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Implementation of Beyond Use Dating

Figure 1. Tevadaptor® Vial Adaptor unit being assembled onto a glass vial.

Extending Practical (In-Use) Shelf Life of Drug Vials with the Tevadaptor® Closed System Transfer Device (CSTD)

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The aim of the studies summarized in this paper was to test the hypothesis that Tevadaptor® CSTD can be used to extend practical shelf life of drugs, by maintaining microbiological and physicochemical integrity when multiple withdrawals are made from non-preserved single use drug vials up to 28 days.

Introduction

The preparation of potentially cytotoxic injectables is recognized by governmental agencies and special interest groups as a hazardous procedure, due to the potential airborne release of drug particles and vapors or droplets during manipulation. Guidelines have been provided for safe handling and protection of the operator undertaking these tasks[2, 3]. This resulted in the development of multiple Closed System Transfer Devices (CSTD), designed to protect the operator, in parallel to minimizing the risk of microbiological contamination of the vial.

There is an increasing pressure on hospital pharmacists to reduce the drug cost burden and to preserve drugs that are of shortage at a time of increasing healthcare costs, especially in the area of oncology. Furthermore, drug costs, especially for biological drugs, represent a significant part of total healthcare spending[4, 5]. One solution to this problem is drug vial optimization (DVO) which can be accomplished by extending the practical beyond use date (BUD) of a non-preserved drug vial, through the use of closed system transfer devices. According to the USP <797>[6], the CSTD in use should have supportive data on both microbiological and physiochemical stability of the drugs, in this way forming a storage container to help extend the practical shelf life of the drug vial after first puncture. Investigations to assess the ability to maintain microbiological sterility alone up to 7 days in a non-preserved drug vial have been reported[7, 8]. However, these studies do not report data on chemical integrity of the Active Pharmaceutical Ingredient (API), which is a prerequisite to supporting an extension of shelf life.

The current study reports data[1] on the use of the Tevadaptor® CSTD (Figure 1), demonstrating the two requirements for BUD: 1) maintenance of microbiological sterility and 2) physicochemical integrity of three high usage hazardous drugs. The combination of these two data sets can support extended BUD of 28 days after first puncture in these drugs (in accordance with USP chapter <797>) and supports the claim of 28 day sterility integrity with the Tevadaptor® device.

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Maintenance of a Sterile Barrier

The ability of Tevadaptor® to maintain a sterile barrier was performed in two environments: A controlled ISO class 5 environment and an uncontrolled "hospital ward" environment.

Controlled ISO class 5 environment
Sterility maintenance within ISO Class 5 was evaluated by assembling Tevadaptor® Vial Adaptor units onto 100ml glass vials containing 50 ml sterile TSB growth medium. 5 ml Aliquots were withdrawn from each vial on days 0, 7, 14 and 28 (n=332) by attaching a Tevadaptor® Syringe Adaptor onto the vial adaptor and then using a 5 ml sterile syringe to withdraw the growth medium. Each syringe was capped, incubated for 14 days at 30-35±1°C and then inspected for signs of microbial growth. Following withdrawal of the final sample on day 28, the vial containing the remaining growth medium (10 mL) was incubated for 14 days at 30-35±1°C and then examined for microbial growth. Standard microbiological procedures were used to assess the microbial contamination in both test syringes and test vials fitted with Tevadaptor®

Uncontrolled "Hospital Ward" environment
Evaluation of sterility maintenance outside an ISO Class 5 environment, representative of a typical hospital ward environment, was performed without using aseptic technique. The Tevadaptor® vial adaptor septa was wiped with 70% IPA and allowed to dry prior to accessing the vial. Aliquots were withdrawn on similar intervals as with the controlled arm of the study and incubated for 7 days at 20-25±1°C and then 7 additional days at 30-35±1°C, and inspected visually for signs of microbial growth during each of the dual stage incubations. Following withdrawal of the final sample on day 28, the vial containing the remaining growth medium (10 mL) was incubated for 7 days at 20-25±1°C and then 7 days at 30-35±1°C, and then examined for microbial growth. Standard microbiological procedures were similar to the controlled arm of the study.

Sterility Testing Results
No signs of microbial growth were observed in any of the samples withdrawn during the 28 day test periods or in the growth media remaining in the vial after transfers performed in either controlled (ISO Class 5) or uncontrolled environments (Table 1).

Table 1
Sterility Testing of Vial and Tevadaptor® Components During 28 Days Simulated Usage under both ISO Class 5 controlled and uncontrolled "Hospital ward" conditions.

Sample time (5 = point)	Container type tested for sterility after sample withdrawal	Controlled (ISO Class 5) conditions Results (following 14 days incubation at 30-35±1°C)	Uncontrolled (non ISO Class 5) conditions Results (7 days 20-25 ±1°C and then 7 days 30-35 ±1°C
zero	5 mL Syringe	No growth observed (n = 332)	No growth observed (n = 332)
7 days	5 mL Syringe	No growth observed (n = 332)	No growth observed (n = 332)
14 days	5 mL Syringe	No growth observed (n = 332)	No growth observed (n = 332)
21 days	5 mL Syringe	No growth observed (n = 332)	No growth observed (n = 332)
28 days	5 mL Syringe	No growth observed (n = 332)	No growth observed (n = 332)
28 days	Residual TSB in Type I glass drug vial	No growth observed (n = 332)	No growth observed (n = 332)
Positive Control		Growth observed with all microbial strains	Growth observed with all microbial strains

In-use physiochemical Stability of three cytotoxic drugs

The physicochemical stability while using the Tevadaptor® with three representative antineoplastic drugs; Cisplatin (1 mg/ml solution, 100 ml vial), Methotrexate (25 mg/ml solution, 40 ml vial) and Paclitaxel (6 mg/ml solution, 50 ml vial), was evaluated.
A Tevadaptor® Vial Adaptor was attached to the test vials, over a 28 day in-use period. Sample withdrawal was performed according to the instructions for use (IFU) of the Tevadaptor® and according to the drug manufacturers' instructions. A new Tevadaptor® Syringe Adaptor and disposable syringe were used for each withdrawal of samples from the vials containing the Tevadaptor® Vial Adaptor, and a fresh syringe was used for each sampling from the control vials. Samples were withdrawn on days 0, 7, 14, 21 and 28. Testing was performed immediately. Methotrexate vials were stored at 2-8°C. Cisplatin and Paclitaxel vials were stored at room temperature. Vial Adaptors were not removed from the vials or changed during the 28 day test period.
Testing included pH measurement of the solution, evaluation of the drug concentration with HPLC diode array profile, and visual inspection for particulates and clarity. Results for test samples were compared to samples withdrawn from control vials using a disposable syringe and needle (without a closed system transfer device being attached).

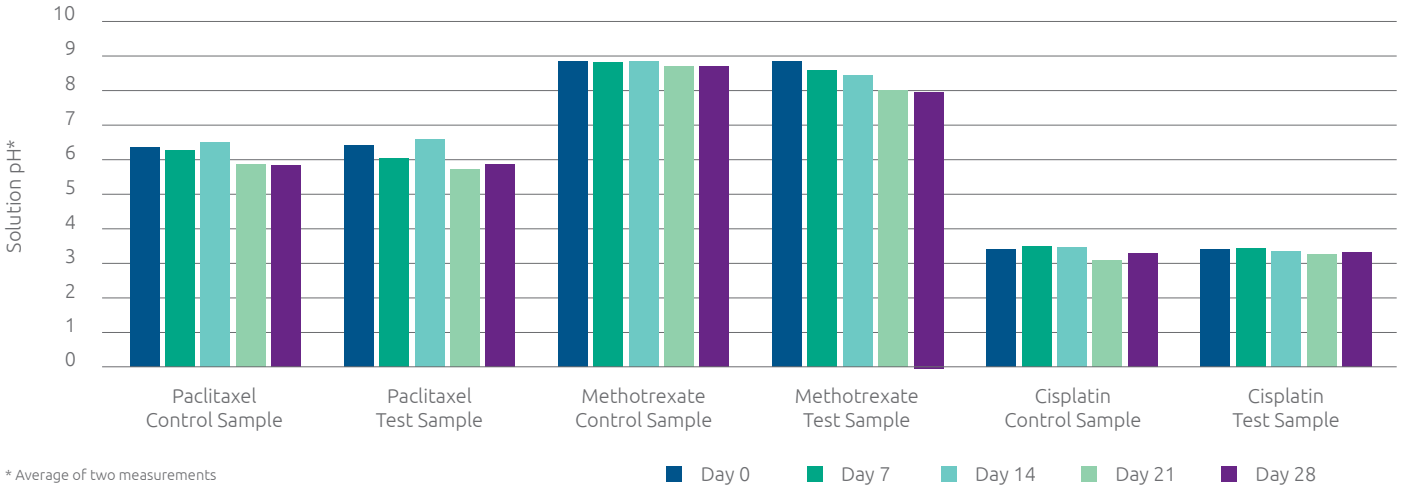
Solution pH

Measured on duplicate test and control samples (n=2) using a calibrated pH meter with a standard single junction glass pH electrode. The pH meter was calibrated on the day of use and prior to measurement of samples (using NIST traceable standard solutions at pH 4.0; pH 7.0 and pH 10.0). Linearity checks were performed on the pH measurement system prior to use.

The acceptance criteria for indicating drug stability was for all test solution samples to remain within ±0.5 pH unit of the appropriate control sample solution.
Test results are summarized below in Figure 2.

With Paclitaxel and Cisplatin all of the results for the test samples were within ±0.5 pH units relative to the control samples. With the Methotrexate samples, the day 0, 7 and 14 test samples were also within ±0.5 pH units of the control samples, but for day 21 and 28, test samples differed by 0.7 pH units. In both sets of the Methotrexate samples (control and test samples) there is a slight negative trend in pH with increasing time. However, even with the negative trend, all of the samples were well within the 7.0-9.0 pH product specification defined in the United States and British Pharmacopoeia Monographs for Methotrexate for Injection [9, 10].

Figure 2
Physiochemical Stability; pH testing.



* Average of two measurements

Assessment of Drug Concentration

High Performance Liquid Chromatography (HPLC) with Diode Array detection (DAD) was utilized to evaluate the chemical integrity of the drug's active ingredient (API). For each drug, stability indicating HPLC methods were developed, based on known published methods [11,12,13]. Each method was validated prior to use in the study. The study acceptance criteria was for chromatographic profile of the test sample to be qualitatively similar to that of the control sample and for the main peak area of the test sample to be within 10% of the value obtained for the control sample. The ability to indicate stability was successfully tested with a forced degradation study for all three HPLC methods (neutral, acidic, alkaline and oxidising conditions, 50°C for 4 hours).
Similarity of the chromatograms was established based on peak purity analysis and a match score analysis available within the Cameleon software operating under windows 2000 control.

The test results are summarized in Figure 3. **Chromatogram profiles of the test and control samples were comparable at all time points.** The percent difference between the main peak of the test samples and control samples was less than 10% for all samples tested, indicting drug product chemical stability throughout the 28 day test period.

Figure 3
Physiochemical stability; HPLC testing for integrity of drug solutions. Evaluation of the % API in the Tevadaptor® test samples relative to the control

Bar graphs representing API content in vials with the Tevadaptor® relative to control samples.

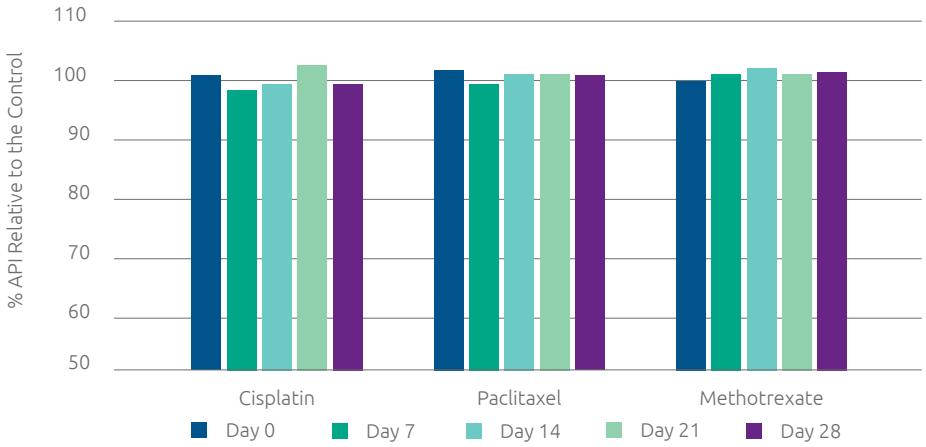


Table 2
Percent API Relative to Control

Sample Point	Cisplatin	Paclitaxel	Methotrexate
Day 0	100.96 %	102.97 %	99.92 %
Day 7	97.82 %	99.00 %	101.11 %
Day 14	99.19 %	101.28 %	102.48 %
Day 21	103.59 %	101.14 %	100.95 %
Day 28	98.87 %	100.39 %	101.39 %

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Solution Clarity, Color and Absence of Particles

Visual inspection of two test samples and two control samples was performed to evaluate the solution for clarity, color and the presence of particulates. The visual inspection was performed against white and black backgrounds (matt) using a white fluorescent light as per the British Pharmacopoeia[14].
The acceptance criteria used for stability assessment was that the solution should remain clear and free from visible particles.

Results showed that **for all three drugs tested, no changes in solution color or clarity were observed over 28 days** (Table 3). The Cisplatin and Paclitaxel solution color remained colorless and that for Methotrexate maintained the same yellow color as at the start of the study and as stated in the summary of product characteristics from the manufacturer. All test samples were found to be free of visible particles at the end of the study (day 28).

Table 3
Physiochemical stability; Visual inspection

Drug	Visual Inspection Results		
	Clarity	Color	Particles
Cisplatin	Clear	Colorless Solution	No particles observed
Paclitaxel	Clear	Colorless Solution	No particles observed
Methotrexate	Clear	Colorless Solution	No particles observed

Physiochemical Stability Study Conclusions

In this Physiochemical Stability study of three single-use and ready to use vials of Cisplatin, Paclitaxel and Methotrexate. In use stability was examined over a 28 day period with drug aliquots being withdrawn weekly. Drug stability in vials from which samples were withdrawn using a standard sterile syringe and needle approach was compared to vials that were fitted with a Tevadaptor® Vial Adaptor and samples were withdrawn using a Tevadaptor® Syringe Adaptor and sterile syringe.
In all of the physiochemical tests conducted for Cisplatin and Paclitaxel, the samples withdrawn using the Tevadaptor® behaved analogously to the control samples withdrawn using a standard syringe and needle. There was no evidence for drug degradation or loss of integrity over the 28 day period following initial puncture of the drug vial. With Methotrexate there were no changes in the HPLC profile or in the appearance of the Tevadaptor® samples relative to the control samples. A slight negative drift in pH was observed in both sets of samples, with a slightly higher drift in the Tevadaptor® samples relative to the control samples. All of the samples (control and Tevadaptor® samples) remained within the 7.0-9.0 pH specification defined in both the British Pharmacopoeia and United States Pharmacopoeia monograph for Methotrexate for Injection.

It can be concluded from this study that the Tevadaptor® retains physiochemical stability integrity in the following drugs: Methotrexate, Paclitaxel and Cisplatin whilst the vial adaptor is connected to the vial and up to 28 days.

Beyond Use dating - Is this possible with Tevadaptor®? Summary & Discussion

With the increasing pressure on hospitals to reduce the drug cost burden, the hospital pharmacist is challenged with identifying means to reduce drug wastage, without impacting drug safety or efficacy. The data presented in this paper proposed to support the pharmacist's decision to extend the practical in-use shelf life of drug products when used with the Tevadaptor®.

According to the USP <797>[2], "valid evidence of stability for predicting beyond-use dating can be obtained only through product specific experimental studies".
We have presented data in the above studies specifically confirming physiochemical stability of three hazardous drugs: Cisplatin, Paclitaxel and Methotrexate in preservative free single-use vials when accessed using the Tevadaptor® over a period of 28 days.
Furthermore, we have presented microbiological testing applied under both ISO Class 5 engineered conditions and in uncontrolled "ward" environment confirming 100% sterility over a 28 day period with the use of the Tevadaptor®. These results therefore apply to preparations and manipulations performed in either aseptic or "normal" ward conditions with high levels of bioburden.

It can be concluded therefore, that the combined data from these studies meets the requirements of USP chapter <797> confirming the hypothesis that Tevadaptor® CSTD can be used to extend the practical shelf life (BUD) of hazardous drugs by maintaining microbiological and physiochemical integrity when multiple withdrawals are made from non-preserved single-use hazardous drug vials, whether inside or outside of an ISO Class 5 environment.

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