

# Container closure integrity testing and process validation of closed system transfer devices for aseptic reconstitution of drug vials connected to fluid bags

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## Background and Importance

The closure integrity and process validation of closed system transfer devices (CSTD) should be assured before implementation in clinical settings. However, no gold standard has been defined for a container closure integrity test of CSTDs.

## Aim

The aim of this study was to investigate the **closure integrity and validate the aseptic procedure of two types of CSTDs** (CSTD A and CSTD B) by using a combination of the **dye ingress test** and a **media fill test**.

## Materials and Methods

### Primary outcomes:

1. Detection of methylene blue in samples of three drug vials connected to both CSTDs.
2. Absence of microorganisms in nutrient media of TSB vials connected to both CSTDs.

**Part 1:** The dye ingress test with methylene blue was used for both CSTDs with ten samples of drug vials of three brands (n = 60) and nine negative (n = 18) and nine positive controls (n = 18) per CSTD. Samples and controls were inspected visually and analyzed with spectrophotometry for detection of methylene blue.

**Part 2:** A media fill test was performed with 300 samples per CSTD (150 carried out in a safety cabinet and 150 under non-classified environmental conditions). Samples were visually inspected for microbiological growth.



Figure 1. Connected CSTD A (left) and B (right).

## Results

**Part 1:** Methylene blue was absent in all samples and negative controls. Methylene blue was detected in all positive controls.



Figure 2. Three positive and negative controls of CSTD A (left) and B (right).

**Part 2:** The results of the media fill test of both CSTDs, when reconstituted under two ventilation strategies, are shown in table 1.

Table 1. Media fill test results of both CSTDs prepared under two ventilation strategies

CSTD	Ventilation strategy <sup>a</sup>	Total samples	Contaminated samples	Determined microorganisms of contaminated samples
A	I	150	1	<i>S. lugdunensis</i>
A	II	150	1	<i>S. epidermidis</i>
B	I	150	0	-
B	II	148	2	Media fill #1: <i>S. epidermidis</i> + <i>B. circulans</i> Media fill #2: <i>S. epidermidis</i> + <i>B. licheniformis</i>

<sup>a</sup> Ventilation strategy I was reconstitution in LAF cabinet (grade A) situated in grade D cleanroom. Ventilation strategy II was reconstitution in non-classified GMP environment.

## Conclusion

Both CSTDs connected to the drug vials met the terms of closure integrity by using the dye ingress. The aseptic procedure of CSTD B was validated with the media fill test when reconstituted in a GMP grade A environment, but failed for CSTD A. Both CSTDs failed the media fill test when reconstituted under non-classified environmental conditions.

## Relevance

The added value of CSTDs in a hospital (pharmacy) remains debatable without a fully demonstrated closure integrity.

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