NHS Yellow Cover Document (YCD) Integrity performance assessment of needle free Closed System Transfer Devices (CSTDs) as terminal closure/ access device for Luer-Lock (LL) syringes and IV bags: ChemoLock™ and ChemoClave™ vented bag spikes in combination with Freeflex® (Fresenius Kabi) and Viaflo™ (Baxter) IV bags respectively; ChemoLock and ChemoClave syringe adaptors in combination with 1mL and 50mL LL syringes (BD).

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Aim and objectives

To obtain YCD compliant integrity data for ChemoLock and ChemoClave closed system transfer device (CSTDs) components as terminal closure for LL syringes and IV bags to support their use in pharmaceutical technical services (PTS). The study aims to satisfy the data requirements of 2018 YCD "Guidance on Handling of Injectable Cytotoxic Drugs in Clinical Areas." allowing ChemoClave and ChemoLock components to be added in pharmacy rather than on the ward reducing exposure of nurses to hazardous drugs [1].

Introduction

YCD guidance for handling cytotoxics in clinical areas requires CSTD syringe caps added to pre-filled syringes to reduce nurse exposure to hazardous drugs [1]. Current practice is to replace syringe caps with CSTD cap on the ward which can result in nurses being accidentally exposed to cytotoxic drugs. A preferred approach is to add CSTD components in pharmacy but requires supporting YCD compliant integrity test data for both pre-filled syringes and IV bags [1,2]. There is currently a paucity of integrity data for ChemoLock and ChemoClave CSTD components. The study provides the required container integrity data for both ChemoLock and ChemoClave CSTD components as closure device for both pre-filled syringes and IV bags allowing addition of CSTD components to take place in pharmacy. ChemoLock and ChemoClave CSTD device components were tested according to the 2013 NHS YCD: microbiological (Method 1 part 1.4) and physical dye intrusion assessment for integrity [2]. For both ChemoLock and ChemoClave connector activation (n=3) was performed as additional challenge. All devices were subjected to both a 2-hour gyratory shaker excursion and 2-hour real-world transport perturbation with continuous 3-axis inertial measurement. The integrity study is the first to include transport excursion to the YCD providing assessment of the impact of shipping on finished product container integrity from mechanical perturbations during transport. We report the efficacy of a laboratory shaker in mimicking real-world transport events.

Materials and methods

The NHS Yellow Cover Document methodologies for assessing integrity of new container systems were applied: (1) microbiological and (2) physical integrity [2]. As CSTD components contain a complex valve mechanism, pre-activation (n=3) was performed prior to testing. Testing was performed on: ChemoClave and ChemoLock injector (CH2000S/ CL2000S) in combination with 1mL and 50mL LL syringes; ChemoClave and ChemoLock vented bag spike (CH-14/ CL-14); as terminal closure in combination with IV bags (Freeflex/ Viaflo respectively). Microbiological integrity was assessed according to Method 1 part 1.4 using Brevundimonas diminuta immersion at 32°C for 14-days. Physical integrity was assessed using dye intrusion methods: YCD Method 3 & European Pharmacopeia 3.2.9 "Rubber closures for containers" [2,3]. The EP method was applied to the ChemoClave combination devices demonstrating applicability of the EP pharmacopeial dye intrusion methodology for both IV bag and syringe containers [3]. Readout for dye intrusion was reported visually and using a spectrophotometer. Positive and negative controls were assessed according to YCD for both arms of test. Prior to test, all CSTDs were subjected to a 2-hour gyratory agitation and 2-hour real-world transport excursion with continuous 3-axis vibration and G-force monitoring using a 3-axis accelerometer. Sampling rate of 100 milliseconds with 3 axis data capture, vector sum and time stamp. Data processed and plotted as a spectral density plot (SDP).

Results

Tested combinations of ChemoLock and ChemoClave CSTD device containers (n=20) passed the YCD acceptance criteria for microbiological integrity test (Method 1 part 1.4) with all devices (n=120) showing no growth after 14-days incubation at 32oC. ChemoLock CL-14 (n=20), ChemoLock CL2000S (n=20) CSTD components were assessed and passed the YCD physical dye intrusion test (Method 3) in combination with IV bags and luer-lock syringes (1mL & 50mL) respectively as shown in figures 1 & 2. The YCD method 3 for dye intrusion was applied to IV bags in combination with ChemoLock and ChemoClave vented bag spike adaptors and method suitability demonstrated without the need for internal vacuum. The EP method was also applied to ChemoClave vented bag spike CH-14 (n=20) in combination with Freeflex (F-K) IV bags as well as ChemoClave CH2000S (n=20) syringe adaptors in combination with luer-lock syringes (BD) at 1mL and 50mL and external vacuum applied to both types of container system, rigid and non-rigid demonstrating system suitability. All ChemoClave CSTD combination devices passed the acceptance criteria of no dye intrusion for combination containers using the EP method as shown in figures 3 & 4 [3]. EP method for dye intrusion testing was shown to be a suitable replacement for YCD method 3.

The PSD from the 2-hour simulated transport perturbation is shown in Figure 5. Frequency data from both simulation and real-world transport events is between milli Hertz to 10 Hertz with vibration data mostly observed in the range of 0.1 Hertz to 5 Hertz. As such the frequency profile from the laboratory simulated transport excursion is highly similar to that of a real-world transport event.

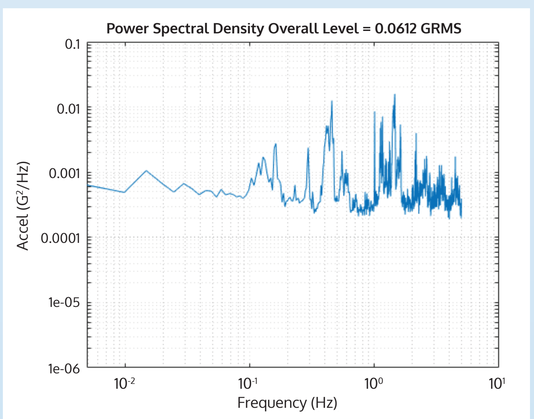

Figure 5. Power spectral density (PSD) plot for simulated transport journey of 2-hours

Real-world PSD plots exhibit discrete temporal events over a short duration with reduced background between these discrete events. The amplitude of recorded events from simulated and real-world transport have some differences in frequency from 1 Hertz to 5 Hertz. Laboratory transport simulation using a shaker table replicates real-world transport perturbations with the advantage of being repeatable allowing it to form part of the YCD container integrity testing. The summed G-force plots from both the simulation and real transport events were also observed to be highly similar.

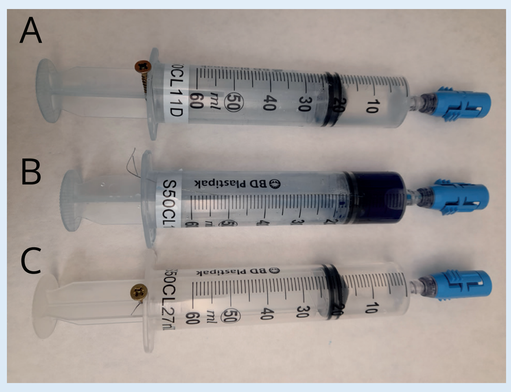

Figure 1. ChemoLock with 50mL LL syringe dye intrusion test

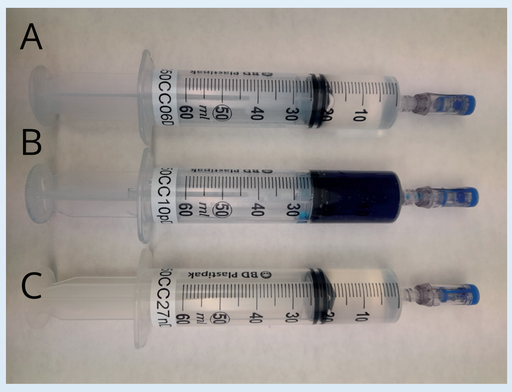

Figure 3. ChemoClave with 50mL LL syringe dye intrusion test

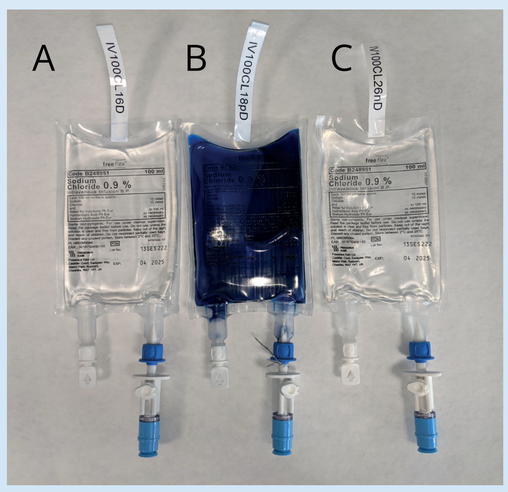

Figure 2. ChemoLock with 100mL IV bag (Freeflex) dye intrusion test

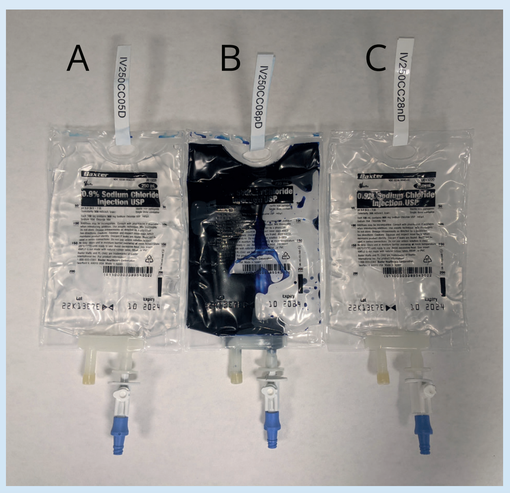

Figure 4. ChemoClave with 250mL IV bag (Viaflo) dye intrusion test

A. CSTD combination Test container; **B.** Positive control container; **C.** Negative control container

Conclusions

Integrity has been demonstrated for ChemoLock CL-14 (n=20), ChemoLock CL2000S (n=20), ChemoClave CH-14 (n=20) and ChemoClave CH2000S (n=20) CSTD components when used as the terminal closure or access device for LL syringes or IV bags (Freeflex/ Viaflo) supporting use in PTS. Adding CSTD components in pharmacy rather than on the ward will further help reduce nurse exposure to cytotoxic drugs. Our conclusion is that simulated transport excursions using a shaker table can replicate and help to assess the impact of transport on finished product container integrity. Real-world transport conditions have infinite variables. The observation that summed G-forces and frequencies experienced from both simulated and real transport events are highly similar opens up the possibility of including this as part of the YCD requirements for integrity testing in the future.

References

[1] Pharmaceutical Quality Assurance Committee 2018. Guidance on Handling of Injectable Cytotoxic Drugs in Clinical Areas in NHS Hospitals in the UK. Edition 1 July 2018.
[2] Pharmaceutical Quality Assurance Committee 2013. Protocols for the Integrity Testing of Syringes. 2nd Edition revised April 2013.
[3] European Pharmacopoeia Monograph 3.2.9 "Rubber closures for containers for aqueous parenteral preparations for powders and for freeze-dried powders", 2023

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