and proposed updates to this list have included large molecule biological products with oncology indications. Both NIOSH and USP <800> recommend the use of closed system transfer devices (CSTDs) during compounding. CSTDs are required for administration of prepared solution in NIOSH. However, USP has suggested that the principles of <800> are broadly applicable to hazardous drug handling activities across all facility types. USP encourages the widespread adoption and use of <800> across all health care settings, which many health care workers have interpreted beyond compounding to include administration and preparation of conventionally manufactured sterile products per approved labeling. Although the use of CSTDs may reduce exposure of health care personnel to chemotherapy agents in health care setting, the impact of CSTDs on quality of biologic drug products, including monoclonal antibodies and other proteins, is not fully understood. To complicate this issue further, there are several commercially available CSTDs in the market which have different fluid paths and material of construction that comes in contact with the drug. Testing every combination of CSTD and drug product for potential incompatibilities can be a labor intensive and impractical approach and cause delay in getting essential drugs to patients. A panel discussion was held at a recent American Association of Pharmaceutical Scientists 2018 PharmSci 360 conference to discuss the impact of CSTDs on biologics. Impact on subvisible and visible particulates and impact to other product quality attributes such as high molecular weight species formation upon contact with CSTDs were reported in American Association of Pharmaceutical Scientists meeting. Impact to deliverable dose, holdup volumes of various CSTDs, and stopper coring were also reported that has significant impact to patient safety. Given the fact that USP chapter <800> will be implemented in December 2019, feedback from health authorities regarding the use of CSTDs for biological drug products is needed to provide an appropriate risk/benefit balance to ensure patient safety and quality of the biologic drug product while also protecting the health care worker and the environment. The purpose of this commentary is to provide an industry perspective on the challenges during the use of CSTDs for biologic drug products and is intended to raise caution and awareness on the benefits and shortcomings of these devices.

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Introduction

Antineoplastic agents are a big part of the arsenal in oncology. There has been a surge in the use of these antineoplastic agents and the demand is only likely to grow in the near future. Small molecule

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antineoplastic agents are typically used as a treatment regimen in many therapies and are usually the primary standard of care. Small molecule antineoplastic agents are typically indiscriminate in their action and toxic to both cancerous as well as healthy cells. However, recently with the advent of biotechnology and bioengineering a series of directed antineoplastic agents have been approved for many cancer indications. These products, mostly monoclonal antibodies (mAbs), are large molecule protein therapeutics that specifically target cancer cells, yet are bucketed as antineoplastic agents along with their small molecule counterparts.

Health care personnel are an integral part of the health care industry who may handle many antineoplastic agents in a hospital or a pharmacy setting. Given the undifferentiating nature of the small molecule antineoplastics, it is imperative to prevent exposure to health care personnel who prepare and help administer therapeutic agents to patients. Hazardous drug is a common term used by the National Institute of Occupational Health and Safety (NIOSH) to classify medications that may induce adverse mutagenic and reproductive responses in health care personnel.¹ Thus, several guidelines have been established for proper handling of drugs that have been classified as hazardous by NIOSH. Various recommendations are in place for biological monitoring as well as environmental monitoring of these hazardous drugs for the safety of the health care personnel. In addition to monitoring requirements, several studies have called for secondary engineering controls to help safeguard the health of personnel in addition to the use of personal protective equipment (PPEs). One such engineering control is the use of closed system transfer devices (CSTDs).

CSTDs have been recommended for compounding and administration of hazardous drugs in guidelines published by NIOSH (NIOSH, 2016).¹ A CSTD is defined as “a drug transfer device that mechanically prohibits the transfer of environmental contaminants into the system and the escape of hazardous drug or vapor concentrations outside the system.” CSTDs are not meant to be a substitute for ventilated cabinets and proper PPE needs to be worn.² U.S. Pharmacopeia (USP) sets the standards for quality and purity of medications and most state pharmacy boards use USP sterile compounding guidelines as the benchmark for best practice. USP chapter <797> first published in 2004 and will be updated in 2019 covered sterile compounding and the update in 2008 described the use of hazardous drugs.³ In addition, a new chapter USP <800>, defining hazardous drug handling requirements, will be implemented in December 2019.⁴ Listed supplemental engineering controls in USP <800> states “CSTDs should be used when compounding hazardous drugs when the dosage form allows” and “CSTDs must be used when administering antineoplastic hazardous drugs when the dosage form allows.” Unlike previous guidelines from NIOSH and other agencies, USP <800> may be enforced by each state’s Board of Pharmacy, their delegated agency, and federal regulators indicating that this chapter could be the single most significant change for health care personnel in the oncology and non oncology space in the United States.

Several studies have shown that the proper use of CSTDs led to reduced occupational exposure of certain hazardous drugs in health care professionals.⁵ Although there has been much focus on the performance standard of CSTDs in the context of drug containment and health care personnel safety, there is a dearth of literature on the compatibility of these devices with biological drug products such as mAbs and their primary packaging components.

Meade⁶ has discussed the use of CSTDs for safe preparation of mAbs and has emphasized the importance of aseptic techniques, PPE, and training. Issues with stoppers, especially stoppers being pushed in for vials containing lyophilized formulations, were also noted as a challenge. A recent report by Zhao et al.⁷ emphasized the need for device and drug developers to properly select and test

stoppers and containers with intended spikes to prevent stopper push in from occurring. Petoskey et al.⁸ recently reported the complexities of CSTDs, especially in terms of lubricants, with an antibody drug conjugate. They report that care should be taken with proper studies to ensure that lubricants and other potential leachables/extractables are not introduced in the drug product by these devices.

Studies encouraging the use of CSTDs for preserving leftover drug product with the intent of using the remainder for an additional round of therapy have also been reported recently.^{9,10} This practice, known as drug vial optimization, assumes that CSTDs do not allow any bacteria or particulate matter into the system during compounding. Ho et al.¹¹ have reported the use of PhaSeal CSTD for potentially extending sterility of unpreserved injectable solutions. However, CSTDs are not qualified to maintain sterility of a used drug product vial and any off label use of these devices carries the risk of microbial growth. Edwards et al.¹² recently reported on the increased cost savings when using the PhaSeal CSTD for preparation of antineoplastic agents. These cost savings were realized due to the use of CSTD in extending the beyond use date of single use vials. Although the cost savings appear prominent, the impact of drug vial optimization on product quality of biologics, especially mAbs, has not been evaluated. It is possible that the active biologic could degrade or potentially form soluble aggregates if the leftover drug product is in contact with the CSTD. The degraded product containing proteinaceous or increased subvisible particles may cause unwanted immunogenicity, thereby increasing risk to the patients.

Given the limited experience with biological drug products, a hot topic and panel discussion around the use of CSTDs for biologics was held at the American Association of Pharmaceutical Scientists 2018 PharmSci 360 conference (November 4-7, 2018, in Washington DC) as a part of the Formulation and Quality track. The panel discussion engaged various company representatives to share their experience and challenges with the use of CSTDs in the United States and globally. This commentary provides an industry perspective on the challenges during the use of CSTDs for biologic drug products and is intended to raise caution and awareness on the benefits and shortcomings of these devices.

Components and Material of Construction for CSTDs

PhaSeal from BD Medical was the first CSTD approved by the US Food and Drug Administration (FDA) in 1998. Since then several CSTDs have been approved for use in the United States that include but not limited to Texium (BD Carefusion, Franklin Lakes, NJ), OnGuard Tevadaptor (B. Braun Medical, Melsungen, Germany), Equashield (Equashield, New York, NY), and ChemoLock/Chemo Clave (ICU Medical, San Clemente, CA). Although the primary purpose of CSTDs is to prevent the escape of hazardous drug or vapor concentrations outside the system, different CSTDs have multiple components and a diverse range of materials of construction. Table 1 lists the basic components of CSTDs, their intended function, and material composition of the fluid path based on information received from vendors. Consequently, based on the CSTD types used, drug solution (or suspension) may be exposed to a wide variety of material types across the fluid path.

Challenges Around Use of CSTDs During Drug Product Development

Impact on Visible and Subvisible Particles

Both extrinsic and intrinsic particles are a significant challenge for biological drug products and have been the topic of discussion in the past several years.¹³⁻¹⁵ Given the heightened awareness

Table 1
Components of Different CSTDs and Material Composition of Fluid Path

Major Components of CSTD	Functional Property	Material Composition of the Fluid Path (Based on CSTD Samples Available in the Market) ^a
Vial adaptor or vial access device	<ul style="list-style-type: none"> Sits on the vial containing drug Connects with the syringe safety device establishing link between syringe and vial Available in 2 different designs: vented and unvented 	<ul style="list-style-type: none"> CSTD-1: PP (polypropylene), PTFE (polytetrafluoroethylene), SS (stainless steel), and TPE (thermoplastic elastomer) CSTD-2: ABS (acrylonitrile-butadiene-styrene), polyisoprene, PC (polycarbonate), DEHP-free PVC (polyvinyl chloride) CSTD-3: PP, PTFE, TPE, SS CSTD-4: Acrylic, PC, silicone CSTD-5: PP, silicone CSTD-6: ABS, acrylic, copolyester, PC, PVC, PTFE, silicone CSTD-7: Copolyester, PC, silicone
Syringe safety device	<ul style="list-style-type: none"> Sits on the syringe to be used for dose withdrawal Connects with vial adaptor establishing link between vial and syringe 	<ul style="list-style-type: none"> CSTD-1: ABS, acrylic, PP, PVC, silicone, SS, TPE CSTD-2: ABS, PC, polyisoprene, DEHP-free PVC CSTD-3: PP, silicone, SS, TPE CSTD-4: PC, PP, silicone, TPE CSTD-5: Polyisoprene, silicone, SS, PP CSTD-6: Blue 278, silicone, PC CSTD-7: PC, silicone, SS
IV bag/line access device	<ul style="list-style-type: none"> Establishes connection between IV bag and syringe containing the drug 	<ul style="list-style-type: none"> CSTD-1: PP, TPE CSTD-2: ABS, PC, DEHP-free PVC CSTD-3: PP, TPE CSTD-4: ABS, PP, PVC, silicone CSTD-5: ABS, PVC CSTD-6: ABS, acrylic, blue 278, PC, PVC, silicone CSTD-7: ABS, acrylic, LDPE (low-density polyethylene), PC, PVC, silicone, SS

^a Not inclusive of all the CSTDs available in the market.

around particles, several commercially available CSTDs were tested using a buffer solution and the impact on visible particle counts was evaluated. The study was designed to evaluate the generation of stopper coring/fragmentation and the introduction of other extrinsic visible particles from CSTDs when withdrawing and reconstituting drug product. In order to detect visible particles in drug product vials at an incidence rate as low as 10% with 95% statistical confidence, forty 20 mm serum stoppered vials and forty 20 mm lyophilization type stoppered vials were prepared for each

CSTD ($n = 80$ vials per CSTD). The 20 cc Type I borosilicate glass vials were filled with buffer and then stoppered and capped under aseptic and particle free conditions. Nine commercially available CSTDs and needle free devices from the 5 vendors were used for this assessment. The solution was withdrawn from each vial using CSTD vial spikes and associated components or 20 mL syringe/21G needle as control. The withdrawn solution was reinjected into the vial slowly. The CSTD vial spike remained attached to the vials to avoid the generation of additional particles in the solution. The vials

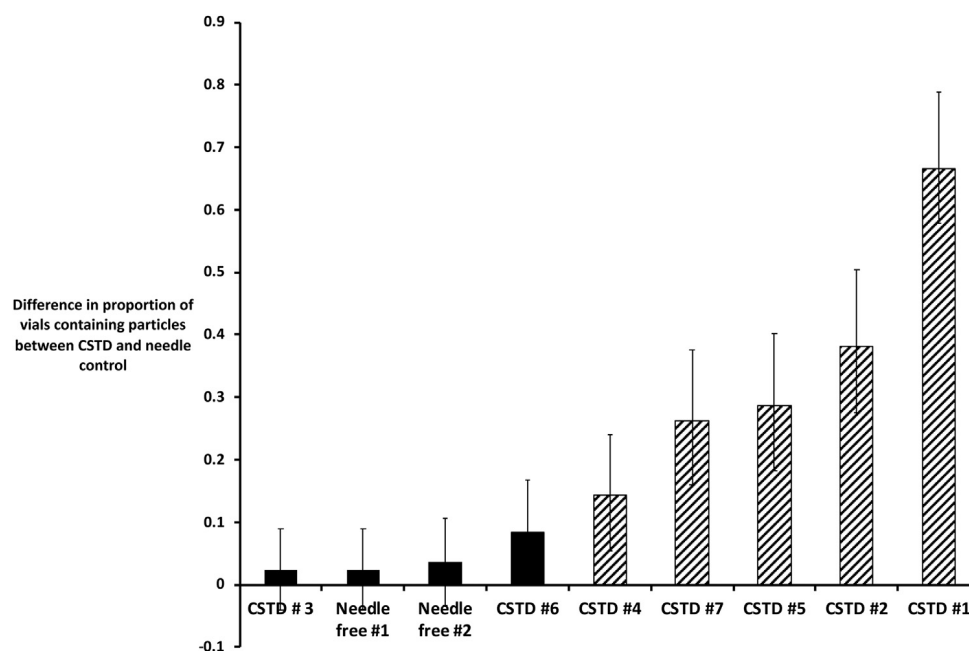


Figure 1. Difference in proportion of vials containing visible extrinsic particles between CSTD and needle control using buffer vials prepared with several commercially available CSTDs or needle-free devices or needle control. Proportion is calculated as number of vials with corresponding CSTD containing at least 1 visible particle/total number of vials tested ($n = 80$). Error bars represent 95% confidence interval. Black bars indicate data comparable to 21G needle controls; dashed bars indicate statistically significant higher rate of vials containing visible particles when compared to 21G needle control. Note: CSTD numbering in this figure is not relevant to Table 1 or Figure 4.

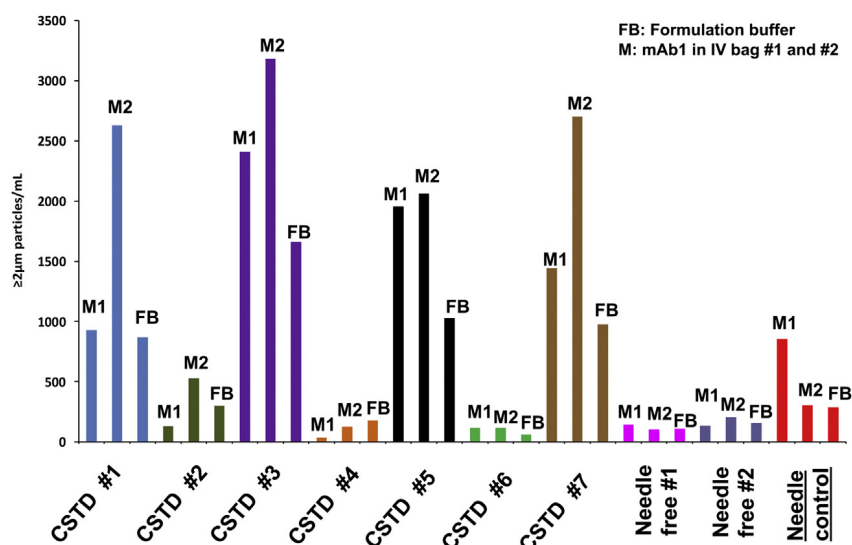


Figure 2. Number of subvisible particles ($\geq 2 \mu\text{m/mL}$) in buffer and mAb1 formulation after dilution into 0.9% sodium chloride IV bags, storage for 24 h at 30°C, followed by simulated infusion using CSTDs, needle-free devices, or 21G needle control. Note: Method of dose preparation for mAb1 in IV bag #1 and #2 and formulation buffer in IV bag is specified in Figure 2 as M1, M2, and FB respectively for CSTD #1 to #7, needle-free devices, and needle control. CSTD numbering in this figure is not relevant to Table 1 or Figure 4.

were visually inspected using USP/Ph. Eur. method (light box with white/black background). The proportion of vials containing visible particles was calculated for each CSTD, and the difference in this proportion between each CSTD and the 20 mL syringe/21G needle control was calculated using the Agresti Caffo method.¹⁶

As shown in Figure 1, 5 CSTDs had a higher number of vials containing extrinsic visible particles as compared to the conventionally prepared syringe and needle control. This difference was found to be statistically significant using the Agresti Caffo method. Particles were identified as rubber stopper, CSTD related material of construction (e.g., silicone and polyethylene), and silicone oil-related lubricants.

Subvisible Particle Analysis

Subvisible particle analysis using light obscuration was also performed for a buffer solution and a monoclonal antibody (mAb1) liquid formulation drug product vials after preparation and dilution into 0.9% sodium chloride intravenous (IV) bags using 9 commercially available CSTDs and needle free devices. In this study, the mAb1 drug product vials were diluted into 0.9% sodium chloride IV bags using commercially available CSTDs or needle

free devices or were conventionally prepared using 20 mL syringe and 21G needle as control. The IV bags were stored for 24 h at 30°C, simulating the potential in use hold time after preparation, followed by simulated infusion mimicking an infusion setup for a patient. No in line filter was used during simulated infusion. Subvisible particle analysis was performed post simulated infusion. A similar preparation was performed for vials filled with buffer as a control to assess extrinsic particles introduced with the use of CSTDs. As shown in Figure 2, slight increase in levels of $\geq 2 \mu\text{m}$ particles were observed in several CSTDs for both the buffer and the mAb1 formulations post dilution, storage followed by simulated infusion. The 4 CSTDs (CSTD #1, 3, 5, and 7) with slightly higher subvisible particles have been found to contain higher levels of silicone oil or related compounds in studies with buffer vials (data not shown); therefore, it is likely that the subvisible particles in mAb1 formulation are contribution from silicone oil-related droplets and presence of protein particles. Minimal to no change in ≥ 10 and $\geq 25 \mu\text{m}$ particles were observed relative to control samples for both buffer and mAb formulations. Moreover, different CSTDs from the same brand showed variability in the subvisible particle levels during this study.

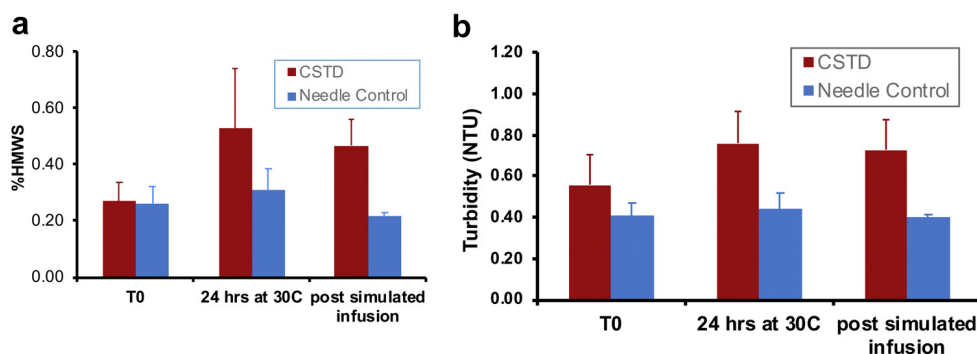


Figure 3. (a) High molecular weight species (HMWS) in mAb1 using size-exclusion chromatography after dilution into 0.9% sodium chloride IV bags by CSTD #1 or needle control (average + standard deviation was determined as follows: for IV bags prepared using CSTD #1, $n = 9$ IV bags for T0 post dilution and T24 h storage at 30°C samples; $n = 10$ IV bags for post simulated infusion samples; for needle control, $n = 5$ IV bags for T0 post dilution, T24 h storage at 30°C, and post simulated infusion). (b) Clarity and opalescence measurements by turbidimeter after dilution into 0.9% sodium chloride IV bag by CSTD #1 or needle control (average + standard deviation was determined as follows: for IV bags prepared using CSTD #1, $n = 9$ IV bags for T0 post dilution and T24 h storage at 30°C samples; $n = 10$ IV bags for post simulated infusion samples; for needle control, $n = 5$ IV bags for T0 post dilution, T24 h storage at 30°C, and post simulated infusion).

Table 2
Visible Proteinaceous Particles in 0.9% Sodium Chloride IV Bags Using mAb1 Formulation Prepared With CSTD #1 From Figures 1 and 2

IV Bags Prepared by CSTD	T0 (Post Dilution)	T24 (Post Storage at 30°C)	Post Simulated Infusion Without In-Line Filter
Number of IV bags with visible proteinaceous particles	9 out of 10	8 out of 10	4 out of 10

Impact of Other Product Quality Attributes

The diluted mAb1 samples in IV bags prepared as described in the section “Impact on Visible and Subvisible Particles” for sub visible particle analysis was further investigated for impact to other product quality attributes including high molecular weight species by size exclusion chromatography, clarity, and opalescence measurements by turbidimeter and visible particles. Samples were taken at T0 (post dilution), post 24 h storage at 30°C, and post simulated infusion. No product quality impact was observed for commercially available CSTDs and needle free devices except CSTD #1. Figure 3a clearly demonstrates that mAb1 formulation has higher amounts of soluble high molecular weight species when prepared with CSTD #1 as compared to the conventionally prepared syringe and needle control. Slight changes in clarity and opalescence were also noticed for these samples as shown in Figure 3b. In addition, visible particles were observed in IV bags when prepared with CSTD #1 (Table 2). The particles were identified as proteinaceous particles.

Impact on Deliverable Dose and Holdup Volume

For those cases where a health care personnel decides to use a CSTD to prepare and administer an FDA approved drug product, the design of certain brands of CSTDs could result in large holdup volumes that prevent the prescribed dose, that is, the dose according to the manufacturer’s label, from being delivered to the patient. The holdup volume is dependent on the geometry of CSTD construction, which varies among different brands. As shown in Figure 4, certain brands of CSTDs have holdup volumes as high as 1.0 mL. Some biologics for oncology indications are low volume vial presentations and the use of a CSTD vial adaptor with a large holdup volume may result in an insufficient amount of drug product being transferred for parenteral administration. Furthermore, highly potent biological drugs for oncology indications are typically administered at low concentrations thereby increasing the risk of adsorptive protein losses due to contact with the CSTD surfaces.¹⁷ Current DP vial configurations and fill volume ensure accurate dosing (without the use of CSTDs), however with some CSTDs there could be a risk of under dosing or incorrect dosing of biologic drugs if pharmacists used those CSTDs for drugs required by USP <800>.

Mitigation strategies to overcome holdup volume challenges include using additional drug product containers for clinical dose preparation. This strategy necessitates using more drug product to administer the prescribed dose if CSTDs are used during preparation which in turn could drive up the costs of biologic drugs. Another option would be to optimize vial configurations and fill volumes to overcome the holdup volume challenges on account of CSTD use. However, given the unspecified and nonstandardized differences in extractable volume and holdup volume for an individual CSTD, it is not feasible to come up with a drug product vial configuration that would support label claim with all available CSTDs. Furthermore, the excess volume in a drug product vial required to compensate for CSTD usage may be higher than the recommended excess volumes as per USP <1151>¹⁸ and the FDA guidance on allowable excess volume and labeled vial fill size in injectable drug and biological products.¹⁹

Challenges Around Use of CSTDs Observed at Clinical Sites

Several compatibility issues were noticed during drug product development studies as presented in the section “Challenges Around Use of CSTDs During Drug Product Development.” However, these challenges were not limited only to laboratory studies but rather observed at various clinical sites as well.

An investigation was conducted to identify particulate matter visually observed in 2 reconstituted investigational drug product vials. The vials had been reconstituted by pharmacists at a clinical trial site using a CSTD and had been rejected and returned to the study sponsor for evaluation due to appearance of visual particulates. When the vials were received by the study sponsor, the vial adaptor from the CSTD system was still in place in the vial stoppers.

The vials were first examined using a Tyndall beam light source. Both vials appeared to be hazy when illuminated with the Tyndall light source. After allowing the particulate matter to settle to the bottom of the vials, the vials were examined by inverted light microscopy. A ring of particulate matter was present in both vials. When further examined, the particulate matter appeared as circular droplets (Fig. 5) which were not miscible with the aqueous formulation. The diameter of the droplets was measured to be approximately 60 µm.

An aliquot of the liquid droplets, which appeared to be oily in nature, was removed from the vial and was submitted for FTIR

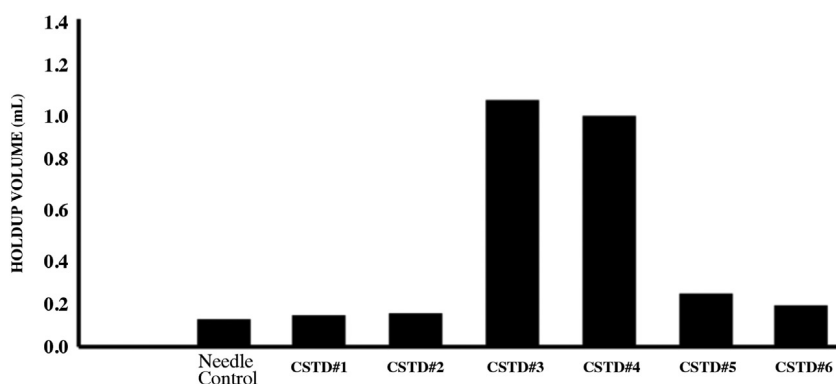


Figure 4. Holdup volumes of different CSTD brands. Holdup volumes were evaluated with sterile water for injection (data are an average of 3 readings).

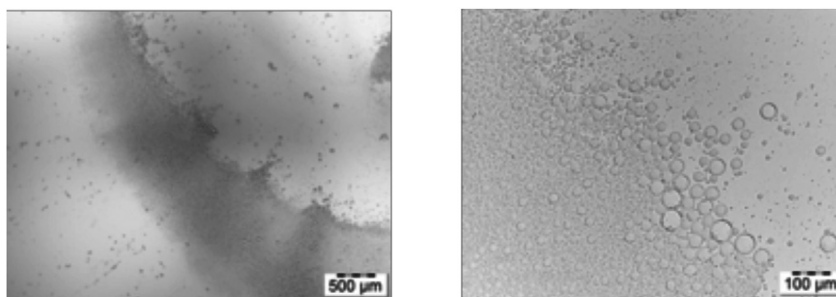


Figure 5. Representative photomicrographs of the settled particulate matter, observed in the 2 reconstituted vials as a result of using a CSTD vial adapter. The photomicrographs were taken *in situ* using a Nikon Eclipse Ti inverted light microscope in transmitted light mode (2× magnification [left] and 10× magnification [right]).

analysis. The plastic needle on the vial adapter (vial spike), the component of the CSTD in contact with the formulation, was examined using a stereomicroscope and showed the presence of an oily residue. A small quantity of the oily residue, likely lubrication to aid stopper puncture, was removed from the vial spike and submitted for FTIR analysis.

FTIR analysis undertaken on the droplets from the vial and the oily residue from the CSTD vial spike confirmed that their spectra (not shown) were consistent with each other and that of a reference spectrum for a common lubricant used in medical devices (not disclosed due to proprietary restriction). This indicates the source of the oily droplets observed inside the vial was the lubricant used on the CSTD vial spike.

Although the vast majority of the vials prepared at the clinical site using the same CSTD system did not contain visible particulates, the same phenomenon was observed on another occasion during dose preparation. This finding supports the conclusion that there is manufacturing variability in the amount of lubricant on the vial spikes for this CSTD system, which further contributes to the challenges of establishing compatibility with a given CSTD system.

Recent Change in Regulatory Landscape and Expectation Around the Use of CSTD

NIOSH of the Centers for Disease Control and Prevention publishes a list of drugs it defines as hazardous where it may be appropriate for health care workers to take protective measures to reduce the potential for occupational exposure. According to NIOSH a drug is considered hazardous if known to exhibit one of the following characteristics in humans and animals: carcinogenicity, teratogenicity (or any other developmental toxicity), genotoxicity, organ toxicity (at low doses), and reproductive toxicity.¹ Debate is ongoing regarding the risks and safety related concerns of environmental and handling exposure to large molecules, particularly those used for oncology applications, as they lack direct cytotoxic activity²⁰ and have minimal internalization from occupational exposure. The NIOSH list has traditionally included antineoplastic small molecules or cytotoxic antibody drug conjugates, but recent updates and proposed updates have included large molecule biological products with oncology indications. NIOSH also recommends use of CSTDs during compounding and administration of hazardous drugs. Although NIOSH has developed a unified CSTD test protocol to evaluate the performance of CSTD systems and their effectiveness,²¹ no emphasis has been given on the risks of potential drug product incompatibility with CSTD components.

The new USP General Chapter <800> states, “CSTDs should be used when compounding hazardous drugs when the dosage form allows. CSTDs must be used when administering antineoplastic hazardous drugs when the dosage form allows. CSTDs known to be physically or chemically incompatible with a specific hazardous

drug must not be used for that hazardous drug.” USP <800> is tied to the requirements for sterile compounding in USP <797>, making preparation of conventionally manufactured sterile products per approved labeling out of scope of USP <800>. However, it is likely that hospital pharmacies may plan to apply USP <800> to all sterile preparations of hazardous drugs whether they are compounded or conventionally manufactured to remain compliant with all USP pharmaceutical compounding compendia. In theory it is possible that CSTDs are not only used for hazardous drugs but could become common practice in hospitals to use these CSTDs for all oncology products, including those biologics which do not meet NIOSH criteria to be classified as hazardous.

The differentiation between compounding and preparation per approved manufacturer labeling by USP <797> and <800> creates additional confusion regarding how this chapter will be applied. Many requirements of USP <800> are related to aspects of hazardous drug control outside of preparation (receipt, storage, transport, administration, environmental monitoring, decontamination, cleaning, spill control, and waste disposal), so all hazardous drugs will likely be handled under USP <800> regardless if they are compounded or prepared per approved manufacturer labeling. USP <800> places the responsibility for assessment of risk and compliance with a “designated person” at each pharmacy, who ultimately determines which controls will be put in place for each hazardous drug. Hence, in order to assure compliance, requirements of an individual institution to use a CSTD during preparation may be more conservative than USP <800> recommends. This is particularly true in the area of investigational compounds which some facilities may designate as hazardous prior to generation of safety data.²² Some pharmacies are using CSTDs with the intent to prevent microbiological ingress during aseptic preparations,²³ even on nonhazardous compounds. As USP <797> and <800> technically do not apply to conventionally manufactured products, it is unclear how drug manufacturers can influence the use of CSTDs with investigational or commercial stage drugs that are assessed as hazardous by clinical sites.

USP <800> states that CSTDs should not be used if they are incompatible with the hazardous drug, however no guidance is provided for how or by whom an incompatibility is established, or what constitutes an incompatibility. Health care provider organizations typically use only 1 CSTD system in their facilities to streamline preparation, reduce errors, and to simplify ordering and inventory. This makes either restricting or requiring the use of a specific CSTD system due to compatibility concerns technically and logistically challenging.

The requirement for the use of a CSTD during administration of antineoplastic hazardous drugs is straightforward for intravenously administered products, and the value of protecting health care personnel who may be exposed to hazardous drugs outside of additional engineering controls is significant. The requirement is

less clear for antineoplastic medications intended for subcutaneous or intramuscular injection. At the time of writing this commentary, the USP <800> FAQ states that expelling air during syringe priming prior to injection does not need to follow all USP <800> containment requirements, but also states that CSTDs must be used for administration of antineoplastic hazardous drugs when the dosage form allows. Drug products intended for subcutaneous or intramuscular injection are limited in total injection volume, and therefore more likely to be impacted by the holdup volume of CSTDs and a potentially significant percentage of the dose may be lost. The functional relevance of a CSTD during administration of a subcutaneous or intramuscular injection is limited given the nature of an injection system, which must ultimately be open in order to provide an injection through a needle.

The lack of clarity regarding how and when requirements to use CSTDs will be implemented, and the likelihood that the requirements will be interpreted differently by different health care personnel, states, and other regulators make it challenging for drug manufacturers to anticipate how their products will be handled, to understand how compatibility with CSTDs should be established, or to place limits around the application of CSTDs to their products.

Recommendations From Panel Discussion

Participants from several biotechnology companies including Amgen, Genentech, Pfizer, GlaxoSmithKline, AbbVie, Bristol Myers Squibb, Lonza, and Gilead Sciences attended the “hot topic” symposium and panel discussion around the use of CSTDs for biologics that was held at American Association of Pharmaceutical Scientists 2018 PharmSci 360 conference as a part of the Formulation and Quality track (November 6, 2018 in Washington DC). The panel discussion engaged various company representatives to share their experiences and challenges with the use of CSTDs in the United States and globally. As a part of this hot topic discussion, the panel and attending members proposed a few recommendations that included the following topics:

- (1) Request regulatory feedback on the use of CSTDs for biological drug products:
 - (a) USP <800> requires risk assessment by health care personnel for investigational products which are in clinical studies and may not have a full understanding on their safety. A significant number of unique CSTDs are now commercially available that have different materials of construction, lubricants, fluid path, and holdup volumes. A comprehensive compatibility study with each commercial CSTD type and an investigational drug product is rather intractable and significantly extends product development timelines. Health authority feedback regarding the use of CSTDs for investigational drug products is needed to ensure compliance and especially for patient safety while balancing risk and benefit to the health care personnel.
 - (b) Similarly, health authority feedback is needed for commercial antineoplastic biological drug products that may or may not be on the NIOSH list to ensure patient safety while eliminating the risk to the health care personnel.
 - (c) Health authority feedback is further needed on various device related aspects of these CSTDs. These include, but not included to, (1) performance testing data provided by CSTD manufacturers; (2) performance testing with representative container closure configurations to characterize stopper coring resulting in particulate formation during use; (3) description of and required controls for the CSTD’s drug product contacting component materials of construction as well as lubricants and solvents used during the device

manufacturing process to ensure CSTD fluid path material compatibility with the drug product being administered; and importantly (4) minimization and harmonization of device holdup volumes across various CSTDs.

- (2) CSTD education and in person training at clinics: CSTDs are composed of several components. Each CSTD has a unique combination and every attempt should be made for proper education and in person health care personnel training at clinics. Given the vast number of CSTDs available in the market, it is impractical for the study sponsor to evaluate every type of CSTD that is commercially available with a given biological drug product. Specific instructions from the study sponsor need to be carefully adhered to prior to dosing. A standard operating procedure for correct CSTD handling is also recommended for each CSTD used as a collaboration between device manufacturer and health care personnel.

Conclusions

mAb aggregation has been a topic of intense discussion for several years due to its potential immunogenic impact.²⁴ Soluble aggregates cannot be removed even if using an in line filter during infusion and could be potentially detrimental to patient safety. It is imperative that significant efforts be made to control protein aggregation and to ensure that product contacting surfaces or preparation methods do not cause additional product quality challenges.²⁵ This is especially important to understand before the product gets to clinical sites because increase in either subvisible particles or insoluble aggregates are not tested in a clinical setting and therefore not reported.

Multiple companies disclosed that they have CSTD related challenges such as particle formation, investigational product quality in compatibility during dose preparation, and administration and dosing accuracy issues due to vial adaptor holdup volumes. Recent literature report indicates that CSTDs may introduce subvisible particles to an ADC drug product.⁸ Literature reports also indicate incompatibility for lyophilized products, especially in terms of stopper push in. Because there are many commercially available CSTDs in the market and it is not feasible to ascertain the preferred CSTDs that any particular clinical site regularly uses, optimization of the drug product formulations becomes a resource intense process that adds to product development timelines and delay in access to life saving drugs for patients. Additionally, CSTD performance requirement guidelines are currently inadequate. Undoubtedly, safety to health care professionals while preparing antineoplastic agents is of utmost importance. Proper use of aseptic techniques, engineering controls, safety hoods, and personnel protective equipment will need to be followed. Although CSTDs may help with reducing exposure, we have noticed that the use of CSTDs raise additional concerns in terms of particulate matter and impact to product quality for biologics that have not been reported earlier. Care should also be taken to ensure that CSTD holdup volumes do not impair approved label claim for biological drug products. CSTD manufacturers need to consider these product compatibility risks while promoting their products for biological drug products. This commentary intends to raise awareness that safe and effective implementation of CSTDs is challenging and that partnership is needed among drug manufacturers, CSTD vendors, and health authorities.

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