Memorial Sloan Kettering Cancer Center

Drug Waste due to Single Dose Vials: History and Solution(s)

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Why is their drug waste?

- Certain drugs have narrow therapeutic windows
  - They are often dosed based on patient 'size' (most often weight, sometimes more complex calculation)
- Many expensive drugs also come packaged in 'single use' vials (either as liquid or powder)
  - The technical term is 'single dose vial', the FDA term is 'immediate container'
- As a result, there is nearly always leftover drug after extracting the dose
- 'Buy and bill' means whole vial purchased and reimbursed
- Pharma companies control the vial sizes

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

How different vials affect waste

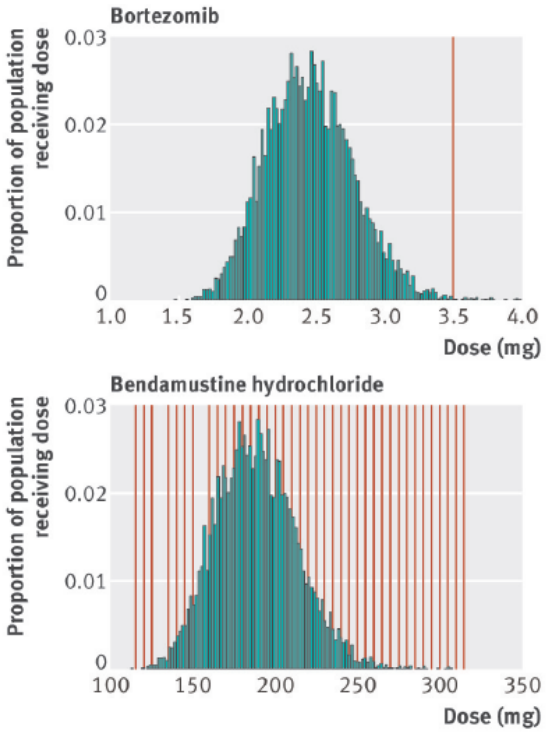

Fig 2 Distribution of FDA approved dose (green histogram) in the US population of cancer patients, and available combinations of full vial contents (red lines) to achieve that dose for bortezomib (top) and bendamustine (bottom)

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

Table 1| **Top 20 infused cancer drugs based on projected 2016 sales sold in single dose vials and dosed based on patient body size**

Drug (brand name), year of FDA approval	Dose of first approved indication (highest approved dose at any time)	Amount of drug in available single dose vials (discontinued vial sizes)*	Vial sharing			2016 expected sales ($m)	2016 expected revenue from leftover drug ($m)
			% of leftover drug using only full vials	% doses with vial sharing	% of leftover drug adjusted for frequency of vial sharing†		
Paclitaxel protein bound (Abraxane), 2005	Breast 260 mg/m^2	100	9	16	8	960.77	76.72
Brentuximab vedotin (Adcetris), 2011	Lymphoma 1.8 mg/kg	50	15	36	10	292.18	29.15
Pemetrexed (Alimta), 2004	Mesothelioma/lung 500 mg/ m^2	100, 500	5	16	4	1269.04	54.64
Bevacizumab (Avastin), 2004	Colorectal 5 (15) mg/kg	100, 400	11	19	9	3159.32	284.49
Ramucirumab (Cryamza), 2014	Gastric 8 (10) mg/kg	100, 500	7	16‡	6	471.55	28.78
Cetuximab (Erbitux), 2004	Head/neck 250 (400) mg/m^2	100, 200	6	19	5	570.22	29.18
Asparaginase Erwinia chrysanthemi (Erwinaze), 2011	All 25000 IU/ m^2	10000	10	16‡	8	170.40	14.13
Eribulin (Halaven), 2010	Breast 1.4 mg/ m^2	1	15	18	13	167.71	21.85
Cabazitaxel (Jevtana), 2010	Prostate 25 mg/m^2	60	23	12	21	127.96	26.89
Ado-trastuzumab emtansine (Kadcyla), 2013	Breast 3.6 mg/kg	100, 160	7	16‡	6	413.96	23.66
Pembrolizumab (Keytruda), 2014	Melanoma 2 mg/kg	(50), 100	24	16‡	21	943.07	197.94
Carfilzomib (Kyprolis), 2012	Myeloma 20 (27) mg/ m^2	60	37	16‡	33	697.65	231.45
Filgrastim (Neupogen), 1991	Neutropenia 5 (10) µg/kg	300, 480	17	0§	17	623.85	106.01
Irinotecan liposome (Onivyde), 2015	Pancreatic 70 mg/m^2	43	7	16	6	118.09	7.13
Nivolumab (Opdivo), 2014	Melanoma 3 mg/kg	40, 100	4	16‡	3	2078.63	68.93
Rituximab (Rituxan), 1997	Non-Hodgkin's lymphoma 375 (500) mg/m^2	100, 500	7	0§	7	3852.75	253.85
Bendamustine (Treanda), 2008	Chronic lymphocytic leukemia 100 (120) mg/ m^2	25, 45, 100, 180	1	6	1	563.44	7.38
Panitumumab (Vectibix), 2006	Colorectal 6 mg/kg	100, 200, 400	10	17	8	237.41	18.72
Bortezomib (Velcade), 2003	Myeloma:1.3 mg/ m^2	3.5	30	16	27	1160.64	308.74
Ipilimumab (Yervoy), 2011	Melanoma 3 mg/kg	50, 200	10	22	7	620.22	46.47
Total	—	—	—	—	—	18 498.86	1836.11

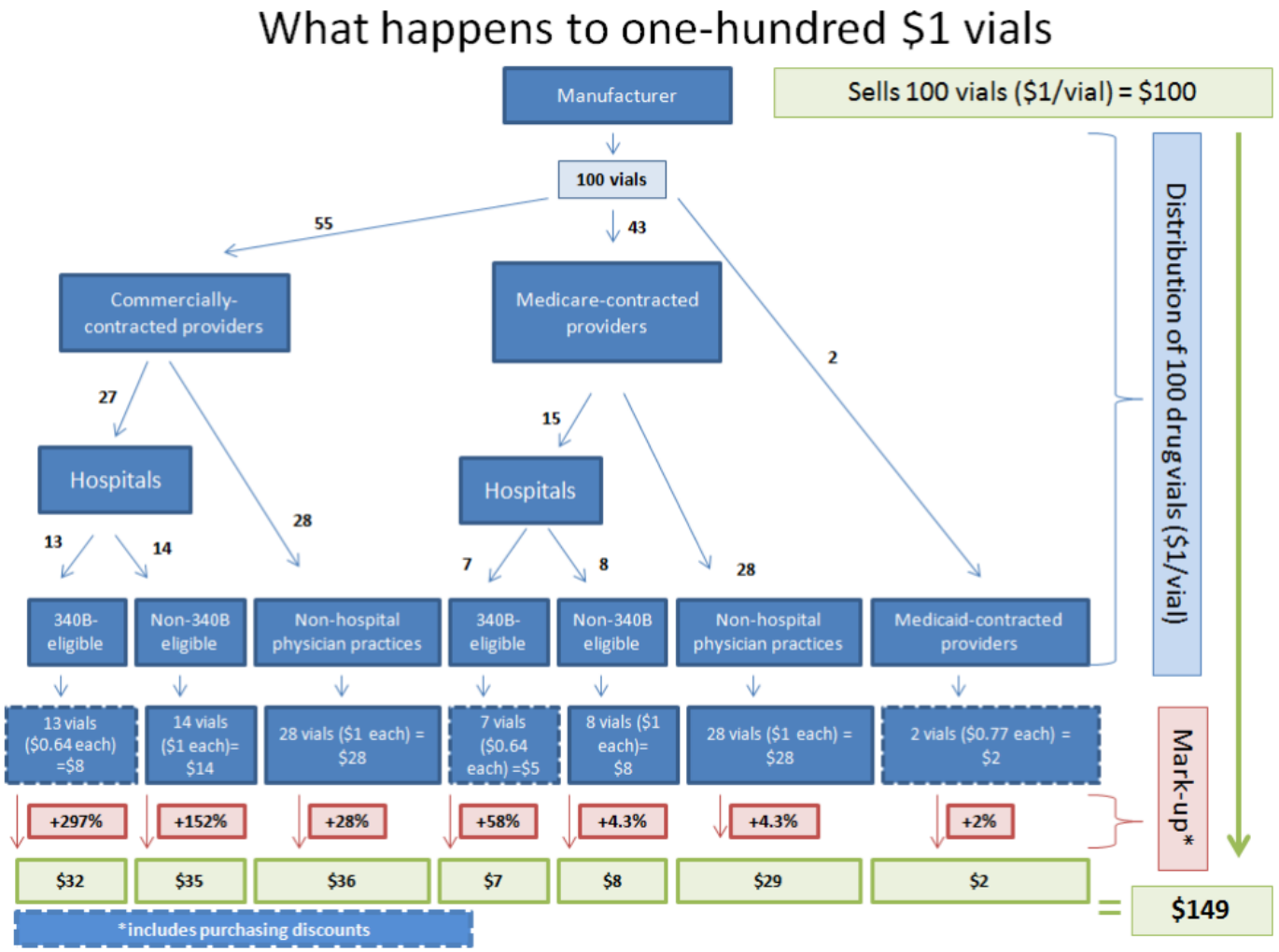
*All amounts in mg except for filgrastim (µg) and asparaginase (IU). Filgrastim also sold in single dose prefilled syringes.

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

Is there evidence the vial size is a focus of the companies?

- Revenue = P*Q (larger vials indirectly increase P)
  - The "Prior" is strong here: there are hundreds of millions at stake, these companies are skilled at understanding the sources of their revenue
- There are actions that suggest focus on this issue
  - Drugs sold in larger vials in the US than overseas
- An added benefit: Doctors and hospitals make a 'mark-up' based on the cost of the drug administered (the Average Sales Price or "ASP").
  - This payment goes up with drug waste
  - All studies show that larger mark-ups attract discretionary prescribing

Figure 1: Distribution and mark-up of one-hundred $1 vials by payer and provider



Enclosure B

Vial Sizes Approved for Selected Drugs in the United States, Canada, and the European Union in 2013 and 2014

HCPCS Code	Brand Name	Short Description	Vial Sizes FDA-Approved in the United States			Vial Sizes Approved in Canada			Vial Sizes Approved in the EU	
J0585	Botox^	Injection, onabotulinumtoxinA	50units	100units	200units	50units	100units	200units	100units	-
J0775	Xiaflex	Collagenase, clost hist inj	0.90mg	-	-	0.90mg	-	-	-	-
J0878	Cubicin*,^	Daptomycin injection	500mg	-	-	500mg	-	-	350mg	500mg
J0894	Dacogen*	Decitabine injection	50mg	-	-	-	-	-	50mg	-
J1745	Remicade	Infliximab injection	100mg	-	-	100mg	-	-	100mg	-
J2357	Xolair^	Omalizumab injection	75mg	150mg	-	150mg	-	-	75mg	150mg
J2796	Nplate	Romiplostim injection	250mcg	500mcg	-	250mcg	500mcg	-	250mcg	500mcg
J9025	Vidaza*	Azacitidine injection	100mg	-	-	100mg	-	-	100mg	-
J9033	Treanda	Bendamustine injection	25mg	100mg	-	25mg	100mg	-	-	-
J9035	Avastin	Bevacizumab injection	100mg	400mg	-	100mg	400mg	-	100mg	400mg
J9041	Velcade^	Bortezomib injection	3.5mg	-	-	3.5mg	-	-	1mg	3.5mg
J9043	Jevtana	Cabazitaxel injection	60mg	-	-	60mg	-	-	60mg	-
J9047	Kyprolis	Injection, carfilzomib	60mg	-	-	60mg	-	-	60mg	-
J9055	Erbitux^	Cetuximab injection	100mg	200mg	-	100mg	200mg	-	100mg	500mg
J9179	Halaven^	Eribulin mesylate injection	1mg	-	-	1mg	-	-	.88mg	1.32mg
J9228	Yervoy	Ipilimumab injection	50mg	200mg	-	50mg	200mg	-	50mg	200mg
J9263	Eloxatin*	Oxaliplatin	50mg	100mg	-	50mg	100mg	-	-	-
J9264	Abraxane^	Paclitaxel protein bound	100mg	-	-	100mg	-	-	100mg	250mg
J9305	Alimta	Pemetrexed injection	100mg	500mg	-	100mg	500mg	-	100mg	500mg
J9310	Rituxan	Rituximab injection	100mg	500mg	-	100mg	500mg	-	-	-

EU—European Union
HCPCS—Healthcare Common Procedure Coding System (HCPCS) is a standardized coding system used to ensure that claims are processed in a consistent and orderly manner.
* Drugs with generic equivalents approved by the FDA during the period reviewed.
^ Drugs with vial sizes *not* marketed in the United States but available in other countries.

BNF

Keytruda 50mg powder for concentrate for solution for infusion vials (Merck Sharp & Dohme Ltd) ▼

Pembrolizumab 50 mg

- 1 vial PoM

FDA U.S. FOOD & DRUG ADMINISTRATION

KEYTRUDA® (pembrolizumab) injection, for intravenous use
Initial U.S. Approval: 2014

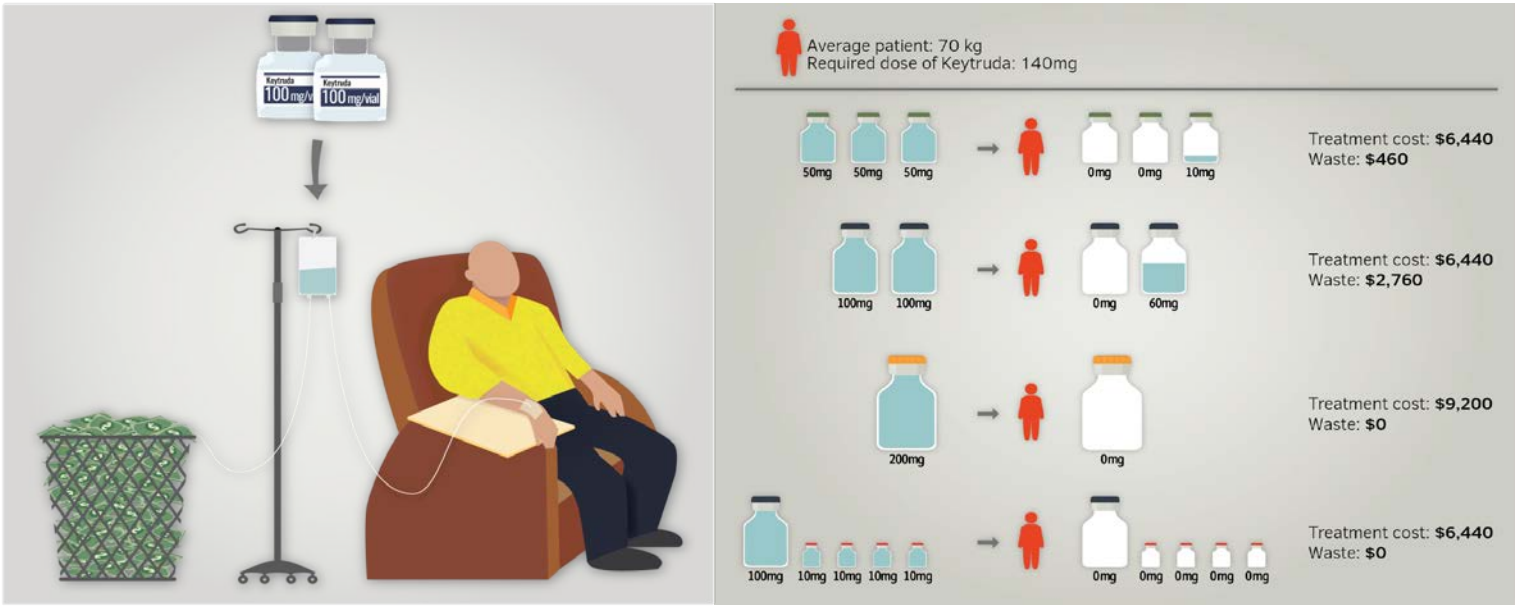
----------DOSAGE FORMS AND STRENGTHS ----------

- Injection: 100 mg/4 mL (25 mg/mL) solution in a single-dose vial (3)

thebmj

Overspending driven by oversized single dose vials of cancer drugs

Peter B Bach and colleagues call for an end to contradictory regulatory standards in the US that allow drug manufacturers to boost profits by producing single dose vials containing quantities that increase leftover drug



The New York Times

Waste in Cancer Drugs Costs $3 Billion a Year, a Study Says

By GARDINER HARRIS MARCH 1, 2016

Comparison of excess revenue due to vial sizes of Keytruda

Table 2| **Projected revenue from sales of pembrolizumab comparing scenarios with revenue only from administered drug, revenue based on 50 mg vial sizes with reimbursement for leftover drug, and revenue based on 100 mg vial sizes with reimbursement for leftover drug. Data based on pooled analyst estimates compiled by Defined Health.**

Year of sales	Revenue from dose only ($m)	Revenue from dose and leftover using 50 mg vials ($m)	Revenue from dose and leftover using 100 mg vials ($m)
2016	762	862	964
2017	1335	1510	1690
2018	1991	2253	2520
2019	2346	2654	2969
2020	2687	3040	3401
Total	9121	10 320	11 544

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

JNCI JOURNAL of the NATIONAL CANCER INSTITUTE

A Phamacoeconomic 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 between personalized and fixed 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.

Published March 2017

Source: Goldstein DA et al. J Natl Cancer Inst. 2017 Nov 1 [Epub ahead of print].

We stopped our analysis in 2014, here are new drugs that have the same problem

Brand Name	Approval Date	Approval Year	Dose of first approved indication (Highest approved dose at any time)	Amount of drug in available single dose vials*
Beleodaq	belinostat	2014	1000 mg/m2	500
Onivyde	irinotecan liposome	2015	70 mg/m2	43
Yondelis	trabectedin	2015	1.5 mg/m2	1
Darzalex	daratumumab	2015	16 mg/kg	400, 100
Imfinzi	durvalumab	2017	10 mg/kg	500, 120
Vyxeos	daunorubicin, cytarabine	2017	44 mg/m2, 100 mg/m2	44
Besponsa	inotuzumab ozogamicin	2017	0.5 mg/m2 (0.8 mg/m2)	0.9
Ogivri	trastuzumab-dkst	2017	2 mg/kg (8 mg/kg)	420
Lumoxiti	moxetumomab pasudotox-tdfk	2018	0.04 mg/kg	1
Elzonris	tagraxofusp-erzs	2018	12 mcg/kg	1000
Herzuma	trastuzumab-pkrb*	2018	2 mg/kg (6 mg/kg)	420
Truxima	rituximab-abbs*	2018	375 mg/m2	500, 100
Gamifant	emapalumab	2018	1 mg/kg	50, 10
Lumoxiti	moxetumomab pasudotox-tdfk	2018	0.04 mg/kg	1
Polivy	polatuzumab vedotin-piiq	2019	1.8 mg/kg	140
Padcev	enfortumab vedotin-ejfv	2019	1.25 mg/kg	30, 20
Enhertu	fam-trastuzumab deruxtecan-nxki	2019	5.4 mg/kg	100

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80 kg, 1.9 m2 patient mass assumed
*All amounts in mg except for Elzonris (mcg)

New thyroid eye disease drug

Typical waste is ½ vial
Treatment is 8 doses
Waste is around $56K

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use TEPEZZA safely and effectively. See full prescribing information for TEPEZZA.

TEPEZZA (teprotumumab-trbw) for injection, for intravenous use
Initial U.S. Approval: 2020

----------INDICATIONS AND USAGE----------
TEPEZZA is an insulin-like growth factor-1 receptor inhibitor indicated for the treatment of Thyroid Eye Disease (1)

----------DOSAGE AND ADMINISTRATION----------
- Initiate dosing with 10 mg/kg for first infusion, followed by 20 mg/kg every 3 weeks for 7 additional infusions (2.1)
- Administer TEPEZZA by intravenous infusion over 60 to 90 minutes (2.3)

----------DOSAGE FORMS AND STRENGTHS----------
For Injection: 500 mg lyophilized powder in a single-dose vial for reconstitution (3)

----------CONTRAINDICATIONS----------
None (4)

----------WARNINGS AND PRECAUTIONS----------
- Infusion reactions: If an infusion reaction occurs, interrupt or slow the rate of infusion and use appropriate medical management (5.1)

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So CMS added a 'waste' (JW) Modifier

- Effective January 1, 2017, providers and suppliers are required to report the JW modifier on Part B claims for discarded drugs and biologicals

03.10.16

Senators Ask For Investigation Into Large One-Size-Fits-All Cancers Med That Costs Patients & Taxpayers Billions

Letter Follows New York Times Report That Nearly $3 Billion Is Wasted On Cancer Medicines That Are Ultimately Discarded

05.20.16

Senators Urge HHS Inspector General To Conduct Study To Determine An Of Federal Waste From One-Size-Fits-All Drug Vials

Manufacturers Are Distributing Expensive Cancer Drugs In Vials That Contain Larger Dosages Than Ne The Average Patient Resulting In The Waste & Unnecessary Cost To Taxpayers

06.09.16

Durbin: Senate Committee Approves Study Of One-Size-Fits-All Cancer Medication That Costs Patients & Taxpayers Billions

Practice Sees Medicare And Private Health Insurers Wasting Nearly $3 Billion Each Year On Cancer Me That Are Ultimately Discarded

Medicare Reimbursement for Partial Vials and Amounts Identified by the JW Modifier in 2013 and 2014

HCPCS Code	Brand Name	Total Partial Vials (includes discard)	Total JW (discard)	Identified Percentage of Discard in Partial Vials
J0585	Botox	$58,295,805	$6,031,393	10.35%
J0775	Xiaflex	8,280,341	2,746,062	33.16%
J0878	Cubicin	58,691,928	2,112,551	3.60%
J0894	Dacogen	69,087,477	12,293,699	17.79%
J1745	Remicade	93,267,221	4,741,588	5.08%
J2357	Xolair	62,445,456	5,594,825	8.96%
J2796	Nplate	48,900,547	9,263,396	18.94%
J9025	Vidaza	102,368,346	17,921,242	17.51%
J9033	Treanda	136,458,496	9,167,291	6.72%
J9035	Avastin	489,986,519	16,284,335	3.32%
J9041	Velcade	234,138,819	46,918,836	20.04%
J9043	Jevtana	35,229,783	6,783,521	19.26%
J9047	Kyprolis	38,323,088	5,777,084	15.07%
J9055	Erbitux	114,317,058	6,047,057	5.29%
J9179	Halaven	23,394,949	2,122,454	9.07%
J9228	Yervoy	117,113,619	5,779,297	4.93%
J9263	Eloxatin	35,140,057	2,268,312	6.46%
J9264	Abraxane	112,341,306	12,498,466	11.13%
J9305	Alimta	223,794,074	10,127,510	4.53%
J9310	Rituxan*	10,115,579	10,115,579	100.00%
Totals		**$2,071,690,468**	**$194,594,498**	**9.39%**

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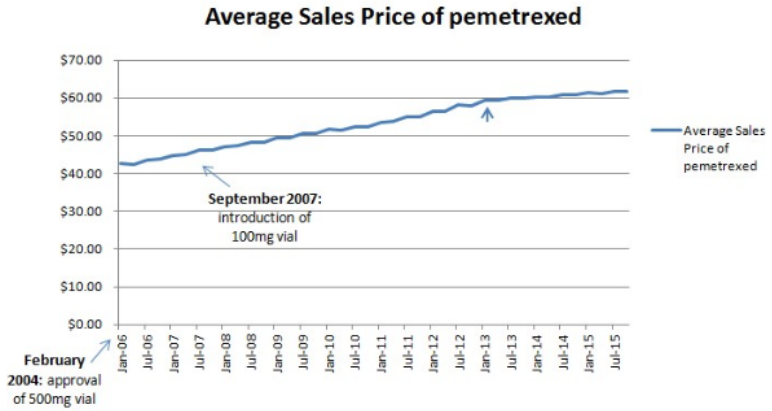
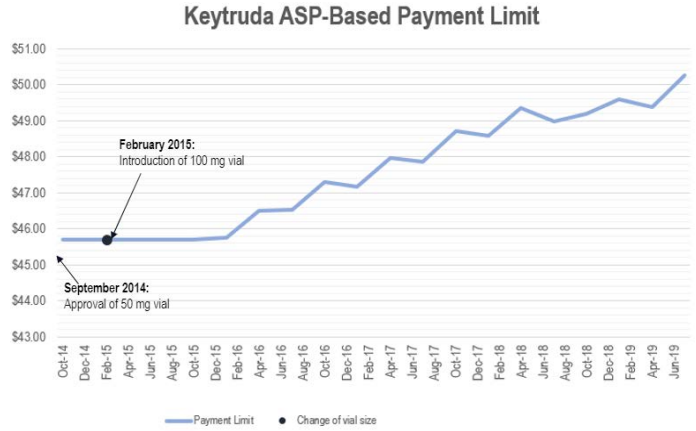
https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/HospitalOutpatientPPS/Downloads/JW-Modifier-FAQs.pdf

Economists will say changing vial sizes will just be compensated for by change in prices

- Yes, in theory, but prices and reimbursement are opaque to payers
  - Cost-effectiveness analyses in US are based on dosed amount, not total amount
  - Empiric evidence with vial changes do not support compensatory response
    - Pemetrexed had new smaller vial, Keytruda had new larger vial





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Possible solutions: more vials or take returns (virtually)

- Potential policy pathways to address the issue include:
  - Require manufacturers to provide various vial size options
  - Require manufacturers to refund leftover drug

> 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⇓ shows. 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 P et al. *BMJ.* 2016; *352*.

https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/HospitalOutpatientPPS/Downloads/JW-Modifier-FAQs.pdf

Have manufacturers provide smaller vials

- Manufacturing costs can be substantial, while vials themselves, are cheap to manufacture.

Generic Name	Smallest Powder Vial Price	Smallest Liquid Vial Price*
Paclitaxel		$4.50
Methotrexate sodium		$2.31
Oxaliplatin	$38.70	$38.70
Cytarabine HCl		$0.88
Cisplatin		$7.76
Doxorubicin HCl	$3.10	$3.10
Dacarbazine		$7.56

*Average dollar value in the vials proposed is $462

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

Require manufacturers to refund leftover drug

Proposals:

- Recovering Excessive Funds for Unused and Needless REFUND Act
  - Require manufacturers of single-use vial drugs under Medicare Part B to provide the program with rebates for discarded drugs
    - The JW modifier makes this possible
- The Prescription Drug Pricing Reduction Act of 2019
  - Require manufacturers to provide a refund to providers for unused amount of single-use vial drugs under Medicare Part B when amount wasted exceeds 10% of amount paid by Medicare

https://www.congress.gov/bill/116th-congress/senate-bill/551/text
https://www.congress.gov/bill/116th-congress/senate-bill/2543/text

Thank You

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