Reducing drug wastage in pharmaceuticals dosed by weight or body surface areas by optimising vial sizes

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Running title:

Reducing drug wastage in pharmaceuticals by optimising vial sizes

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Abstract

Background

When pharmaceuticals are dosed based on patient characteristics (for example weight or body surface area), an amount of product will be unused and must be disposed of. This wastage represents inefficiency and can distort decision making.

Methods

We present a method for the analysis of optimum fill volumes of pharmaceuticals to minimise wastage across a patient population, using publicly available data. Wastage for patients at each 'step' e.g. by kg of bodyweight is calculated, the frequency of each of these steps in the structure of the population is then estimated using the method of moments, with wastage then estimated for each 'step' multiplied by its prevalence. Illustrative examples of pembrolizumab and cabazitaxel show how wastage could be reduced using UK population data, whilst simultaneously reducing administrative burden.

Results

Changing the available vial sizes for pembrolizumab (available as 50mg/100mg vials) to 70mg/100mg, wastage could be cut from 13.3% to 8.7%. For cabazitaxel (only 60mg vials available), increasing the fill to 70mg could reduce wastage from 19.4% to 18.8%, or alternatively adding a 12.5mg vial reduce this to 6.5%. A secondary finding is that wastage is higher when the larger vial size is perfectly divisible by the smaller vial size.

Conclusions

Reductions in wastage have the potential to reduce the cost of manufacturing medicines, which is not necessarily low for novel products. These cost reductions could lead to increased profit (at the same prices), constant profit with a better return rate (at lower prices), or a combination of the two. Most importantly they would improve the efficiency of the health care sector, increasing funding available to treat patients.

Key points for decision makers

- Where the dose of pharmaceuticals must be calculated on a per patient basis (e.g. mg/kg) there exists a degree of wastage
- Through modelling of the structure of the patient population, optimum preparation sizes can be calculated to reduce this wastage at the population level
- Where the larger vial size is perfectly divisible by the smaller vial size e.g. 50mg and 100mg, wastage is markedly higher – ideally such scenarios would be avoided

1. Background

Recent years have seen a focus on ways to limit the escalating costs of novel pharmaceuticals, especially in oncology. Suggested ways of reducing these costs include pressure on the pricing of pharmaceuticals by companies [1,2], and reducing the costs of development (in the hope this leads to lower costs to healthcare systems) [3,4]. More recently, attention has been paid to drug wastage [5] and the level of wastage for a 'typical' patient with two estimates being that between 6% and 26% of novel pharmaceuticals are wasted [6,7]. The reduction of wastage as a cost control mechanism has prompted research on the impact of fixed compared to variable dosing [8], overage (a mandated percentage overfill of vials) [9], and dose banding (a tolerance in the planned vs administered dose) [10].

Wastage occurs when there is leftover drug in a vial once a patient's dose has been constructed. Although this can occur for various reasons, the most common are when a drug has variable dosing – such as by bodyweight or body surface area (BSA). As medicines become increasingly specialised either treating subgroups of patients or rare conditions, it is unlikely vial sharing will be possible (which is also prohibited in some jurisdictions). Even where vial sharing is possible as a waste reduction mechanism - typically where multiple patients are treated at the same time in the same centre - there is a scheduling and administrative overhead which offsets some of the savings.

Bach et al. illustrate the issue of wastage succinctly using the example of pembrolizumab, dosed at 2mg per kg of bodyweight and available (in the UK) with vial sizes of 50mg and 100mg [5]. The 'typical' patient they highlight to be 70 kg and therefore requiring 140mg of drug - logically provided by a one 50mg and one 100mg vial leading to 10mg of wastage. Unless multiple patients are being treated in a single clinic (when some of this may be able to be used), the 10mg must be disposed of as wastage. Stating wastage of 10mg for the typical patient however is an oversimplification of the issue - were the patient 75kg there would be no wastage. The reality is that patient characteristics vary and wastage must be considered for all patients, and then the mean wastage calculated, reflecting the distribution in wastage over the entire population.

Our objective was to outline a process to limit the wastage by selecting the optimum vial sizes to reduce the wastage across a patient population. We do this by considering the characteristics of patients likely to be treated for a condition, and vial sizes which may be credibly produced. The findings are outlined using the illustrative examples of pembrolizumab and cabazitaxel.

2. Methods

In order to determine the combination of vial sizes that produce the lowest wastage in the patient population, the distribution of patient characteristics must be appropriately considered – for example many diseases appear more commonly (or only) in one gender or occur more commonly with increasing age. Combinations of vial sizes can then be considered, and the mean wastage calculated over the whole population.

To estimate the distribution, two approaches could be used: data from a relevant clinical trial (who likely represent the target patient population), or matched general population data. Previous work has shown that the general population may have indistinguishable characteristics to patients with several conditions (including multiple cancers) [6], and thus may be a more appropriate source due to the volume of data available compared to small clinical trials. Such an assumption would not hold

in a disease such as diabetes, which is linked to obesity, or diseases of advanced age such as Alzheimer's, which would affect patient characteristics.

Further consideration must then be given to practicalities of treating patients – wastage could be zero by using sufficiently small vials, however an unacceptable number would be needed to treat each patient. In addition to the mean number of vials used at the health system level we also consider restrictions on the acceptable number of vials required to treat an individual - for the largest patients, an unreasonably high number of vials should not be required. The mathematical optimization problem is therefore to minimise the total population costs of formulating one dose of treatment to the patient population, and is described broadly in Figure 1, and defined mathematically as:

Minimise:

$$\sum_{1}^{i} g_i()$$

Subject to:

$$\frac{\sum_1^i \sum_1^j n_{ij}}{i} \leq x$$

Where $g_i()$ is a nested optimisation function, identifying the lowest 'cost' combination of vials to make up the required dose for each patient, i, and is derived as:

Minimise:

$$\sum_{1}^{j} n_{ij} \times c_j$$

Subject to:

$$\sum_{1}^{j} n_j \times v_j \geq d_i$$

$$\sum_{1}^{j} n_{ij} \leq y$$

Where:

- n_{ij} is the number of vials of size j for patient i
- c_j is the cost of one vial of size j
- v_j is the fill volume of a vial of size j
- d_i is the total amount of drug required to treat patient i
- x is the maximum number of vials used to treat the patient population on average
- y is the maximum number of vials that can be used to treat any individual patient

The optimum vial size(s) however should not be seen as a strict minimisation problem. First, dosages must be easily calculated by healthcare professionals without mistakes being made. It therefore

seems reasonable that only round numbers should form a part of the decision set i.e. v_j should contain only round numbers. A second consideration is that for reasons other than wastage e.g. ease of manufacturing, congruence with other treatments, non-optimum vial sizes may (legitimately) be selected for manufacturing.

In our illustrative examples of pembrolizumab [11] and cabazitaxel [12], we aim to consider all vial combinations that would reduce wastage without increasing the mean number of vials, constrained by a maximum of 8 vials for any plausible patient weight. Imposing such additional constraints ensures we do not simply have a shift in costs – with lower manufacturing costs offset by a larger numbers of vials that must be transported, stored, and then administered. We have used products with linear pricing, such that c is simply the number of milligrams in the vial, simplifying the problem.

To estimate the distribution of patient characteristics, we use data from adults in the Health Survey for England 2015 (6852 observations) [13]. To this data a lognormal distribution was fitted separately by gender – the lognormal has been shown in prior work to be the best fit to the distribution of patients [6].

For the illustrative example of pembrolizumab in metastatic melanoma, 100,000 patients are simulated from the fitted log-normal distributions- 77,000 male and 23,000 female to account for the pivotal KEYNOTE-006 study being 77% male [11]. The range of doses required (dosed at 2mg/kg) ranged from 49mg to 411mg with an interquartile range of 130mg to 289mg, and a mean and median of 210mg. Based on the range of doses required, we then estimated the mean wastage that would be seen using only vial sizes that may be considered acceptable.

Our second illustrative example is cabazitaxel, which is used for the treatment of prostate cancer at a dosage of 25mg/m^2 with only a 60mg vial available. To perform the analysis, we again sample 100,000 patients from the Heath Survey for England data, using only the data from males.

3. Results

In the UK, where both 50mg and 100mg vials are available for pembrolizumab, we estimate wastage in metastatic melanoma to be 13.2% in the absence of vial sharing, shown in bold in Table 1. With only a single vial size available (as in the US where only a 100mg vial is available), the wastage increases, and is estimated at 23.5%. The results of this analysis demonstrate that there are a number of alternative combinations that could cut wastage, some quite dramatically. For example, a change to a 60mg (rather than 50mg) vial would cut projected wastage from 13.3% to 8.0%.

[Table 1]

Applying constraints to look only at combinations that have the same or lower mean vials (which we estimate to be 2.1), and lead to lower wastage than the existing combination, the option set reduces to that shown in Table 2. Here the most obvious candidate would be a combination of 70mg and 100mg vials as this would require only an increase in the smaller vial size i.e. minimal change, which would reduce projected wastage to 8.6%.

[Table 2]

In the example of cabazitaxel, we find that the existing vial size of 60mg results in approximately 19.4% wastage (Table 3).

[Table 3]

To these options we then apply our criteria of allowing only combinations that would result in lower wastage than the existing vial size, and not require an increase in the mean number of vials), giving the options set in Table 4.

[Table 4]

The results of this analysis show that increasing the (single) vial size to 70mg would reduce wastage by a small amount. Adding a smaller vial size however would have a dramatic benefit, for instance adding a 12.5mg vial would reduce estimated wastage from 19.4% to 6.5% – a reduction of approximately two thirds.

4. Discussion

The results of this analysis demonstrate how wastage can be reduced by a few simple steps to select appropriate fill volumes, considering the distribution of patient characteristics. The results also demonstrate that where the larger vial is perfectly divisible by the smaller vial i.e. one is a multiple of the other, wastage is higher. This is unsurprising, as vial sizes that are not divisible can create more combinations with no wastage - using the cabazitaxel example a 60mg & 10mg option would have estimated wastage of 7.1%, this improves to 6.5% by increasing the smaller vial to 12.5mg. Despite this seemingly obvious finding, many novel pharmaceuticals are available only with perfectly divisible vial sizes.

Using the illustrative examples of pembrolizumab and cabazitaxel, we demonstrate that without increasing the mean number of vials administered, wastage can be substantially reduced. Such is the level of wastage seen with cabazitaxel, the discount scheme agreed with the manufacturer (Sanofi) required to gain NICE approval includes the manufacturer pre-preparing infusions [14]. We believe similar reductions in wastage could be seen in many newly launched medicines, and have highlighted our suggested steps in Figure 1.

An important issue to consider when optimizing vial sizes would be the population intended to be treated. This should consider not only the gender split, but also any differences between patients in different geographies and, if relevant, in different indications. As the optimization depends on these factors, it would also seem prudent where there are multiple geographies and indications to include predicted market share as this would reflect the number of patients actually treated in each indication.

The cost of the wastage intended to be prevented is threefold. First, additional product needs to be manufactured beyond what is actually required by patients. Whilst the cost of manufacture has historically been low with small molecules, this is not necessarily the case for biologics, of which a large number are monoclonal antibodies grown using complex production processes. Equally the growth in ‘orphan’ drugs precludes the use of high volume manufacture, further increasing cost per unit. The second cost is that of disposal – pharmacists must appropriately dispose of unused medicines, which itself incurs both a financial and a time cost to the health care system. The third and final cost is that ‘throwing away’ expensive product acts as a disincentive for physicians to use novel medicines. Whilst not a true cost (the cost of goods is much lower and accounted for in pricing), the psychological cost may affect clinical decisions. It is also likely to lead to money being spent to try and schedule administrations to minimise wastage at the clinic or hospital level by vial sharing - which again may be wasteful compared to the underlying cost of goods.

For existing products, the addition or alteration of vial sizes would result in an efficiency gain to health care system and reduced drug costs. This may reduce profit for companies due to a reduction in the volume of drugs sold though is not guaranteed as lower wastage may help a product gain traction in the market. This is especially the case where multiple treatments are available for a given indication, so reduced wastage (and cost) may help increase market share.

For products in development, the effect on pharmaceutical costs and company profits is less clear. In a scenario where companies 'price to the margin', reduced wastage from appropriate sizing of vials would translate in to a lower cost of goods and higher profit. An alternative scenario is where companies set a target profit per patient, and the reduction in cost of goods is entirely passed on to the health service with profit unchanged. This would result in lower costs, and static profits (though a lower operating cost). The reality is likely to lie somewhere in between the extremes, giving manufacturers more flexibility to lower prices to achieve market access. Whichever case occurs, waste is of no benefit to society, as the resources used in excess production are squandered.

As well as by companies, the analysis proposed may also be used as a tool by payers to estimate the wastage likely to be seen in practice, and push companies to reduce this. This may be through the form of an input to price negotiations, or even through inclusion of wastage recommendations from regulators, such as those issues by the US Food and Drug Administration [15].

Whilst this analysis does not include the impact of vial sharing, this would be possible, given estimates of the level of sharing that could occur (for example from existing products). Similarly, future research may wish to consider how to analyse wastage in products that do not have linear pricing (in some cases, small vials have a higher cost per unit), which would affect how decisions are made for individuals, and thus the population. Equally where products are dispensed in packs (and not single doses) the ideal pack size should also be investigated with the aim of reducing waste which can be a substantial cost[16]. We have also not explored the issue of whether it would be better to size vials based on general population data, or data from a population who have the condition under study e.g. the trial population(s). However, these limitations do not detract from the central finding that analysis to determine optimum vial sizes could be highly beneficial.

Whilst there exists a large body of research around drug costs, we believe this is some of the first analysis that specifically looks to reduce these by looking at wastage. Relatively simple analyses to determine the optimum vial sizes whilst a product is in clinical development could produce an outcome that dominates the status quo (reducing both wastage and administration time). At present this is not occurring, with many drugs available only in vials that are perfectly divisible, or do not appear optimally sized given the patient population. Whilst vial size considerations do not override other approaches to encourage efficiency (such as extended stability, or innovative packaging), a rational approach could lead to better outcomes for all involved – manufacturers, health care systems, and ultimately, patients.

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Compliance with Ethical Standards

For transparency AJH has worked with the majority of large pharmaceutical companies and JP is currently an employee of Amgen Inc., however this work was performed prior to his employment and is not sponsored, endorsed, or funded by Amgen Inc. in any form – for this reason JP had no affiliation at the time of this work. No funding was received for the research contained in this manuscript.

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Table 1: Estimated percentage wastage for pembrolizumab in metastatic melanoma at different combinations of vial sizes

Size of smaller vial (mg)	Size of larger vial (mg)																		
	10	**12.5**	**15**	**20**	**25**	**30**	**40**	**50**	**60**	**70**	**75**	**80**	**90**	**100**	**125**	**150**	**175**	**200**	**250**
10							2.8	2.8	2.8	2.8	1.3	2.8	2.8	2.8	1.5	2.8	2.4	2.8	2.8
12.5							0.9	3.7	1.5	1.4	3.7	1.6	2.3	3.7	3.7	3.7	3.7	3.7	3.7
15						4.3	1.3	1.3	4.3	1.6	4.3	1.8	4.3	2.2	2.6	4.3	3.6	4.1	4.3
20				5.7		2.8	5.7	2.8	5.7	2.8	2.5	5.7	2.8	5.7	3.8	3.8	4.8	5.7	5.7
25					7.1	1.3	1.6	7.1	2.4	3.3	7.1	3.8	3.3	7.1	7.1	7.1	7.1	7.1	7.1
30						8.4	2.8	2.8	8.4	3.1	4.3	3.6	8.4	4.4	6.2	8.4	7.2	7.6	8.3
40							10.9	3.1	5.7	4.3	6.7	10.9	5.8	5.7	8.7	7.5	8.3	10.9	10.8
50								**13.2**	5.1	5	7.1	5.6	7.3	**13.2**	7.1	13.2	9.2	13.2	13.2
60									15.4	7.7	6.3	6.1	8.4	8	13.2	8.6	13.6	13.1	15.2
70										17.3	13	10.1	8	8.7	11.7	13.4	10.7	14.8	16.6
75											18	14.1	9.9	9.2	10.8	18	11.9	13.4	17.6
80												18.8	12.8	10.7	10.8	15	14.5	13.6	18.6
90													20.7	16.2	12.6	12.5	18.8	17.4	19.2
100														**23.5**	16.4	13.2	15.8	23.5	21.8
125															29.3	19.4	15.3	17.8	29.3
150																28.7	18.1	15.7	21.9
175																	26.1	19	19.5
200																		27	23.4
250																			36.7

Only showing combinations that result in a mean of 4 or fewer vials, and a maximum of 8 vials for an individual patient. Commercially available vial combinations shown in bold with outline and underline, vial sizes where the larger vial size is perfectly divisible by the smaller vial size shaded in grey

Table 2: Estimated mean percentage wastage for combinations of vial sizes that could cut wastage for pembrolizumab in metastatic melanoma without increasing the number of vials used

		Size of larger vial (mg)				
		100	**125**	**150**	**175**	**200**
Size of smaller vial	**12.5**				13.2	a
	50	**13.2**		13.2		13.2
	70	8.7	11.7		10.7	
	75	9.2	10.8		11.9	
	80	10.7	10.8			
	90		12.6	12.5		
	100			13.2		

Commercially available vial combinations shown in bold with outline and underline, vial sizes where the larger vial size is perfectly divisible by the smaller vial size shaded in grey

Table 3: Estimated percentage wastage for cabazitaxel in prostate cancer at different combinations of vial sizes, showing only combinations that result in a mean of 4 or fewer vials, and a maximum of 8 vials for an individual patient

Size of smaller vial (mg)	Size of larger vial (mg)																		
	10	**12.5**	**15**	**20**	**25**	**30**	**40**	**50**	**60**	**70**	**75**	**80**	**90**	**100**	**125**	**150**	**175**	**200**	**250**
10	7.1	1.7	3.3	7.1	3.3	7.1	7.1	7.1	7.1	7.1	7	7.1	7.1	7.1	7.1	7.1	7.1	7.1	7.1
12.5		9.3	1.8	2.8	9.3	3.3	6.6	9.3	6.5	8.3	9.3	9.3	9.3	9.3	9.3	9.3	9.3	9.3	9.3
15			10.1	3.3	3.3	10.1	5.5	6	10.1	8.5	10.1	10.1	10.1	10.1	10.1	10.1	10.1	10.1	10.1
20				11.8	5.6	7.1	11.8	7.1	11.8	8.8	10.3	11.8	11.8	11.8	11.8	11.8	11.8	11.8	11.8
25					20.2	6.4	10.5	20.2	8.7	15.3	20.2	20.1	20.1	20.2	20.2	20.2	20.2	20.2	20.2
30						14.3	8.8	10.2	14.3	9	10.3	11.8	14.3	14.3	14.3	14.3	14.3	14.3	14.3
40							28.2	24.5	11.8	18.1	23.4	28.2	28.2	28.2	28.2	28.2	28.2	28.2	28.2
50								37.6	14.7	15.6	20.2	24.5	31.8	37.6	37.6	37.6	37.6	37.6	37.6
60									**19.4**	9.3	10.4	11.8	14.3	16.3	19.4	19.4	19.4	19.4	19.4
70										18.8	18.2	18.2	18.3	18.4	18.7	18.8	18.8	18.8	18.8
75											23.5	23.4	23.4	23.5	23.5	23.5	23.5	23.5	23.5
80												28.2	28.2	28.2	28.2	28.2	28.2	28.2	28.2
90													36.2	36.2	36.2	36.2	36.2	36.2	36.2
100														42.5	42.5	42.5	42.5	42.5	42.5
125															54	54	54	54	54
150																61.7	61.7	61.7	61.7
175																	67.2	67.2	67.2
200																		71.3	71.3
250																			77

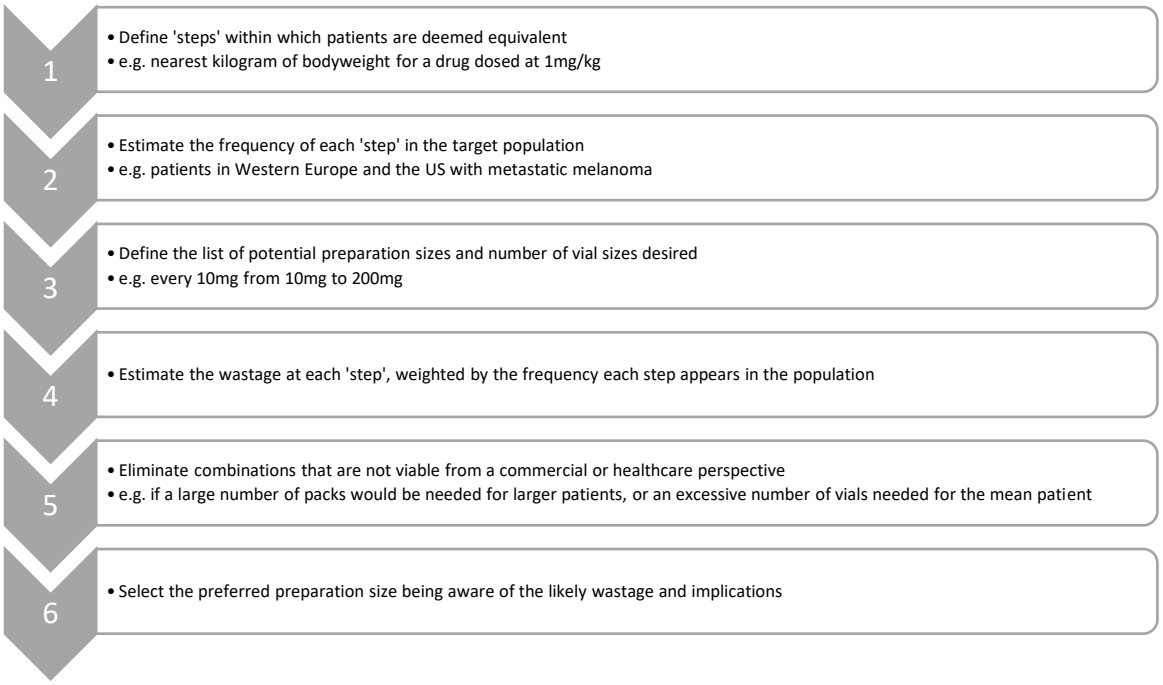
Only showing combinations that result in a mean of 4 or fewer vials, and a maximum of 8 vials for an individual patient. Commercially available vial size shown in bold with outline and underline. Vial sizes where the larger vial size is perfectly divisible by the smaller vial size shaded in grey

Table 4: Estimated mean percentage wastage for combinations of vial sizes for cabazitaxel which result in equal or lower wastage, using equal or few vials at the population level

		Size of larger vial (mg)									
		60	**50**	**60**	**70**	**75**	**80**	**90**	**100**	**125**	**150**
Size of smaller vial (mg)	**10**			7.1							
	12.5			6.5							
	15			10.1							
	20	11.8		11.8							
	25			8.7	15.3						
	30	8.8	10.2	14.3	9	10.3	11.8	14.3			
	40			11.8	18.1						
	50			14.7	15.6						
	60			**19.4**	9.3	10.4	11.8	14.3	16.3	19.4	19.4
	70				18.8	18.2	18.2	18.3	18.4	18.7	18.8

Commercially available vial size shown in bold with outline and underline. Vial sizes where the larger vial size is perfectly divisible by the smaller vial size shaded in grey

Figure 1: Suggested process for optimising vial size for single dose therapies



Contributions

The analysis was performed by AJH and JKP. The manuscript with drafted by AJH and JKP with the final version approved by AJH and JKP.

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Data sharing

All data used in the analysis is publicly available.