Review of microbial contamination of vials used for compounding with closed-system drug-transfer devices

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Introduction:

Vials that are punctured under ISO5 conditions must have a beyond-use date of **6 hours**, per the United States Pharmacopeia chapter <797> to ensure their sterility. Some institutions are using **closed-system drug-transfer devices (CSTD)** when compounding sterile antineoplastic drugs. CSTDs offer a closed environment, so authors are arguing that the sterility is maintained and thus **extend the beyond-use date.**

Objectives:

To perform a **literature review on microbial contamination of vials** used for compounding antineoplastic drugs with CSTDs.

Methods:

A literature review was performed on 2018/08/08. The following terms were searched on PubMed, Embase, CINALH: CSTD and beyond-use date. The proceedings of three relevant conferences were searched (Groupe d'évaluation et de recherche sur la protection en atmosphère contrôlée from 2013-2017, Professional Practice Conference 2013-2018 and Canadian Association of Pharmacy in Oncology 2016-2018). We included any study that presented results on microbial contamination following sterile compounding with CSTDs.

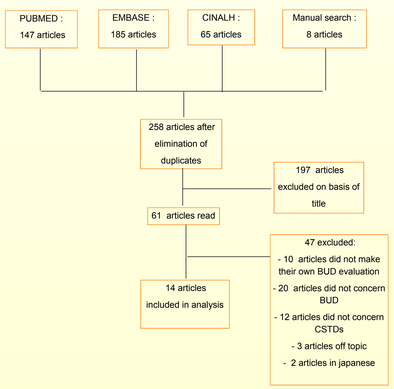
Results:

A total of 397 studies were found and 13 **met our inclusion criteria (Fig 1)**. A total of 1392 vials were tested, 1320 vials using a CSTD (n=11 studies) and 72 vials without using a CSTD (n=3 studies).

The microbial contamination was mainly evaluated at varying time after initial puncture of the vial, 24 hours (n=8 studies), 48 hours (n=6 studies), 72 hours (n=6 studies), 7 days (n=7 studies), 14 days (n=3 studies). Studies evaluating microbiological contamination over time intervals (n= 9) are summarized in **Table 1.** Of the 4 other studies that evaluated contamination differently (e.g. airborne contamination, extreme conditions), 2 studies reported vial contamination.

Figure 2 summarized the number of studies with or without microbial contamination.

No study showed a significant difference in the percentage of contamination with and without using a CSTD.



Legend: BUD (Beyond use date), CSTD (closed-system drug-transfer device)

Fig1: Selection of studies for inclusion in review

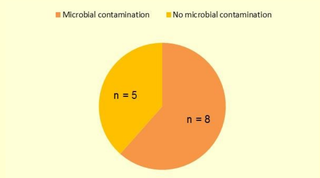


Fig 2: Microbial contamination studies

Conclusions:

The majority of antineoplastic drugs vials used for compounding under sterile conditions **showed little or no microbial contamination**. Future studies **should compare microbial contamination with and without a CSTD**, to validate the potential added benefit of CSTDs on maintaining sterility, when compounding is performed with an aseptic method.

Table 1: Contamination of vials prepared with CSTDs

References	Methods and manipulations	Culture and detection techniques	Incubation times evaluated	Global contamination	Comments and limitations
Rowe 2012	Handing according to USP<797> + CSTD (Phaseal(R)) 56 vials of antineoplastics Comparator : 45 vials of TSB	0.5mL on blood agar 0.5mL of TSB agar Incubation at room temperature	6, 24, 48, 72 hours 7, 14 days	6/322 Antineoplastic vials contaminated 5/270 TSB vials contaminated 1.86% of contamination at 7 days	No group control without CSTDs Conflict of interest: Carmel Pharma
McMichael 2011	Handling according to USP<797> + CSTD (Phaseal(R)) 332 vials of TSB	Incubation at 37°C 14 days Macroscopic and microscopic evaluation of seringue contaminated Inoculation agar	24, 48, 72 hours 7 days	17/1328 agar contaminated 1.8% of contamination at 7 days	No comparator Conflict of interest: Carmel Pharma
Carey 2011	Handling according to USP<797> + CSTD (Phaseal(R)) 332 vials of TSB	Incubation of the bag at 35°C 14 days Macroscopic evaluation	24, 48, 72 hours 7 days	1/1660 sample contaminated 1/332 vial contaminated 0.3% of contamination at 7 days	No comparator Conflict of interest: Carmel Pharma
Sanchez Rubio 2012	Unknown handling area + CSTD (Phaseal(R)) 24 vials of TSB	Incubation at 20-25°C 14 days Macroscopic evaluation	0, 24, 96 hours 7 days	0% vial contaminated at 7 days	No comparator Conflict of interest: unspecified
Sanchez Rubio 2013	Biological safety cabinet ISO5 Handling + CSTD (Phaseal(R)) 80 vials of TSB	Incubation at 20-25°C 14 days Macroscopic evaluation	0, 24, 96 hours 7 days	0% vial contaminated from 0 to 7 days	No comparator Conflict of interest: unspecified
Ho 2016	Biological safety cabinet ISO5 handling + CSTD (Phaseal(R)) 12 vials of 5-FU 5-FU injected in TSB bags	Incubation at 25-35°C 14 days Macroscopic evaluation	6, 24, 48, 72 hours 5, 7, 14 days	0% vial contaminated from 6 hours at 14 days	No comparator Conflict of interest: Celgene, Millennium, SeattleGenetics, Merck, Astellas, and Onyx
Wall 2017	Handling does not meet all USP <797> standards + CSTD (Phaseal(R)) 121 vials of antineoplastics from daily production	Incubation at 35°C 14 days Count of the number of CFUs	24, 48, 72, 96 hours 5, 6, 8 days	0.65% vials contaminated at 8 days	Poster No comparator Conflict of interest: unspecified
Whitehead 2018	1 CSTD (not specified) and 2 conventional systems (needle and spike) 22 vials of alfaxalone without preservative (18 tests and 4 negative controls)	Incubation at 36°C 18-24 hours Macroscopic evaluation	Everyday during 14 days	1 vial contaminated at day 3 (needle) 2 vials contaminated at day 7 (needle and CSTD) 3 vials contaminated at day 13 (2 needles and 1 spike) No significant difference between the 3 groups	CSTD unspecified Conflict of interest: Lurox Pty Ldt
Perks 2016	Biological safety cabinet ISO5 Handling + CSTD (Equashield(R)) 192 vials of TSB	Incubation at 37°C 14 days Macroscopic evaluation	Everyday during 5 days	0% vial contaminated at 5 days	Abstract No comparator Conflict of interest: unspecified

Legend: CSTD (Closed-system drug-transfer device, 5-FU (5-Fluoruracile), TSB (Tryptic Soy Broth)

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