Contemporary Approaches to Decreasing Drug Waste
Optimizing Processes and Technology

A Midday Symposium and Live Webinar conducted at the 52nd ASHP Midyear Clinical Meeting and Exhibition

Wednesday, December 6, 2017
11:30 a.m. – 1:00 p.m.
Orlando, Florida

Agenda

11:30 a.m. – 11:35 a.m.
Welcome and Introduction
Lindsey B. Amerine, Pharm.D., M.S., BCPS

11:35 a.m. – 11:55 a.m.
Framing the Problem of Cancer Drug Waste in the U.S.
Peter B. Bach, M.D., MAPP

11:55 a.m. – 12:20 p.m.
Use of Drug Vial Optimization to Decrease Drug Waste
Lindsey B. Amerine, Pharm.D., M.S., BCPS

12:20 p.m. – 12:45 p.m.
Employing Processes and Technology to Reduce Drug Waste
Corbin Bennett, Pharm.D., M.P.H.

12:45 p.m. – 1:00 p.m.
Faculty Discussion and Audience Questions

Provided by ASHP
Supported by an educational grant from BD

www.ashpadvantage.com/go/drugwaste
Contemporary Approaches to Decreasing Drug Waste: Optimizing Processes and Technology

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Provided by ASHP
Supported by an educational grant from BD

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- Lindsey B. Amerine, Pharm.D., M.S., BCPS
  - Amgen: advisory board
  - BD: speakers bureau
  - Taiho Oncology: advisory board

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Contemporary Approaches to Decreasing Drug Waste: Optimizing Processes and Technology

Learning Objectives

• Review the scope of drug waste in the United States, including its impact on healthcare costs for both the healthcare system and patients.
• Explain available processes and technologies, such as drug vial optimization, that can be implemented to decrease drug waste.
• Review potential workflow changes that facilitate the safe and efficient compounding and delivery of hazardous drugs in accordance with USP Chapter <800> standards.

Framing the Problem of Cancer Drug Waste in the U.S.

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Memorial Sloan Kettering Cancer Center
New York, New York
bachp@mskcc.org
@peterbachmd
Recent Efforts

- Indication Specific Pricing
- Medicare Part B Payment Pilot
- Tracking of Recent Pricing Trends
- R&D Premiums
- Outcomes-based contracting vs. value-based pricing
- Manufacturer Buy-Outs

www.drugpricinglab.org

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Contemporary Approaches to Decreasing Drug Waste: Optimizing Processes and Technology

How companies raise revenues without expanding indications

Introduce product into market at one dose and price
- Raise the dose
- Increase the dosing frequency or shorten the dosing interval
- Raise the price
- Find another way to increase drug used per patient

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Overview of drug waste analysis

• Many cancer drugs dosed based on body weight or size
• They typically come in single-dose vials, meaning what is not used most often has to be discarded
  – Sometimes the leftover can be shared with the next patient
• Reimbursement and patient share of costs based on all drug in vial, not amount patient receives
• Given the multi-billion dollar market for these drugs, leftover drug in vial might add up to a lot

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Fig 1 Study flowchart

Source: Bach PB et al. BMJ. 2016; 352.
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What is total cost to the system?

- Incremental revenue for companies = $1.8B
- But total cost to the U.S. healthcare system is around $3B
- Why?
  - As medical benefit drugs move through the system they get marked up through reimbursement
    - Medicare pays 4.3% over the price of a drug
    - Commercial insurers pay more than 20% over the price in doctor’s offices and 100% more in hospitals
- The blended mark-up exceeds 50%

Source: Bach PB et al. BMJ. 2016; 352.

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<table>
<thead>
<tr>
<th>Drug (brand name), year of FDA approval</th>
<th>Dose of first approved indication (highest approved dose at any time)</th>
<th>Amount of drug in available single-dose vials (discontinued vials)</th>
<th>% of lower drug using only half doses</th>
<th>% dose with visual sharing</th>
<th>% of lower drug adjusted for frequency of visual sharing</th>
<th>2016 expected sales ($m)</th>
<th>2018 expected revenue from lower drug ($m)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patekall protein bound (Oceanwara, 2009)</td>
<td>Breast 200 mg/m²</td>
<td>100</td>
<td>9</td>
<td>16</td>
<td>8</td>
<td>560.77</td>
<td>76.72</td>
</tr>
<tr>
<td>Bevacizumab vedere (Avastin), 2011</td>
<td>Lymphoma 1.8 mg/m²</td>
<td>50</td>
<td>15</td>
<td>36</td>
<td>19.2</td>
<td>7</td>
<td>29.15</td>
</tr>
<tr>
<td>Panitumab vedere (AstraZeneca, 2006)</td>
<td>Mesothelioma 500 mg/m²</td>
<td>100, 50</td>
<td>5</td>
<td>16</td>
<td>4</td>
<td>120.69</td>
<td>54.64</td>
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<tr>
<td>Benznidazol (AstraZeneca, 2006)</td>
<td>Colorectal 5 (15 mg/m²</td>
<td>100</td>
<td>40</td>
<td>1</td>
<td>19</td>
<td>3</td>
<td>319.2</td>
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<tr>
<td>Ranitidine (Oxycare), 2014</td>
<td>Gastritis 10 (mg/m²</td>
<td>100</td>
<td>30</td>
<td>7</td>
<td>16</td>
<td>6</td>
<td>471.56</td>
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<tr>
<td>Celecoxib (Celestone), 2004</td>
<td>Headache 20 (mg/m²</td>
<td>100</td>
<td>3</td>
<td>6</td>
<td>19</td>
<td>5</td>
<td>570.22</td>
</tr>
<tr>
<td>Asparaginase (Erbitux panaflora, Shionohe, 2011)</td>
<td>All 2000 mg</td>
<td>1000</td>
<td>10</td>
<td>16</td>
<td>18</td>
<td>17.06</td>
<td>14.13</td>
</tr>
<tr>
<td>Eribulin (Kazufes), 2011</td>
<td>Breast 1.4 mg/m²</td>
<td>1</td>
<td>15</td>
<td>10</td>
<td>13</td>
<td>167.71</td>
<td>21.85</td>
</tr>
<tr>
<td>Cabazitaxel (Zoseda), 2010</td>
<td>prostate 25 mg/m²</td>
<td>60</td>
<td>23</td>
<td>12</td>
<td>21</td>
<td>17.06</td>
<td>26.89</td>
</tr>
<tr>
<td>Aspergillus immunotherapy (Kefros), 2013</td>
<td>Breast 3.5 mg/m²</td>
<td>100</td>
<td>7</td>
<td>16</td>
<td>6</td>
<td>413</td>
<td>23.38</td>
</tr>
<tr>
<td>Pentoxifylline (Keytruda), 2014</td>
<td>Melanoma 2 (mg/m²</td>
<td>100</td>
<td>24</td>
<td>16</td>
<td>21</td>
<td>943.07</td>
<td>197.94</td>
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<tr>
<td>Carfilimib (Phoebus), 2012</td>
<td>Myeloma 20 (mg/m²</td>
<td>60</td>
<td>37</td>
<td>16</td>
<td>33</td>
<td>675.95</td>
<td>213.45</td>
</tr>
<tr>
<td>Filgrastim (Neupogen), 1991</td>
<td>Neutropenia 5 (mg/m²</td>
<td>100</td>
<td>40</td>
<td>17</td>
<td>5</td>
<td>620.65</td>
<td>108.61</td>
</tr>
<tr>
<td>Vincristine (Coxel), 1981</td>
<td>Pancreatic 70 mg/m²</td>
<td>43</td>
<td>7</td>
<td>10</td>
<td>6</td>
<td>116.89</td>
<td>7.10</td>
</tr>
<tr>
<td>Noktemal (J過來), 2014</td>
<td>Melanoma 4 (mg/m²</td>
<td>100</td>
<td>8</td>
<td>16</td>
<td>3</td>
<td>2070.63</td>
<td>68.93</td>
</tr>
<tr>
<td>Ruxtram (Ruxsar), 1997</td>
<td>Non-Hodgkin’s lymphoma 975 (mg/m²</td>
<td>100</td>
<td>50</td>
<td>3</td>
<td>17</td>
<td>3525.75</td>
<td>253.65</td>
</tr>
<tr>
<td>Benadryl (Trenda), 2005</td>
<td>Chronic lymphoid leukemia 100 (mg/m²</td>
<td>100</td>
<td>0</td>
<td>100</td>
<td>0</td>
<td>563.44</td>
<td>7.06</td>
</tr>
<tr>
<td>Panoximib (Sorbit), 2006</td>
<td>Colorectal 8 (mg/m²</td>
<td>100</td>
<td>40</td>
<td>10</td>
<td>17</td>
<td>257.41</td>
<td>16.72</td>
</tr>
<tr>
<td>Sorbit (Vilacin), 2002</td>
<td>Myeloma 1 (mg/m²</td>
<td>100</td>
<td>30</td>
<td>10</td>
<td>20</td>
<td>1160.54</td>
<td>138.74</td>
</tr>
<tr>
<td>Taxotem (Tamox), 2011</td>
<td>Melanoma 3 (mg/m²</td>
<td>100</td>
<td>20</td>
<td>10</td>
<td>32</td>
<td>620.22</td>
<td>46.47</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Source: Bach PB et al. BMJ. 2016; 352.
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How different vials affect waste

Fig 2 Distribution of FDA approved dose (green histogram) in the US population of cancer patients, and available combinations of full vial contents (red lines) to achieve that dose for bortezomib (top) and bendamustine (bottom)

Source: Bach PB et al. BMJ. 2016; 352.

Published March 2016

Projected cumulative revenue from 2016-2020 sales of pembrolizumab comparing scenarios with different vial sizes ($M)

NSCLC = non-small cell lung cancer

Source: Bach PB et al. BMJ. 2016; 352.
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Published March 2017

A Pharmacoeconomic Analysis of Personalized Dosing vs Fixed Dosing of Pembrolizumab in Firstline PD-L1-Positive Non–Small Cell Lung Cancer
Daniel A. Goldstein, Noa Gordon, Michal Davidescu, Moshe Leshno, Conor E. Steuer, Nikita Patel, Salomon M. Stemmer, Alona Zer

Abstract
Background: In October 2016, pembrolizumab became the new standard of care for firstline treatment of patients with metastatic non-small cell lung cancer (mNSCLC) whose tumors express programmed death ligand 1 in at least 50% of cells. The US Food and Drug Administration-recommended dose is 200 mg every three weeks. Multiple studies have demonstrated equivalent efficacy with weight-based doses between 2 mg/kg and 10 mg/kg. The objective of this study was to compare the economic impact of using personalized dosing (2 mg/kg) vs fixed dosing (200 mg) in the firstline setting of mNSCLC.

Methods: We performed a budget impact analysis from the US societal perspective to compare fixed dosing with personalized dosing.

Results: Our base case model demonstrates that the total annual cost of pembrolizumab with fixed dosing is US $3,440,127,429, and with personalized dosing it is US $2,614,496,846. The use of personalized dosing would lead to a 24.0% annual savings of US $825,630,583 in the United States.

Conclusions: Personalized dosing of pembrolizumab may have the potential to save approximately $0.825 billion annually in the United States, likely without impacting outcomes. This option should be considered for the firstline management of PD-L1-positive advanced lung cancer.


Possible solutions: more vials, take returns

Several policy options merit exploration. Regulators could require manufacturers to provide drugs in a reasonable set of size options to ensure the amount of wasted drug is low, say 3%. This is achievable, as table 3 illustrates. If all of our suggestions were adopted, it would lower revenue from leftover drug from $1.8bn to $400m and, including the reductions to doctor and hospital mark-ups on leftover drug, would save around $2bn in total. An alternative would be to leave manufacturers free to select their vial sizes but also require them to refund the cost of leftover drug. This could be achieved through certified disposal and a virtual return.

Source: Bach PB et al. BMJ. 2016; 352.
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### Manufacturers will say they can’t make more vials in a cost-effective way

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Smallest Powder Vial Price</th>
<th>Smallest Liquid Vial Price*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paclitaxel</td>
<td>$4.50</td>
<td></td>
</tr>
<tr>
<td>Methotrexate sodium</td>
<td>$2.31</td>
<td></td>
</tr>
<tr>
<td>Oxaliplatin</td>
<td>$38.70</td>
<td>$38.70</td>
</tr>
<tr>
<td>Cytarabine HCl</td>
<td>$0.88</td>
<td></td>
</tr>
<tr>
<td>Cisplatin</td>
<td>$7.76</td>
<td></td>
</tr>
<tr>
<td>Doxorubicin HCl</td>
<td>$3.10</td>
<td>$3.10</td>
</tr>
<tr>
<td>Dacarbazine</td>
<td>$7.56</td>
<td></td>
</tr>
</tbody>
</table>

*Average dollar value in the vials proposed is $462

**Source:** Bach PB et al. *BMJ.* 2016; 352.

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Table 3: Proposed additional single dose vial sizes to reduce the amount of waste on leftover drug for 18 out of 20 top selling cancer drugs in our analysis of which we propose one additional size and estimation of effect on waste in 2016.

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Currently available vial sizes (mg)</th>
<th>Proposed additional vial size</th>
<th>Estimated waste in 2016 (Sm)</th>
<th>Value of drug in additional vial ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paclitaxel</td>
<td>100, 30</td>
<td>77</td>
<td>8</td>
<td>203</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>50, 10</td>
<td>29</td>
<td>6</td>
<td>119</td>
</tr>
<tr>
<td>Pemetrexed</td>
<td>500, 100</td>
<td>60</td>
<td>55</td>
<td>116</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>400, 100</td>
<td>20</td>
<td>284</td>
<td>60</td>
</tr>
<tr>
<td>Ramucirumab</td>
<td>500, 100</td>
<td>40</td>
<td>29</td>
<td>432</td>
</tr>
<tr>
<td>Cetuximab</td>
<td>200, 100</td>
<td>50</td>
<td>20</td>
<td>267</td>
</tr>
<tr>
<td>Asparaginase E. chrysanthemi</td>
<td>100000</td>
<td>30000</td>
<td>14</td>
<td>1129</td>
</tr>
<tr>
<td>Eribulin</td>
<td>1, 0.25</td>
<td>22</td>
<td>6</td>
<td>256</td>
</tr>
<tr>
<td>Capecitabine</td>
<td>60, 2.5</td>
<td>27</td>
<td>3</td>
<td>372</td>
</tr>
<tr>
<td>Ado-trastuzumab emtansine</td>
<td>160, 100</td>
<td>20</td>
<td>24</td>
<td>564</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>100, 50</td>
<td>10</td>
<td>198</td>
<td>457</td>
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<tr>
<td>Carfilzomib</td>
<td>60, 2.5</td>
<td>231</td>
<td>19</td>
<td>78</td>
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<tr>
<td>Vedolizumib</td>
<td>45, 10</td>
<td>14</td>
<td>1</td>
<td>389</td>
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<tr>
<td>Nivolumab</td>
<td>100, 40</td>
<td>10</td>
<td>69</td>
<td>254</td>
</tr>
<tr>
<td>Rituximab</td>
<td>500, 100</td>
<td>40</td>
<td>254</td>
<td>53</td>
</tr>
<tr>
<td>Panitumumab</td>
<td>400, 200, 100</td>
<td>30</td>
<td>19</td>
<td>303</td>
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<tr>
<td>Bortezomib</td>
<td>2.5, 0.25</td>
<td>309</td>
<td>48</td>
<td>117</td>
</tr>
<tr>
<td>Ipilimumab</td>
<td>200, 50</td>
<td>10</td>
<td>46</td>
<td>1368</td>
</tr>
<tr>
<td>Total</td>
<td>—</td>
<td>—</td>
<td>1843.11</td>
<td>434.25</td>
</tr>
</tbody>
</table>

*Based on October 2015 ASP files.”
International Units.
$No longer marketed.

**Source:** Bach PB et al. *BMJ.* 2016; 352.
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Avastin Distribution

Spoilage Replacement Program

The Genentech Spoilage Replacement Program provides for replacement of infused, injected, and self-administered products, which are prescribed and prepared for a labeled indication, yet not administered due to unforeseen patient clinical circumstances, subject to certain limitations and conditions set forth by Genentech.

Please contact Genentech Customer Service at (800) 551-2231 to submit a request for replacement of spoiled product or to obtain additional information about the Program.

To request replacement product:

- Contact Genentech Customer Service at (800) 551-2231 to obtain the Genentech Spoilage Replacement Program Form.
- Complete the Genentech Spoilage Replacement Program Form and fax it back to Genentech Customer Service at (877) 329-6737 within 30 days of the spoilage event.
- The request may take up to 3 business days to review. If approved by Genentech, further instructions for returning product or completing a Certificate of Destruction will be provided.
- The spoiled product or completed Certificate of Destruction must be received by Genentech within 60 days of approval of the spoilage request.

Replacement product generally ships within 11 business days following receipt of the spoiled product or completed Certificate of Destruction.


What’s next?

- Medicare now requiring the JW modifier for discarded but billed drug (https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/HospitalOutpatientPPS/Downlodgs/JW-Modifier-FAQs.pdf). Creates possibility that Medicare will then be able to garner refund from manufacturer and sequester coinsurance billing to only used portion.

Q4. Is the JW modifier required on claims for single-dose drugs and biologicals? Effective January 1, 2017, the modifier must be used in order to obtain payment for a discarded amount of drug in single dose or single use packaging under the Medicare discarded drug policy. The modifier is not required if no discarded drug is being billed to any payer. (Overfill is discussed in question #7.)
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Which of the following statements is true?

a. Drugs are sold in the same size vials in all Western countries
b. It is not economically feasible to sell drugs in multiple vial sizes
c. Pembrolizumab personalized dosing for first-line NSCLC is projected to save $825m/yr in U.S.
d. Drug companies are required to provide refunds for leftover drug

Key Takeaways

- Drug waste related to single dose IV cancer drugs costs the U.S. healthcare system an estimated $3 billion
- Pharmaceutical companies’ package size choices produce $1.8 billion in revenue for these drug companies
- Potential policy pathways to address the issue
  - Require manufacturers to provide various vial size options
  - Require manufacturers to refund leftover drug
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Use of Drug Vial Optimization to Decrease Drug Waste

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North Carolina Cancer Hospital
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Rationale for Investigating Drug Vial Optimization (DVO)

- Significant pressure to reduce drug costs
  - Already optimized contracts and moved to cheaper medications
  - Focused on improving operational efficiency and reducing waste within the pharmacy
- Recognized that the department of pharmacy was throwing away partial vials of medications already purchased
- Wanted to quantify the amount and determine if there was a method to use the remaining amount

Drug Vial Waste

- Issues
  1. Cost
  2. Disposal
  3. Personnel exposure
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DVO Concept

- PhaSeal was CSTD being used
- PhaSeal protector
  - Protects employees because it is “closed”

CTSD = closed system transfer device

Studies Supporting DVO Concept

- Rowe et al.
  - One mL of antineoplastic drug (19 studied) with CSTD was removed at 6, 24, 48, and 72 hr and at 7 and 14 days
  - Resulted in overall contamination rate 1.86% with positive cultures deemed to be single isolates

- McMichael et al.
  - Drug vial contents with CSTD removed at 24, 48, 72, 96, and 168 hr
  - Resulted in overall contamination rate 1.8% indicating that there is a 98.2% probability of vial sterility at 168 hr

- Carey et al.
  - Follow-up study performed by injecting culture media into IV bag to keep the CSTD sterility maintained
  - Remaining methods followed the first study and resulted in 0.3% contamination rate, indicating a 99.7% probability that a vial would not be contaminated with bacterial growth at 168 hr when using the CSTD

Studies demonstrate ability to extend BUD beyond 6 hours with CSTD

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Drug Vial Optimization Definition

DVO
Optimizes contents in the vial by extending the period of sterility of the drug vial content to the drug’s chemical stability or a maximum of 7 days, whichever is earliest

Which of the following is true of drug vial optimization?

a. Used for nonhazardous drugs without a CSTD
b. Reduce waste by prolonging period of sterility of drug vial contents
c. Reduce waste by prolonging period of chemical stability of drug vial contents
d. Has not been studied
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**UNC Medical Center Implemented Comprehensive DVO program in 2011**

- Protected drug vials
- Drugs that are stable for an extended time
  - Bortezomib (C) – SQ
    - VIAL BEYOND USE DATE: 7 days
    - Refrigerate: 6 hr

- Institutional practices and procedures
  - Direct observation
  - Hand hygiene and garbing
  - Aseptic technique
  - Cleaning and disinfecting

- Quality assurance testing

**USP ISO Standards and Environmental Quality**

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**Pre- and Post-Implementation Strategies to Mitigate Risk Associated with DVO**

**Pre-Implementation**
- Site-specific sterility testing
- Drug compendium
- Staff competency and training
- Bin for “reusable” vials
- Development of BUD stickers or barcodes for vials

**Post-Implementation**
- Quality assurance testing
- Perform microbial testing using trypticase soy agar and sheep blood agar plates each month
- Track waste monthly to identify trends

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### Standard Process for DVO

1. **Label enters cleanroom**
2. **Technician pulls new vial for preparation**
3. **Technician places CSTD adaptor on vial and compounds medication**
4. **After finishing the preparation, technician places BUD sticker/barcode on partial vial**

- **Partial vial is placed in zippered bag inside large zippered bag with other supplies and final preparation**
- **As part of pharmacist product verification, DVO BUD sticker/barcode is checked for accuracy**
- **Partial vial is placed into bin for reusable vials**

- **As next label for same drug enters cleanroom, technician checks reusable bin first, then cleanroom storage location for partial vials, then cleanroom storage location for full vial**

- **Used drug vials that expire are placed in hazardous waste bin and documented as waste each night at close of business**

- **Waste is tracked electronically each month to identify trends**

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### RESULTS OF A COMPREHENSIVE DVO PROGRAM
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Annual Cost of Drug Waste with 19 Drugs Measured Each Year

Financial Impact of DVO on Drug Expense Budget

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DVO Reduces CSTDs Used

Impact of DVO on CSTD Purchases

Since DVO implemented, chemotherapy volume increased 30% with no change in CSTD adaptor purchases

Quality Assurance Testing to Mitigate Risk

- More than 1,240 plates tested
- Only two plates have shown contamination (single isolates) and both were determined to be user contaminants from Epidemiology
- Contamination rate lower than rates reported in literature
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DVO Clinical Metrics of Success

- Central line-associated bloodstream infection (CLABSI) – laboratory confirmed bloodstream infection in a patient with a central line
- One of the most deadly and costly hospital-associated infections
- Can be prevented by following checklists in placing, cleaning, and removing central lines

<table>
<thead>
<tr>
<th>Period</th>
<th>Total CLABSI</th>
<th>Average CLABSI Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1 2010 to Q3 2011 (21 months)</td>
<td>58</td>
<td>2.45</td>
</tr>
<tr>
<td>Q4 2011 to Q2 2013* (21 months)</td>
<td>54</td>
<td>1.99</td>
</tr>
<tr>
<td>Q3 2013 to Q1 2015 (21 months)</td>
<td>70</td>
<td>2.93</td>
</tr>
<tr>
<td>Q2 2015 to Q1 2016 (12 months)</td>
<td>31</td>
<td>2.44</td>
</tr>
</tbody>
</table>

*Drug vial optimization implemented in October 2011 (Q4 2011).
A comprehensive DVO program is most likely to result in __________.

a. Increase in CSTD purchases
b. Decrease in CLABSI rates
c. Decrease in drug waste
d. Increase in drug purchases

Key Takeaways

• Available data demonstrate the ability of drug vial optimization to safely extend drug vial contents using a CSTD
• Comprehensive drug vial optimization programs require infrastructure before, during, and after implementation
• Drug vial optimization can decrease drug waste without compromising patient safety
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Employing Processes and Technology to Reduce Drug Waste

Corbin Bennett, Pharm.D., M.P.H.
Senior Director of Oncology and Outpatient Infusion Pharmacy Services
National Pharmacy Programs and Services
Kaiser Permanente
Fresno, California

Kaiser Permanente Pharmacy

https://batchgeo.com/map/d84c7e71e068e9eb167198aa33144b93 (accessed 5 Nov 2017).

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Kaiser Permanente’s Pharmacy “Footprint”

Kaiser Permanente Pharmacy Fast Facts
Our pharmacists and staff are often the last interaction and serve as a primary point of contact for members throughout the care delivery process.

<table>
<thead>
<tr>
<th></th>
<th>Outpatient</th>
<th>Inpatient</th>
<th>Clinic Administered Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Sold Prescriptions</td>
<td>81.5 Million$\dagger$</td>
<td>44 Million²</td>
<td>10.6 Million²</td>
</tr>
<tr>
<td>Doses administered</td>
<td>44.2 Million</td>
<td>34 Million</td>
<td>21.3 Million</td>
</tr>
</tbody>
</table>

Our Member Reach

550 KP Pharmacy Patient Sites⁴
- 395 Outpatient and Inpatient Pharmacies +
- 90 Clinic Administered Sites
- 27 Call Center and Central Fill Operations

Employing 15,500 KP Pharmacy Staff Members⁵

~170,000 + Daily Member Interactions⁶
One of the highest volume and most frequent member touch points across our Kaiser Permanente network.

Drug Waste Reduction Strategies

- Dose rounding
- Dose capping
- Using overfill
- Patient scheduling
- Creating a virtual marketplace for excess drug
- Drug vial optimization
- Inventory management

Source:
(1) KP Pharmacy Outpatient Prescription Volume, 2016;
(2) National Pharmacy Acute & Transitional Care Services Leadership & Regional Operations Teams;
(4) KP Pharmacy Facilities Count Feb 2017 (with KP Washington);
(5) KP Pharmacy Employee Count – PeopleSoft 2016;
(6) Total KP Pharmacy Estimated Daily Member Interaction, 2017 (with KP Washington).

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Drug Waste - Types

- Unused drug in single-dose vials (SDVs)
- Expired drug
- Unused drug in multiple-dose vials (MDVs)

All of the following statements regarding dose rounding are true EXCEPT

a. Supported by HOPA and NCCN
b. Used for palliative therapy only
c. Used for cytotoxics and monoclonal antibodies
d. Involves rounding within 10% of prescribed dose

HOPA = Hematology/Oncology Pharmacy Association
NCCN = National Comprehensive Cancer Network
Dose Rounding

- HOPA – “Dose Rounding of Biologic and Cytotoxic Anticancer Agents”
  - Monoclonal antibodies and other biologic agents dose rounded to the nearest vial size within 10% of the prescribed dose
  - Cytotoxic agents be considered independently for dose rounding within 10% of the prescribed dose
  - Use the same threshold for palliative and curative treatment


Kaiser Permanente (KP) - Dose Rounding

- Dose round cytotoxics and monoclonal antibodies up to 10% for all palliative patients
- Approved by Interregional Chiefs of Oncology and Pharmacy and Therapeutics Committees
- Dose rounding protocols with pharmacist collaborative practice agreements in some KP regions
Dose Capping

• Maximum dose administered regardless of patient’s weight or body surface area (BSA)
• Must be based on clinical evidence / trials


Dose Capping

• Nivolumab: What is the dose?
• Historically 3 mg/kg every 2 weeks
• September 13, 2016 – Food and Drug Administration (FDA) modified dosage regimen for nivolumab (Opdivo, Bristol-Myers Squibb Co.) for the currently at that time approved indications for renal cell carcinoma (RCC), metastatic melanoma, and non-small cell lung cancer (NSCLC)
• FDA determined overall exposure at flat dose of 240 mg every 2 weeks is similar to 3 mg/kg every 2 weeks (less than 6% difference)

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Dose Capping

• Historical weight-based 3 mg/kg dosing still used when clinically appropriate
• Dose CAPPING nivolumab at 240 mg for solid tumor indications approved by KP Chiefs of Oncology
• Updated order sets to reflect change
  • NIVOLUMAB (DOSE CAPPED)
    Nivolumab (3 mg/kg, max 240 mg); q14d

Nivolumab Dose Rounding Rationale

In study MDX1106-03, increasing doses of nivolumab were tested in order to evaluate efficacy response in patients with different type of tumours. There was a greater percent of objective responses observed in NSCLC subjects treated with 3 mg/kg (24.3%) and 10 mg/kg (20.3%) nivolumab than with 1 mg/kg (3%) nivolumab. There was no apparent relationship between nivolumab dose and ORR in melanoma and RCC (Table 10).

<table>
<thead>
<tr>
<th>Nivolumab Dose (mg/kg)</th>
<th>% Objective Response Rate (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All NSCLC</td>
<td>NA</td>
</tr>
<tr>
<td>Melanoma</td>
<td>NA</td>
</tr>
<tr>
<td>N=17</td>
<td>N=18</td>
</tr>
<tr>
<td>RCC</td>
<td>NA</td>
</tr>
</tbody>
</table>

- Mean study weight was 81 mg (Avg Adult = 80 kg); 3 mg/kg x 80 mg = 240 mg
- Dose/Exposure & Response appear to be relatively flat in Melanoma and RCC.
- Greatest response seen at doses > 3mg/kg for NSCLC

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Dose Capping plus Rounding

• Dose Rounding nivolumab down no more than 10% to minimize drug waste in advanced renal cell carcinoma, metastatic melanoma, and metastatic non-small cell lung cancer

• Two 100-mg vials plus one 40-mg vial = reduced waste!

Nivolumab

<table>
<thead>
<tr>
<th>Kaiser Permanente Subspecialty Endorsements</th>
<th>Indication</th>
<th>240 mg Dose Cap</th>
<th>Dose Rounding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melanoma</td>
<td>Unresectable or metastatic melanoma</td>
<td>N/A</td>
<td>√</td>
</tr>
<tr>
<td></td>
<td>+ Ipilimumab (4 doses)</td>
<td>N/A</td>
<td>√</td>
</tr>
<tr>
<td></td>
<td>Maintenance</td>
<td>N/A</td>
<td>√</td>
</tr>
<tr>
<td>Lung</td>
<td>Metastatic NSCLC</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
<td>Classical Hodgkin lymphoma</td>
<td>NO</td>
<td>√</td>
</tr>
<tr>
<td>Head and neck</td>
<td>Metastatic or recurrent SCCHN</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>Locally advanced or metastatic urothelial carcinoma</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td></td>
<td>Advanced renal cell carcinoma</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Oncology chiefs</td>
<td>Off-label</td>
<td>Pending</td>
<td>Pending</td>
</tr>
</tbody>
</table>

SCCHN = squamous cell carcinoma of head and neck

Courtesy of David Chen, Pharm.D., KP Northern California Drug Use Management, 10/12/17.
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Overfill

• Use manufacturer vial overfill to reduce waste
• Why overfill?
  – Cost!
• Potential to combine with dose rounding to further maximize savings

Overfill and Dose Rounding

• Nivolumab overfill
  • 40-mg vial – 5 mg of overfill
  • 100-mg vial – 5 mg of overfill
• Example: 64-kg patient at dose of 3 mg/kg
  • Total dose 192 mg
  • Round down to 180 mg (2.8 mg/kg)
  • Compound using four 40-mg vials (160 mg + 20 mg overfill)
• Cost savings ~20%

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Overfill and Dose Rounding

<table>
<thead>
<tr>
<th></th>
<th>Bevacizumab</th>
<th>Rituximab*</th>
<th>Cetuximab</th>
<th>Total Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost</td>
<td>Confidential</td>
<td>Confidential</td>
<td>Confidential</td>
<td>Confidential</td>
</tr>
<tr>
<td>Estimated waste</td>
<td>4.1%</td>
<td>2.0%</td>
<td>15.9%</td>
<td>3.6%</td>
</tr>
<tr>
<td>Overfill mg per vial</td>
<td>7 mg</td>
<td>5 mg</td>
<td>2 mg</td>
<td></td>
</tr>
<tr>
<td>Savings using overfill</td>
<td>Confidential</td>
<td>Confidential</td>
<td>Confidential</td>
<td>Confidential</td>
</tr>
<tr>
<td>Savings with 10% round down to full vial</td>
<td>Confidential</td>
<td>Confidential</td>
<td>Confidential</td>
<td>Confidential</td>
</tr>
</tbody>
</table>

*Two thirds of rituximab mg are used in Hematology/Oncology

Savings of 2.3% of total cost

Courtesy of David Chen, Pharm.D., KP Northern California Drug Use Management, 10/12/17.

Overfill and Dose Rounding

- Physician education and communication
- Pharmacy education and communication
- Systems
  - Dose calculator for Pharmacy

Instructions to calculate a nivolumab dose for an individual patient:
1. Choose an indication for nivolumab from the pull down menu in the green field
2. Enter a weight in kilograms in the yellow field without the units
3. You may copy and paste the compounding instructions onto the label

Compound using 4 x 40 mg vial(s) and 0 x 100 mg vial(s)

Courtesy of David Chen, Pharm.D., KP Northern California Drug Use Management, 10/12/17.
Collaborative Effort

• Physicians
  – Evaluate and approve dose rounding as appropriate
  – Determine most appropriate weight (i.e., ideal, adjusted, actual) to use as basis for dosing

• Pharmacy
  – Maximize use of manufacturer overfill
  – Use dose rounding based on weight recommendations of physicians

Nivolumab Waste Minimization Strategy Recap

<table>
<thead>
<tr>
<th>FDA-Approved Indication</th>
<th>240-mg Flat Dose Cap</th>
<th>Dose Rounding</th>
<th>Maximizing Overfill</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unresectable or metastatic melanoma</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Nivolumab single agent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nivolumab + ipilimumab</td>
<td></td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Maintenance nivolumab</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Advanced RCC</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Metastatic NSCLC</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Classical Hodgkin Lymphoma</td>
<td></td>
<td></td>
<td>√</td>
</tr>
</tbody>
</table>

Courtesy of David Chen, Pharm.D., KP Northern California Drug Use Management, 10/12/17.
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**Checkpoint Inhibitors**

<table>
<thead>
<tr>
<th></th>
<th>Weight-Based Dosing</th>
<th>Flat Dosing</th>
<th>Multiple Vial Sizes</th>
<th>Dose Rounding</th>
<th>Dose Capping</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab</td>
<td>3 mg/kg</td>
<td>240 mg</td>
<td>Yes</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>2 mg/kg</td>
<td>200 mg</td>
<td>No</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Atezolizumab</td>
<td>15 mg/kg</td>
<td>1200 mg</td>
<td>No</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Avelumab</td>
<td>10 mg/kg</td>
<td>None</td>
<td>No</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Durvalumab</td>
<td>20 mg/kg</td>
<td>1500 mg</td>
<td>Yes</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

Courtesy of David Chen, Pharm.D., KP Northern California Drug Use Management, 10/12/17.

**Trastuzumab (Herceptin) Vial Size**

- July 7, 2017 – 440-mg MDV discontinued
- Move from 440-mg MDVs to 150-mg SDVs resulting in significant additional cost

<table>
<thead>
<tr>
<th></th>
<th>440-mg Vial</th>
<th>150-mg Vial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>Lyophilized sterile powder</td>
<td>Lyophilized sterile powder</td>
</tr>
<tr>
<td>Diluent</td>
<td>20 mL Bacteriostatic water for Injection (BWFI) - SUPPLIED</td>
<td>7.4 mL Sterile Water for Injection (SWFI) – NOT SUPPLIED</td>
</tr>
<tr>
<td>Concentration</td>
<td>21 mg/mL</td>
<td>21 mg/mL</td>
</tr>
<tr>
<td>Vial type</td>
<td>MDV (1.1% benzyl alcohol as preservative)</td>
<td>SDV (no preservative)</td>
</tr>
<tr>
<td>Vial expiration</td>
<td>28 days</td>
<td>6 hours</td>
</tr>
<tr>
<td>Storage</td>
<td>Refrigerate (2°C to 8°C)</td>
<td>Refrigerate (2°C to 8°C)</td>
</tr>
</tbody>
</table>

Courtesy of David Chen, Pharm.D., KP Northern California Drug Use Management, 10/12/17.
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Trastuzumab Vial Size

• Waste reduction strategy
  – 10% dose rounding down in palliative patients to full vials
  – Reduce visit frequency – change from 2 mg/kg once weekly to 6 mg/kg every 3 weeks
  – Staging - use 150-mg SDV for patients visiting early in the day, reserve 440-mg MDV for last patient of the day

Courtesy of David Chen, Pharm.D., KP Northern California Drug Use Management, 10/12/17.

Trastuzumab Vial Size

• Waste reduction strategy (continued)
  – Patient scheduling - stack patients on same day
    • Successful with other drugs, i.e., “Bortezomib Days”
  – Consider centralization of compounding
  – Consider internal stability and sterility studies to use SDV as MDV

Courtesy of David Chen, Pharm.D., KP Northern California Drug Use Management, 10/12/17.
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Marketplace

- Oncology Waste and Surplus Application (OWASA)

OWASA: Waste Log

- Captures waste by date, site, drug, reason, and amount
- Creates a waste manifest
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**OWASA: Surplus Log**

- Surplus entries allow for real-time posting of available drugs

**USP Chapter <800>**

- Protects patients, personnel, and the environment from exposure to hazardous drugs

- Section 5.4 “Closed System Drug-Transfer Devices (CSTDs) **should** be used when compounding HDs when the dosage form allows. CSTDs must be used when administering antineoplastic HDs when the dosage form allows.
  - Potential to use CSTD for reduction in drug waste
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USP Chapter <800>

• Section 11.4 “Disposal of all hazardous drug (HD) waste, including, but not limited to, unused HDs and trace-contaminated PPE and other materials, must comply with all applicable federal, state, and local regulations.”
  – Deploy waste strategy – Most-in-One containers vs. “The Rainbow” (one bin for each waste stream)

PPE = personal protective equipment

Drug Vial Optimization

• Extending the sterility beyond-use date (BUD) of SDVs to 72 hours using a CTSD
• Required program elements
  – DVO policy
  – Adherence to USP Chapter <797>
  – DVO readiness checklist
    • Compliant facilities
    • Staff training and demonstrated competency
    • Quality assurance program
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Drug Vial Optimization

• Quality assurance program

Inventory Management

• Use technology to reduce obsolescence
• Reduce inventory turns
• Perpetual inventory systems
  – Interface with compounding workflow systems and electronic medical record
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Key Takeaways

• Drug waste is a cost driver in healthcare
• Organizations can implement work practices to reduce drug waste and cost
• Dose rounding is an effective process in reducing drug waste

Acknowledgments

Thank you to the Kaiser Permanente Drug Use Management teams, Chiefs of Oncology, Julie Kakuda, and David Chen
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What will you do as a follow-up to today’s program? (Select all that apply)

a. Discuss drug waste issues with my healthcare colleagues
b. If using CSTDs, develop process for keeping track of vials
c. If using CSTDs, ensure vials are used within appropriate BUD
d. Identify processes or technology to help minimize drug waste
e. Review inventory practices for opportunities to ↓ drug waste

Useful Resources


• Drug Pricing Lab (Memorial Sloan Kettering)
  – General website: https://drugpricinglab.org/

  – Available at https://www.nccn.org/professionals/OrderTemplates/PDF/HOPA.pdf (accessed 5 Nov 2017)
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✓ Deadline: January 31
✓ elearning.ashp.org
✓ Code: ________________
✓ Complete evaluation
✓ Additional instructions in handout

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www.ashpadvantage.com/go/drugwaste

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3. Enter the Attendance Codes that were announced during the sessions and click Submit.

4. Click Claim for any session.

5. Complete the Evaluation.

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On-demand activity of today’s live symposium coming in March 2018

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