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ORIGINAL RESEARCH ARTICLE

Sterility testing using a closed system transfer device in oncology medication compounding: a novel method for testing partially used vials

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Abstract

Background The National Association of Pharmacy Regulatory Authorities (NAPRA) Model Standards for non-hazardous sterile preparations and the model standards for pharmacy compounding of hazardous sterile preparations, calls for partially used single dose vials to be used or discarded within six hours of first access. This may lead to significant wastage, particularly with less utilized and expensive medications like oncology treatments. If demonstrated that sterility of these partially used vials can be maintained through a compounding procedure, there may be an opportunity to consider their re-uses.

Objective The primary objective is to determine the ability of a compounding procedure, including a closed system transfer device (CSTD), to maintain sterility for partially used vials at two compounding centres at Trillium Health Partners. A secondary objective was to evaluate a novel method for verifying sterility.

Methods A CSTD was incorporated into the standard compounding methods at two hazardous compounding centres. Using growth media to detect any bacterial or fungal contamination that might have occurred during compounding, storage, and repeated access, the vials were tested in various growth conditions.

Results There was no growth noted in all compounded samples. The CSTD, when used in our environment with certified personnel, maintained sterility for 14 days, even with repeated access.

Conclusions This study demonstrates that under our local compounding procedure using CSTD we were able to maintain vial sterility when stored under typical conditions and accessed several times for up to 14 days. This method may be considered to assess a facility's local compounding procedures and provide valuable information regarding storage and utilization of partial vials, which may result in reduced waste and cost avoidance for the health care system.

Introduction

In September 2016, the Ontario College of Pharmacists adopted the Model Standards for Non-hazardous Sterile Preparations [1] and the Model Standards for Pharmacy Compounding of Hazardous Sterile Preparations [2] and approved implementation by January 1, 2019 [3]. These standards [1, 2], established by the National Association of Pharmacy Regulatory Authorities, describe the pharmacy requirements for sterile compounding of hazardous and non-hazardous preparations including facilities and equipment, personnel training, policies and procedures, product and preparation requirements, and quality assurance processes. These standards also established a beyond use date (BUD) based on the risk of microbial contamination for single-use and multi-use vials. Single-use vials were given a six hour BUD if punctured in a primary engineering control (PEC) that maintains ISO class 5 air quality, while multi-use vials were given 28 days [2].

Prior to implementation of the NAPRA standards, it was common practice for facilities in Ontario to retain partially used vials, so that the content could be used for future compounding needs if the drug was physically stable. Discarding partially used vials has raised many concerns among healthcare professionals as it increases drug wastage and cost to the healthcare system and results in greater demand for products which, at times, could be in short supply. Cancer

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Key Points

This study demonstrates that closed system transfer devices (ChemoLock™ System) when used under our local compounding conditions and procedures are able to maintain sterility of a partially used vial for up to 14 days.

Using growth media vials as a means to test for intrusion of contaminants is a unique method that supports testing of compounding technique and the ability of a closed system transfer device to create a product that maintains sterility.

Further exploration of this technique is warranted as a means to devise systems to reduce wastage of partially used vials.

Care Ontario's (CCO) Beyond-Use Date Mitigation Strategy Working Group estimated a $13–26 M increase in the provincial drug budget when all cancer centres in Ontario adopt BUD standards for single-use vials [4].

Subsequent to the release of these standards, new evidence suggested that using a closed system transfer device (CSTD) could prevent contamination of the vial and microbial incursion [5–7]. This precipitated a recommendation, from the CCO Beyond-Use Date Mitigation Strategy Working Group, that "CSTDs may be used with single-dose vials to extend the current BUD of six hours, if supported by facility level sterility testing, but should not exceed 7 days" [4]. Moreover, beyond extending BUD, implementing CSTDs has additional benefits. These include reducing exposure to hazardous drugs and maintaining the sterility of medications throughout the preparation and administration process.

Trillium Health Partners offers chemotherapy at two locations: Peel Regional Cancer Centre (PRCC) and Betty and Buster Lockwood Cancer Detection and Treatment Centre at the Queensway Health Centre (BBL). Based on our current data, our wastage at these two centres is estimated to total approximately $1.2 M per year upon implementation of the BUD for part vials [8]. Demonstrating that a CSTD can maintain sterility for a period of 7 days or more may allow significantly reduced wastage.

Objective

This investigation was undertaken to determine whether, under local compounding and storage conditions which had not yet implemented NAPRA standards for facilities and equipment, using a CSTD (ChemoLock, ICU Medical, Inc., San Clemente, CA, USA) would prevent microbial contamination or incursion of simulated single-use vials for up to 7 days.

Methods

Compounding environment

The PRCC and BBL compounding areas utilized in this study were partially compliant with the NAPRA compounding standards [2]. Both contained primary engineering controls (biological safety cabinets), appropriate temperature controls, some aspects of air filtration and pressure gradients, as well as appropriate work surfaces and furniture. However, each room did not meet some aspects of these standards. The PRCC did not have an appropriate anteroom or pressure gradient monitoring systems and did not have an adequate number of air exchanges per hour. BBL lacked the required level of HEPA filtration and adequate number of air exchanges per hour. It also had inappropriate wall and ceiling surface finishes and a lack of external venting. These limitations led the Ontario College of Pharmacists to note that each room was only partially compliant with the NAPRA standards. Other aspects of the NAPRA standards, including personnel training and certification, policies and procedures, maintenance logs, preparation requirements and quality assurance were all in place at both areas.

Closed system transfer device devices

The ChemoLock CSTD (ChemoLock™, ICU Medical, Inc., San Clemente, CA, USA) was used for both vial puncture and syringe transfer. ChemoLock is a two-piece system, (an injector and a port), where both components' membranes may be disinfected to prevent microbial ingress. The injector attaches to an ISO standard luer lock syringe and the port is the access point on the vial spike. When the port and injector mate and are locked together, the fluid path opens and allows for the two-way transfer of fluids. When disconnected, the injector and port self-seal and close.

The vial spike used in this study incorporated a four-clip attachment feature that provides secure attachment to a vial, and a hazardous vapor containment feature that utilizes an external balloon to capture displaced air from the vial for drugs requiring reconstitution.

The intended use of the ChemoLock Closed System Transfer Device is to prevent the transfer of environmental contaminants, including bacterial and airborne contaminants, into the system and the escape of drug or vapor concentrations outside the system.

Growth media and incubation conditions

In order to test for growth of Gram-positive bacteria, Gram-negative bacteria, anaerobic microorganisms, yeast and mold, two types of growth media were used; Tryptic Soy Broth (TSB) and Fluid Thioglycollate Medium (FTM). All media vials had manufacturer's sterility certificates as well as growth promotion certificates. Two temperature ranges (20–25 °C and 30–35 °C) were used for incubation to ensure optimal growth conditions for different microorganisms.

Controls

At each compounding location, five media vials each of TSB and FTM from every lot used were segregated to act as two negative and three positive controls. The vials were placed under the hood during the compounding process but were not manipulated. They were then stored under conditions identical to those of the test samples.

Before incubation, positive control FTM vials were inoculated with less than 10^2 CFU of one each of the following American Type Culture Collection Stock (ATCC) strains: *Clostridium sporogenes*, *Pseudomonas aeruginosa* and *Staphylococcus aureus*. Positive control TSB vials were inoculated with less than 10^2 CFU of one each of the following ATCC Stock strains: *Bacillus subtilis*, *Aspergillus brasiliensis* and *Candida albicans*. The inoculation was done at the end of the study period to ensure that the growth promoting ability of the media was not adversely altered during the process.

Procedure

Compounding was conducted at both Trillium Health Partners compounding sites by certified oncology pharmacy technicians. They followed proper technique, as outlined in the NAPRA Sterile Preparations compounding standards, in order to replicate the normal compounding conditions under which chemotherapy admixture would be completed.

Under standard compounding procedures at each location, ten vials of TSB with a neck size of 20 mm, and ten vials of FTM with neck size of 20 mm, were accessed using ChemoLock vial adaptors following manufactures' directions for use (DFU) in a certified ISO class 5 biological safety cabinet. The ten-vial sample number was based on commonly accepted sterility testing procedures in USP Chapter 71. For each vial, a 1 mL aliquot was withdrawn and discarded at 0, 24, 48 and 168 h to simulate vial manipulation and the multiple accesses that would occur during actual compounding procedures. The date and time of puncture for each vial were recorded in addition to the details of the personnel involved. When accessing FTM vials, care was taken to avoid injecting any air in the syringe back into the FTM media as it would decrease its sensitivity to anaerobic organisms. During the course of the study, the media vials were stored at room temperature since refrigeration is more likely to inhibit microbial growth. Before each puncture, each vial was visually inspected to identify any risk of contamination.

At the end of the 7 days, samples were shipped to the microbiology testing facility, (Sporometrics Inc., Toronto, ONT, CA) under temperature control, after the completion of each cycle. The three positive control vials for TSB and FTM were inoculated with the appropriate strains by injecting spore suspension with a sterile syringe. Prior to incubation, the microbiology technician ensured that the media solution was in contact with all the vial surfaces.

Sample vials, positive, and negative controls were then incubated at 20–25 °C for 7 days, followed by incubation at 30–35 °C for an additional 7 days. Vials were visually inspected for growth every two days with data recorded contemporaneously. Positive growth was noted at the time of observation. This process was repeated for 2 weeks for a total of 80 sample vials at two locations.

Vial inoculation totals

Using the procedures outlined above, compounding samples were created at each investigation site: 10 vials of TSB and 10 vials of FTM for a total of four sets of 10 vials. With each 10-vial set, 3 positive controls and 2 negative controls were created for a total of 12 positive controls and 8 negative controls. The samples and controls were processed and delivered to the microbiology testing facility for sterility testing as per the procedures outlined, above.

Results

All samples tested from each site exhibited no growth throughout the entire 14-day study period. All positive controls exhibited growth of the inoculated ATCC Stock strains: *Bacillus subtilis*, *Aspergillus brasiliensis*, *Candida albicans*, *Clostridium sporogenes*, *Pseudomonas aeruginosa* and *Staphylococcus aureus* within the incubation period as outlined in Table 1. Positive controls demonstrated growth within 48 h of incubation. All negative controls exhibited no growth throughout the entire incubation period. At the onset of the study, one compounded sample contained microscopic inorganic particles which were later determined to be fibers from the alcohol swabs used during disinfection of the vials.

The summary of test results is presented in Table 1.

Table 1 Test results

Media	Vial neck size (mm)	Inoculant	Peel Regional Cancer Site		Queensway Health Centre Site	
			Growth	Time to growth	Growth	Time to growth
TSB	20	Study 1	No	No growth	No	No growth
		Study 2	No	No growth	No	No growth
		Study 3	No	No growth	No	No growth
		Study 4	No	No growth	No	No growth
		Study 5	No	No growth	No	No growth
		Study 6	No	No growth	No	No growth
		Study 7	No	No growth	No	No growth
		Study 8	No	No growth	No	No growth
		Study 9	No	No growth	No	No growth
		Study 10	No	No growth	No	No growth
		+ Control *Bacillus subtilis*	Yes	48 h	Yes	48 h
		+ Control *Aspergillus brasiliensis*	Yes	48 h	Yes	48 h
		+ Control *Candida albicans*	Yes	48 h	Yes	48 h
		− Control	No	No growth	No	No growth
		− Control	No	No growth	No	No growth
FTM	20	Study 1	No	No growth	No	No growth
		Study 2	No	No growth	No	No growth
		Study 3	No	No growth	No	No growth
		Study 4	No	No growth	No	No growth
		Study 5	No	No growth	No	No growth
		Study 6	No	No growth	No	No growth
		Study 7	No	No growth	No	No growth
		Study 8	No	No growth	No	No growth
		Study 9	No	No growth	No	No growth
		Study 10	No	No growth	No	No growth
		+ Control *Clostridium sporogenes*	Yes	48 h	Yes	48 h
		+ Control *Pseudomonas aeruginosa*	Yes	48 h	Yes	48 h
		+ Control *Staphylococcus aureus*	Yes	48 h	Yes	48 h
		− Control	No	No growth	No	No growth
		− Control	No	No growth	No	No growth

Discussion

Current NAPRA guidelines indicate that the appropriate storage time for preservative-free vials is 6 h after reconstitution or first access. This recommendation is meant to address the risk of microbial contamination of a vial over time and the potential risk to patients with subsequent use. The abbreviated storage time guideline has led to drug waste and cost concerns, particularly in fields like oncology where medication cost is high. An expert panel from Cancer Care Ontario suggested that closed-system transfer devices might reduce the wastage of these medications, particularly given the supply chain issues with genericized medications [4].

This investigation was carried out in our current clinical environment to better understand the risk, to our patients, of longer storage times using a CSTD vial access system. This study sought to answer two questions. First, would the CSTD design prevent infiltration of contaminants? If the design inadequately protected the contents from contamination, BUD extension would not be possible. Second, would the CSTD perform as expected in our clinical environment? The design of this study was, therefore, predicated on being able to prove both the sterility of our processes and the devices, simultaneously, in our compounding rooms which do not completely meet NAPRA environmental standards. By providing evidence of maintained sterility in our local environment, we could effectively describe the risk of vial contamination to our patients. The results are directly attributable to the combination of our processes, personnel and facilities.

This study demonstrated the ability of the ChemoLock CSTD to maintain sterility of a compounded solution in

a hospital environment which did not meet NAPRA compounding environment conditions, but did follow NAPRA requirements for handling non-hazardous sterile preparations and hazardous sterile preparations. Similar to a study performed by Perk et al [6], we found that single use vials could maintain sterility for more than 7 days. All compounded samples and negative controls from both study sites were negative for microbial growth over the 14 day study period. Unlike the Perks trial this study was done in non-NAPRA compliant IV room using an alternative CSTD system. This suggests that the use of the ChemoLock CSTD is an acceptable method to maintain sterility of vials for a period of time longer than the NAPRA 6 hour BUD window. However, any BUD time extension requires that product physical stability supports the extended time.

Other studies have tested CSTD using chemotherapy agents such as fluorouracil [5, 9] again showing the ability of CSTD to maintain sterility. The use of chemotherapeutics, which have been shown to inhibit growth of bacteria, may have reduced bacterial growth and reduced the ability to detect contamination. In this study design, the authors wanted to optimize the opportunity for microbial growth during the testing and create an environment in which any contamination would most likely be identified. Using a growth medium for testing afforded both bacteria and/or fungi, introduced during compounding or vial storage, the greatest opportunity to propagate and be detected thus presenting the highest possibility to detect contamination.

Positive controls were included in the protocol to confirm that the study conditions would allow for growth of organisms. The growth of all inoculated ATCC Stock strains: *Clostridium sporogenes*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Bacillus subtilis*, *Aspergillus brasiliensis* and *Candida albicans* provides evidence that the study procedures were sufficient to promote growth if any contamination was present from either the compounding procedure or the storage. The negative controls were put in place to differentiate the influence of compounding versus storage. Given that the environment in which the compounding was carried out was not NAPRA compliant, there was a chance of contamination during compounding. The lack of growth in the negative controls suggests that the inoculum led to growth in the positive controls and that compounding technique and CSTD storage did not impact sterility.

Although the results of this study suggest that ChemoLock CSTD can be used to provide longer sterile storage of products, these results should not be used to indiscriminately extend BUD dating. The use of these products supported longer sterility in our environment with our personnel and our procedures. All these conditions are factors that may not represent other sterile compounding environments and personal and therefore, the use of these devices should be tested, before implementation, at other facilities. Also testing at the same site will need to be periodically repeated to continue to validate that the processes and devices are still maintaining sterility.

The testing did not include viruses and prions as this was beyond the scope of this project and there was no testing for particulate matter as these were beyond the scope of the study. Although contamination with other organisms is always a possibility, using bacteria and fungi as a surrogate was a reasonable measure of testing. Preventing contamination with bacteria and fungi does not demonstrate protection against all other contaminants such as prions and viruses. However, given the technical confines of this study we accepted this as a limitation.

USP <71> identifies multiple methods for the evaluation of sterility in compounding environments, the method described in this study, along with a membrane filtration method. The membrane filtration method consists of passing the test fluid through a membrane, followed by the transfer of the membrane to growth media. The additional step of filtration is to prevent the dilution of the growth media. In our case, the study method was selected as most representative to assess the prevention of microbial ingress into the vial during simulated clinical use. Dilution of the growth media was not a concern, since all the media vials were incubated.

This study parallels the work by Perks et al [6]] in using media vials as a surrogate for chemotherapy. In that study, the authors tested the evaluated CSTD for its ability to minimize microbial contamination of simulated single-use vials using TSB as their media for growth and *S. epidermidis ATC 12228* as their positive control incubated at 37 °C. In this study, ChemoLock CSTD was tested with two types of media, TSB and FTM and five different microorganisms to ensure detection of Gram-positive bacteria, Gram-negative bacteria, anaerobic microorganisms, yeast and mold**.** Incubation was also carried out under 2 different temperature ranges to ensure optimal growing conditions for each organism tested.

Conclusions

In a non-NAPRA compliant practice setting, using NAPRA compliant compounding procedures with trained and certified personnel, these results suggest that ChemoLock CSTD can be used to support sterile compounding and storage of products for up to 14 days.

The authors believe that the procedure described in this study is a technique that can be utilized by other organizations to test the sterility of the drug vials compounding with the utilization of a CSTD in their environment, with their procedures, and their personal. By using a process that optimizes the chance of detecting contamination, we believe this provides additional confidence in the study results which

will enable clinicians interpreting the data to make rational decisions about vial BUD dating in their environment. BUD extension may result in improved medication supply in times of shortage and significant cost savings through the reduction of drug waste.

Declarations

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Conflicts of Interest Neither authors have received grants, honorariums or own stock in ICU Medical or any company that manufactures closed system transfer devices.

Availability of data and material All data is available and will be stored for 10 years.

Code Availability, consent to participate, consent for publication, ethics approval Not applicable.

Authors Contributions All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by AWM and MY. The first draft of the manuscript was written by AWM and MY and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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