# A NEW PERSPECTIVE ON DRUG VIAL OPTIMIZATION

by
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**ACKNOWLEDGEMENTS**

"*To my mom and family for their continued support and to the tremendous people of MD Anderson*"

## ABSTRACT

Arlin Ashemore: A New Perspective on Drug Vial Optimization
(Under the direction of Kevin Garey)

**Purpose***:* Historically, MD Anderson Cancer Center pharmacy areas utilized a strategic process referred to as, *drug vial optimization* (DVO) to extend the beyond-use date for single-use intravenous drug products. Under this strategy, partially used vials of drug were available for a greater period of time to satisfy medication orders prior to having to be discarded. This ultimately resulted in a reduction of drug waste and associated reduce drug cost. Recently updated USP chapter <797> guidelines has since halted the ability to utilize this strategy further. It became prudent to identify a new waste mitigation strategy. MD Anderson Cancer Center Outpatient Pharmacy began a focused effort of ordering the smallest vial size commercially available of rituximab to in an effort to minimize partial vial waste. This process is referred to as, *drug vial size optimization* (DVSO).

M**ethods***:* A retrospective review of data related to rituximab administration and waste reports at MD Anderson outpatient-pharmacy between March 2019 and January of 2020 was conducted.

**Results**: For MD Anderson outpatient pharmacy, it was discovered that the percent of waste of weekly rituximab use increased from near zero percent to 6.9% ($p<0.001$) per week following cessation of the DVO process. Following implementation of DVSO, the percent of waste of weekly rituximab reduced to 3.9% to a new weekly average of 3.0% ($p<0.001$).

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| | |
|---|---|
| ATC | Ambulatory Treatment Center |
| BUD | Beyond-Use Date |
| CMS | Centers for Medicare and Medicaid Services |
| CSTD | Closed System Transfer Device |
| DVO | Drug Vial Optimization |
| FDA | Food and Drug Administration |
| GDP | Gross Domestic Product |
| ISO | International Organization for Standardization |
| MDA | MD Anderson Cancer Center |
| NHEP | National Health Expenditure Projections |
| USP | United States Pharmacopeia |

## Introduction

The financial impact following the removal of a particular drug compounding strategy has yet to be determined at MD Anderson Cancer Center. Over recent years, drug spending trends from a health-systems perspective have continued to increase at an alarming rate. The Centers for Medicare and Medicaid Services (CMS), in their release of the National Health Expenditure Projections (NHEP), forecast increases in US drug expenditures to expand from the documented $3.6 trillion high in 2018 to $6.0 trillion by year 2027. Uniformly, US health spending is projected to grow at a rate that out paces US gross domestic product (GDP) by 0.8 percentage points over the same time period; resulting in a net cumulative rise in health share composite of GDP from 17.9 percent to 19.4 percent.[1] The ultimate reason behind the rise in drug costs is complex. Numerous forces have given aid in perpetuating the current cost vectors that have been predicted by the NHEP. Some of those more prominently announced include administrative cost of drug development (i.e. research and development), basic market fundamentals of supply and demand intrigued by natural disasters and drug shortages, increased focus given to the treatment of rare disease states, and perhaps the most looming contributing factor being the new emerging market of genome-directed personalized medication.[2]

## History of Drug Vial Optimization:

Oncology and the expensive treatment for various cancers or disease states often serve as a subtle but consistent support to rising drug cost, in addition to aforementioned attributable factors. As such, major health-system networks whom focus in the procurement and delivery of specialized oncologic drug therapies that help support the treatment for their patients have a had a continued vested interest in the identification and development of cost mitigation strategies that

can be used to compete against the hefty price tags that are regularly associated with cancer care treatment. One major cost mitigation strategy began in 2011. A multicenter study, led by Dr. Derek McMichael and colleagues, conducted research within the health institutions of MD Anderson Cancer Center in Houston, Texas; SwedishAmerican in Rockford, Illinois; Indiana University Medical Center in Indianapolis, Indiana; and the James Cancer Hospital at the Ohio State University in Columbus, Ohio. Their work focused on the possibility of the practical application to support closed system transfer devices (CSTDs) as a means to extend the beyond-use date (BUD) for single-use nonpreserved vials, the packaging conditions of which that many expensive chemotherapy agents are supplied in. Extending the BUD for these therapies would in theory result in reduced waste as the medication would be sterile for a longer time period and thus be available for use to compound a greater number of medication orders, minimizing the amount of discarded drug.

At the time of the study, the United States Pharmacopeia (USP) Chapter <797> standards limited acceptable BUD standards for nonpreserved, single-use drug vials to 6 hours after manipulation within International Organization for Standardization (ISO) class 5 conditioned areas or 1 hour when manipulated in non-ISO class 5 conditioned areas. The standards established by USP Chapter <797> were aimed to mitigate risk of patient exposure to antimicrobial growth from partially used drug vials. CSTDs by design protect users from exposure to the hazardous medications upon manipulation but also prohibit environmental contaminants from entering the system, thus maintaining a sterile environment after manipulation. At the participating institutions, PhaSeal™ CSTDs' ability to maintain sterility over time was analyzed and ultimately proven to preserve sterility for up to 7 days.[3] This

extended BUD medication compounding strategy would commonly be referred to as, drug vial optimization (DVO).

In 2012, the financial impact of the DVO strategy was assessed by, Doctor Erinn Rowe and colleagues. Dr. Rowe asseverated that through the use of CSTDs, single-use vials where never opened to surrounding air particulates and thus rendered uncompromised sterility. Corresponding sterilization test were performed, much like those conducted by Dr. McMichael and his team, and the results were consistent. From a sterility perspective, the use of CSTDs provided a 98.2% contamination success rate while financially, a cost reductions impact of $700,000 was realized after one year of analysis. This was followed ultimately by an estimated $43.8 million cost reduction over six years. [3,4,5]

**MD Anderson-The Previous DVO Process:**

Like the efforts given at UNC, DVO was a practice utilized at MD Anderson Cancer Center, specifically within the outpatient ATC areas. Evidence for extending the BUD of partial vials was supported by rigorous internal testing of various chemotherapy agents conducted on a weekly basis. Select compounding technicians and pharmacists were chosen to complete an initial Microbiology Lab training program to establish both sterilization testing proficiency and competency. Upon completion, those individuals would then go on to begin conducting sterilization testing. The equipment and materials used during testing included partial drug vials of chemotherapy agents that contained at minimum 1 ml of product with an attached PhaSeal protector, test tubes containing thioglycollate medium with indicator and dextrose, 1 ml syringes, PhaSeal injectors (size N35), and a micro laboratory incubator . Thioglycollate medium with

indicator and dextrose were stored at refrigerated conditions (2-8$^{o}$C) and removed 2 hours prior to testing to allow for the medium to warm to room temperature. Before use the expiration date of the testing medium was validated to ensure safe use and, in addition, if the left at room temperature for greater than a period of 48 hours would then be readily discarded from sterility testing. Partial, single dose vials that had PhaSeal protectors attached and been previously used within 5 days of testing were included for testing. Vials not meeting the aforementioned inclusions parameters and or those containing liposomal formulated product were excluded from testing.

To perform testing, thioglycollate media test tubes were labeled with drug name (including manufacturer, lot number, and expiration date), BUD of the partial vial, and initials of the performing tester, date and time of test, and the pharmacy where the test was conducted. The tester, using aseptic compounding technique, would extract 0.5 ml of drug from the partial vial using the PhaSeal injector. The product was then injected into the thioglycollate tube, gently mixed, and placed within a sample containment rack. This process was repeated for the given number of samples to be tested for each batch. In addition, each batch contained one positive control (inoculated thioglycollate medium tube with contaminated broth media) and one negative control. The sample rack was then placed within an incubator at 35$^{o}$C for 7 days. Samples were removed and compared to sample illustrations representing positive-growth and negative-growth incubated thioglycollate media. Any samples suggestive of possible contamination, based on any signs of turbidity upon inspection, were isolated and submitted to the MD Anderson Microbiology Lab department to be further evaluated. Data on yielded samples were collected, including date of testing, observation (positive or negative result), lot number, expiration date of

the medium, and original identifying information from the drug vial. Repeat testing was completed weekly for an indefinite time period. Based on the evidence provided from sterility testing, BUDs of 5 days were utilized for all single dose vial chemotherapy agents that met the sterility inclusion criteria. This process was utilized for several years until July 6th of 2019 when USP chapter <797> updates were released that fundamentally prohibited further DVO practices to be utilized at healthcare institutions.

| **Table 1** | **Beyond-Use Date Comparison** | |
|---|---|---|
| | **USING DRUG VIAL OPTIMIZATION** | **FOLLOWING USP <797> UPDATE:** |
| **Beyond-Use date** | **5 days** | **≤ 12 hours** |

**MD Anderson-Post DVO Process:**

Though several other reports have been published that support the sterility studies of MD Anderson and those of Drs. McMichael and Rowe, compliance with USP Chapter <797> updates remains critical.[6] As such, BUD designations at all MD Anderson pharmacies for those single-use drug vials were subsequently updated to reflect the new standards outlined with the updates. Acceptable BUD were limited to no greater than twelve hours, based on manufacturer recommended storage requirements for refrigerated conditions (2°–8° Celsius), room temperature conditions (20°–25° Celsius) and stability data.

**Study Purpose:**

As a result of the changes in the appropriate BUD standards, it has long since been anticipated that cost as they relate to drug waste should increase. To date the precise financial impact has yet to be ascertained, but perhaps more importantly, a new strategy to potentially off-set these assumed cost increases have yet to be identified. As we begin to pivot away from DVO, a look towards optimizing drug vial size may be a solution in providing such a cost reduction strategy.. Utilizing the smallest vial size available as a means to produce the minimum partial residual drug following compounding of an order may be referred to as, *drug vial size optimization* (DVSO) strategy was employed at the MDA outpatient-pharmacies. At MD Anderson Cancer Center (MDA) in particular, a unique opportunity existed to determine both what the long-term financial impact may yield on a major oncology healthcare center following interruption of the DVO waste mitigation process and to assess the potential benefit of employing the DVSO process.

The primary aim of the study was to assess whether the average MDA expenditure cost of waste per week would be impacted following cessation of the DVO and also following implementation of the DVSO process of utilizing only smallest vial sizes available. The primary aim was studied utilizing two primary ratios:

- Ratio one: the total amount of waste produced per total amount of medication utilized (i.e. administered to the patient and the amount wasted) per week.

- Ratio two: the total amount of waste produced per total amount of drug orders per week.

The study focused on a single pharmaceutical agent that was identified as one of the primary expensed chemotherapy agents, by cost, utilized at MDA outpatient-pharmacy ambulatory treatment areas. The study was conducted over a period of 10 months.

Additional outcomes analyzed during the study include the discrete comparison of various MDA outpatient-pharmacy ambulatory treatment areas with regards to ratio-1 and ratio-2 and the impact on the general financial impact following the cessation of the DVO process.

## Methods

### Study Design:

The following study was conducted at The University of Texas MD Anderson Cancer Center, outpatient pharmacy areas. The study time period was conducted between March of 2019 and January of 2020. Waste data was collected using standardized waste reports for MDA outpatient-pharmacy areas. These reports were analyzed for a period of three months prior to DVO cessation (baseline), six months utilizing the DVSO strategy and the 4 week intra-period that existed between the two processes. The waste reports specifically were comprised of a list of 136 pre-determined commonly used drug agents that were identified to track their respective waste over time. Waste report data for the respective drug agents was collected on a on a daily basis by designated pharmacy technicians working within their respective areas, under the guidance of pharmacy managers. For each respective drug agent, the aggregate daily wasted drug amount was documented within monthly reports that captured weekly totals of drug waste. Drug waste was reported using the appropriate corresponding units of measure (ex. Milligrams, grams, or units) for each respective medication.

The waste reports allowed for documentation of two primary forms of waste; *prepared drug waste* (i.e. fully compounded and ready for administration) and *open vial drug waste (*i.e. partially used drug vials). As a principle impetus for the study was to determine the financial impact of disallowing extended-BUD of partially used single-use vials, attention was given to data related to *open vial drug waste*. Data relating to *prepared drug waste* was excluded. From the list of 136 drug agents, all drugs not included within the MDA outpatient-pharmacy list of ten most expensed drugs by cost were excluded. Any medication that was not compounded for administration at each outpatient-pharmacy involved in the study was excluded. Any medication considered to be short stable (i.e. BUD less than 12 hours following manipulation) was also excluded. Lastly, some medications are only dosed using one or two unique drug strengths and as such are provided in vial sizes that contain the exact amount of product necessary per administration. Any medications meeting this criteria was also be excluded. Ultimately, rituximab qualified as the principle drug to be analyzed during the study.

Administration data was obtained by electronic medical record queried report generation provided by MDA pharmacy analytics team. The reports provided the ordered dose, administration date and the specific compounding pharmacy for the ten most expensed drugs from March 2019 to February 2020. Administration data for rituximab was included. All other medication administration data was excluded.

Operationally, MDA outpatient-pharmacy facility is comprised of three separated pharmacies. They were noted as a-Pharmacy, b-Pharmacy and c-pharmacy through the duration of the study. Data was collected from each of these three areas to determine the MDA outpatient-pharmacy waste over the study time period. Administration and waste data from c-pharmacy over the study time period was unsubstantial and was ultimately excluded from analysis.

Ratio-one, total amount of waste produced per total amount of medication was determined by dividing the weekly total of rituximab waste by the sum of total amount of rituximab administered and total amount of rituximab wasted, per week. Ratio-two, the total amount of waste produced per total amount of drug orders per week was determined by dividing the weekly total of rituximab waste by the total amount of rituximab orders per week. Ratio-one and ratio-two were studied as an aggregate of MDA outpatient-pharmacy areas. Ratio-one and ratio-two were then studied within each individual MDA outpatient-pharmacy (i.e. a- pharmacy and b-pharmacy).

To derive the total cost of waste, each drug was evaluated and assigned pre-determined *cost per unit of measure*. The product of the total weekly wasted open vial drug and the pre-determined cost per unit of measure was used to ultimately determine the waste cost.

| **Figure 1** | **Cost of Waste Calculator** | | |
|---|---|---|---|
| **COST OF WASTE** | ***Weekly Total Waste*** | × | ***Cost per Unit of measure*** |

Analysis was conducted utilizing SPSS® statistics software. Ratio-one was reported as a percent. Ratio-two was reported in milligrams. The general financial impact was reported in US dollars per month. To assess the potential long-term financial impact of interrupting the DVO process the average monthly cost for the three processes (i.e. DVO process, USP <797> updates and DVSO) will be annualized and difference between the three values will be obtained. For the DVO process, average monthly cost will be obtained from MD Anderson outpatient-pharmacy waste data from March 2019 through June 2019. For USP <797> updated process, average monthly cost will be obtained from MD Anderson outpatient-pharmacy waste date from July 2019 through August 2019. For DVSO process, average monthly cost will be obtained from MD outpatient-pharmacy from September 2019 through January 2020. The potential long-term financial impact will be reported in U.S Dollars per year.

## Results

### Combined Pharmacy Data:

The period of DVO utilization, March of 2019 through July 6$^{th}$ 2019, waste of rituximab was near zero excluding a single occurrence of reported partial vial waste during the month of April. Ratio-one (total waste/total amount used) was at near zero percent through this time period. Following cessation of the DVO process on July 6$^{th}$, ratio-one increased to 4.2% (M=6.9%, SE= 0.005, $p<0.001$). In the four week period that existed between cessation of the DVO process and implementation of DVSO, ratio-one peaked to 8.8%. Ratio-one decreased to 3.7% (M=3%, SE=0.005, $p<0.001$) following initiation of DVSO on August 8$^{th}$. This trend was consistent with regards to ratio-two (total waste/total ordered doses). In the period during DVO utilization, ratio-two was zero percent.

**Figure 2. Proportion of Total Waste to Total Amount of Drug Used: Combined MDA Outpatient-Pharmacies**

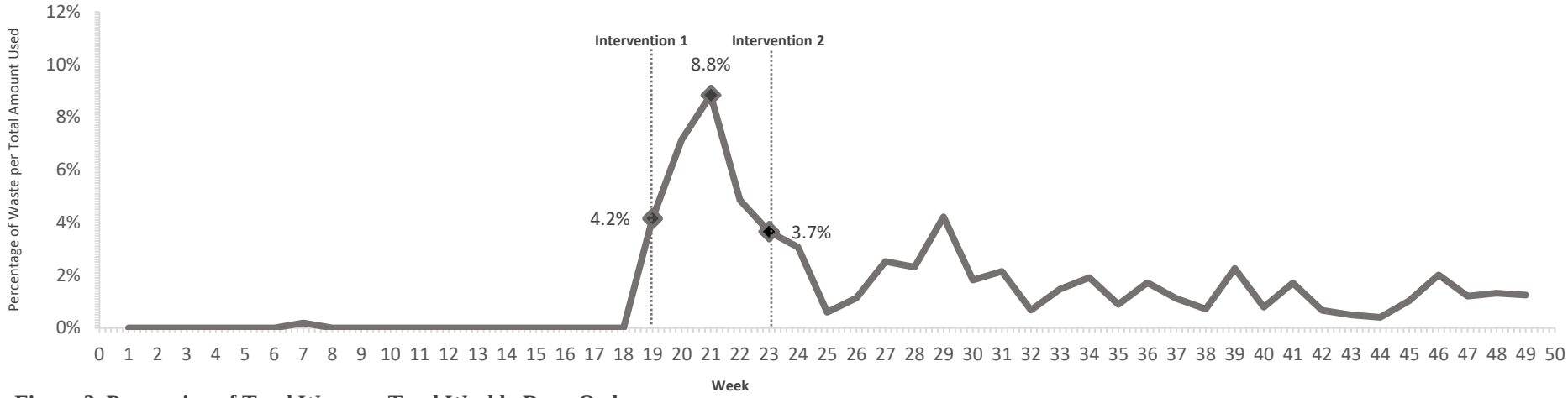
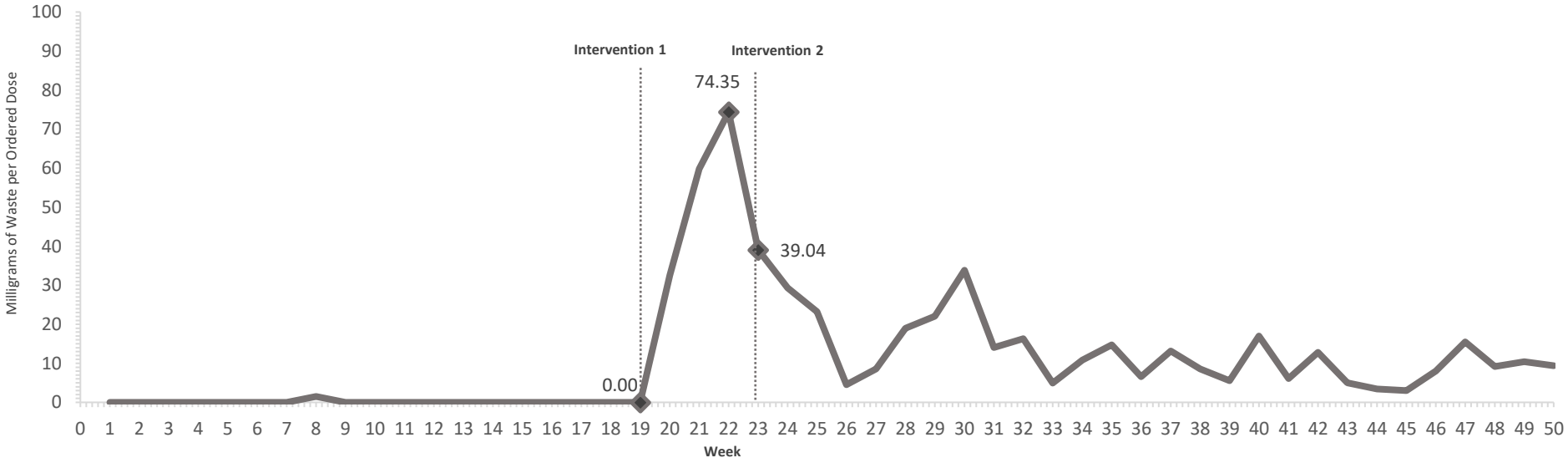



**Figure 3. Proportion of Total Waste to Total Weekly Drug Orders: Combined MDA Outpatient-Pharmacies**



Following cessation of the DVO process ratio-two increased to 33.53 mg per week (M=56.29 mg, SE=4.21, $p<0.001$) and peaked to 74.35 mg per week in the four week period that existed between cessation of the DVO process and implementation of DVSO. Following implementation of DVSO, ratio-2 decreased to 39.04 mg per week (M=23.87 mg, SE=4.37, $p<0.001$).

**Discrete Pharmacy Data:**

In the time period of DVO utilization ratio-one was largely zero percent for both a-pharmacy and b-pharmacy. Following cessation of the DVO process ratio-one increased for both a-pharmacy and b-pharmacy, 1.5% and 4.8% respectively and peaked to 14% and 8 % during the four week period that existed between cessation of the DVO process and implementation of DVSO. Following implementation of DVSO, ratio-one declined for both a-pharmacy and b-pharmacy to 1.2% and 10.9%, respectively. Ratio-two was near zero for the entire period that existed during DVO utilization. Following cessation of the DVO process, ratio-two increased for both outpatient-pharmacies, peaking at 66.4 mg per week for a-pharmacy and 123.1 mg per week for b-pharmacy. Upon implementation of DVSO, ratio-two declined to 20.3 mg per week for a-pharmacy and 105.7 mg per week for b-pharmacy.

**Figure 4. Proportion of Total Waste to Total Amount of Drug Used: Discrete MDA Outpatient-Pharmacy Areas**

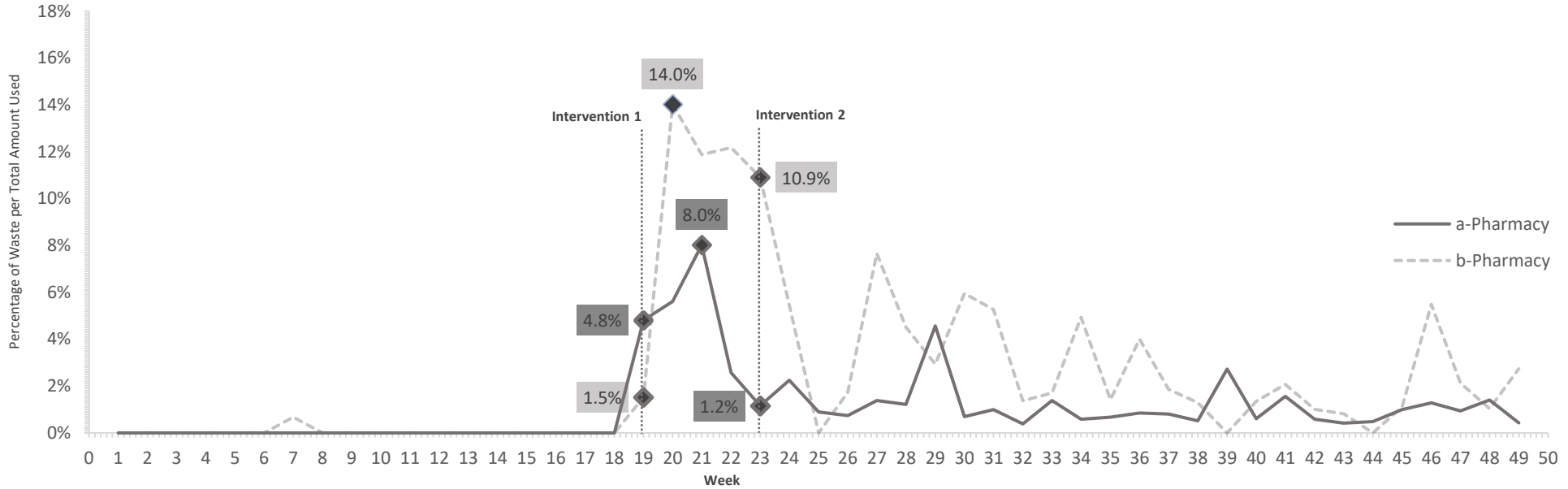
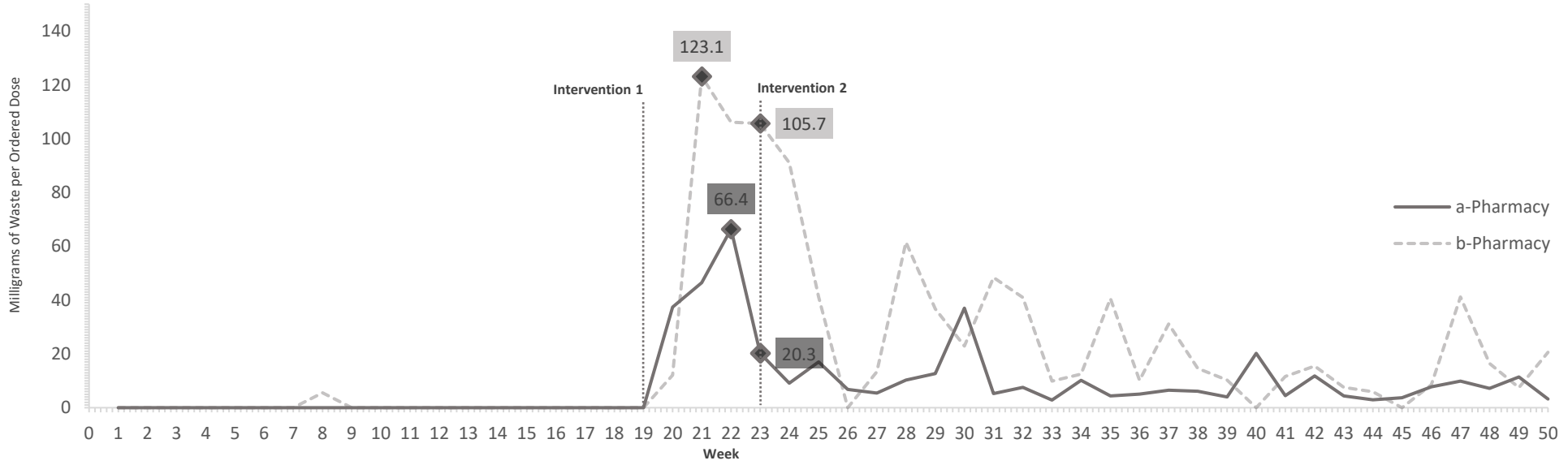



**Figure 5. Proportion of Total Waste to Total Weekly Drug Orders: Discrete MDA Outpatient-Pharmacies Areas**



## Discussion

The DVO process was a highly effective waste mitigation strategy that resulted in near zero partial vial waste being reported from March 2019 through July 6th, 2019 for MDA outpatient-pharmacy areas. Following cessation of the DVO process, the average waste that was produced for MDA outpatient-pharmacy areas grew from zero to a high of 74.35 mg per ordered dose of rituximab. The implementation of DVSO led to a statistically significant reduction in average produced waste. At the time of implementation average waste per order declined to 39.04 mg for MDA outpatient-pharmacy areas and would go on to average 11.86 mg per ordered dose over the final duration of the study period (August 8th, 2019 through January 31st, 2020).

### Dose Potential:

Ratio-2 goes on to suggest greater implications when comparing the three process variants. During time period-1 under the DVO process, the average proportion of waste per ordered dose equated to 0.08 mg. When multiplying this value by the average ordered doses of rituximab per week, the resulting waste would equal 4.26 mg per week. During time period-2 when no waste mitigation strategy was utilized, the average proportion of waste per ordered dose equated to 47.01 mg. Multiplying this value by the weekly average of ordered doses of rituximab results in an estimated 2,504.35 mg per week. Finally, under the direction of DVSO the previously stated 11. 86 mg average proportion of per ordered dose would translate to an estimated weekly average of 631.81 mg. Over the time period of the study, the average dose of rituximab was 753.88. mg. The waste produced under these process variants may be thought of in terms of dose potential for additional patients. Using the average dose of rituximab during the study period, the

waste produced per week during time period-1 (DVO) would translate to a less than 1% dose creation. Time period-2 (no waste mitigation strategy) would translate to an additional 332.19% (3.2 doses) dose creation per week. Time period-3 (DVSO) would translate to 83.81% dose creation.

**Figure 6. Dose Potential from Partial Vial Waste, Based on Average Dose of Rituximab**

| | DVO | No Process | DVSO |
|---|---|---|---|
| **Two Weeks** | 0.01 | 6.61 | 1.67 |
| **One Month** | 0.02 | 13.22 | 3.34 |
| **One Year** | 0.27 | 158.64 | 40.02 |

**Cost Production:**

Ratio-2, total waste per ordered dose, may be translated to into dollar waste value as well.

For MD Anderson outpatient-pharmacy, rituximab cost $9.02 per mg. For time period-1, average cost of waste per ordered dose would equal to $0.72. For time period-2, the average cost of waste per ordered dose would equal $424.03. For time period-3, the average cost of waste per ordered dose would equal $106.98. Based on the study average of 53 doses of rituximab ordered weekly yearly projections of the estimated cost of wasted drug under time period-1, time period-2 and time period-3 would amount to $1,831.68, $1,078,732.32 and $272,157.12 respectively.

**Conclusion:**

The study design had several limitations. One major limitation for the study was the reliance of pharmacy personnel to accurately and consistently document the weekly waste of rituximab. The manual recording of waste may have led to over or under estimation of the produced waste. Also the waste produced as a result of compounding error, canceled doses and the like was not

accounted for during the study and have given a more accurate representation of the outcomes had they been accounted for.

Given the limitations of the study the impact resulting from DVO cessation remains dramatic. From a financial perspective, without the use of DVO the projected cost of unused partial vial waste is an estimated $1M annually and would at best be an approximated $275,000 under DVSO. From a medical perspective, and perhaps more importantly, the partial vial waste generated following DVO cessation would be enough to treat additional 158 patients per year or 40 patients under DVSO. Based on the study results, DVSO is an effective waste mitigation strategy to suppress the more alarming financial and medical ramifications that would occur under DVO cessation. However DVSO is not a perfect remedy to ease the loss of DVO.

There are many headwinds that exists that constantly fight against 100% efficiency of the DVSO process. The first issue being one of storage. It requires 5 times the physical storage capacity within inventory to store, in terms of rituximab, the same amount of drug in the smallest vial size possible as opposed to the larger available vial size. This limitation becomes further challenging as rituximab must be stored under refrigerated conditions. Another limitation is one of compliance. Though the DVSO process can be employed fully, it remains the responsibility of the inventory overseer to purchase solely the smallest available vial size and the technician performing the drug compounding to commit to utilizing the vial. It may be preference of the compounding technician to use a larger vial due to ease of manipulation and reduced supplies, steps and time required to complete the production of the drug order. The aforementioned limitation elucidated several other additional limitations that may exists under DVSO. Each vial

requires its own respective BD PhaSeal drug access device to engage compounding. As such, the use of smaller vial sizes may inadvertently increase supply cost and also require greater production time per doses as step in the manipulation process increase. Other considerations also include the possibility of increased production error as more vials are required to satisfy drug orders, the increased repetitive motion that may compromise employee personnel's physical ability to perform effectively and the also the threat of drug shortages to depend on DVSO to be engaged consistently without fluctuation due to external strains in the drug supply chain. The mentioned limitations will become magnified even further as the notion to scale the DVSO process from a single drug (rituximab) to several others becomes considered.

The projected reduction in annual cost due to partial vial waste from $1M to $275,000 is substantial and may suggest reasonable credence for expanded DVSO processes to other therapies beyond rituximab. However, when considering the aforementioned limitations of the DVSO process coupled with the near negligible $1,800 in annual cost due to partial vial waste and the potential treatment of 153 additional patients under the DVO process, a stance to a move back to DVO is reasonable. In fact it may even be responsible. As drug cost continue to increase, there is a new adverse effect of chemotherapy agents and it is referred to as, *financial toxicity*. The cost to produce, procure and pay for these agents is ballooning to an inflection point where patients are having to decide between receiving treatment for their disease and burdening the related financial cost or acquiescing to the ultimate outcome of the disease and burdening the emotional cost. DVO is not the silver bullet to combating rising drug cost but it is the highest caliber waste mitigation strategy produced to date.

**Resources:**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## Appendices:

## Example of Waste Report:

| ACB ATC Pharmacy Drug | Prepared Drug Waste | | | | | | | Open Vial Waste | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Cost per Mg | Wk1 11/1 | Wk2 11/4-11/8 | Wk3 11/11-11/15 | Wk4 11/18-11/22 | Wk5 11/25-11/29 | Bag Monthly Cost | Wk1 11/1 | Wk2 11/4-11/8 | Wk3 11/11-11/15 | Wk4 11/18-11/22 | Wk5 11/25-11/29 | Vial Monthly Cost |
| Ado-Trastuzumab Emtansine (Kadcyla) | [redacted] | | | | | | $0.00 | | 78.57 | 29.73 | 83.2 | 25.79 | [redacted] |
| Aldesleukin (IL-2) (MM IU) | | | | | | | $0.00 | | | | | | |
| Arsenic Trioxide | | | | | | | $0.00 | 3.8 | | 27.67 | 21.97 | 8.85 | |
| Asparaginase, E.Coli (units) | | | | | | | $0.00 | | | | | | |