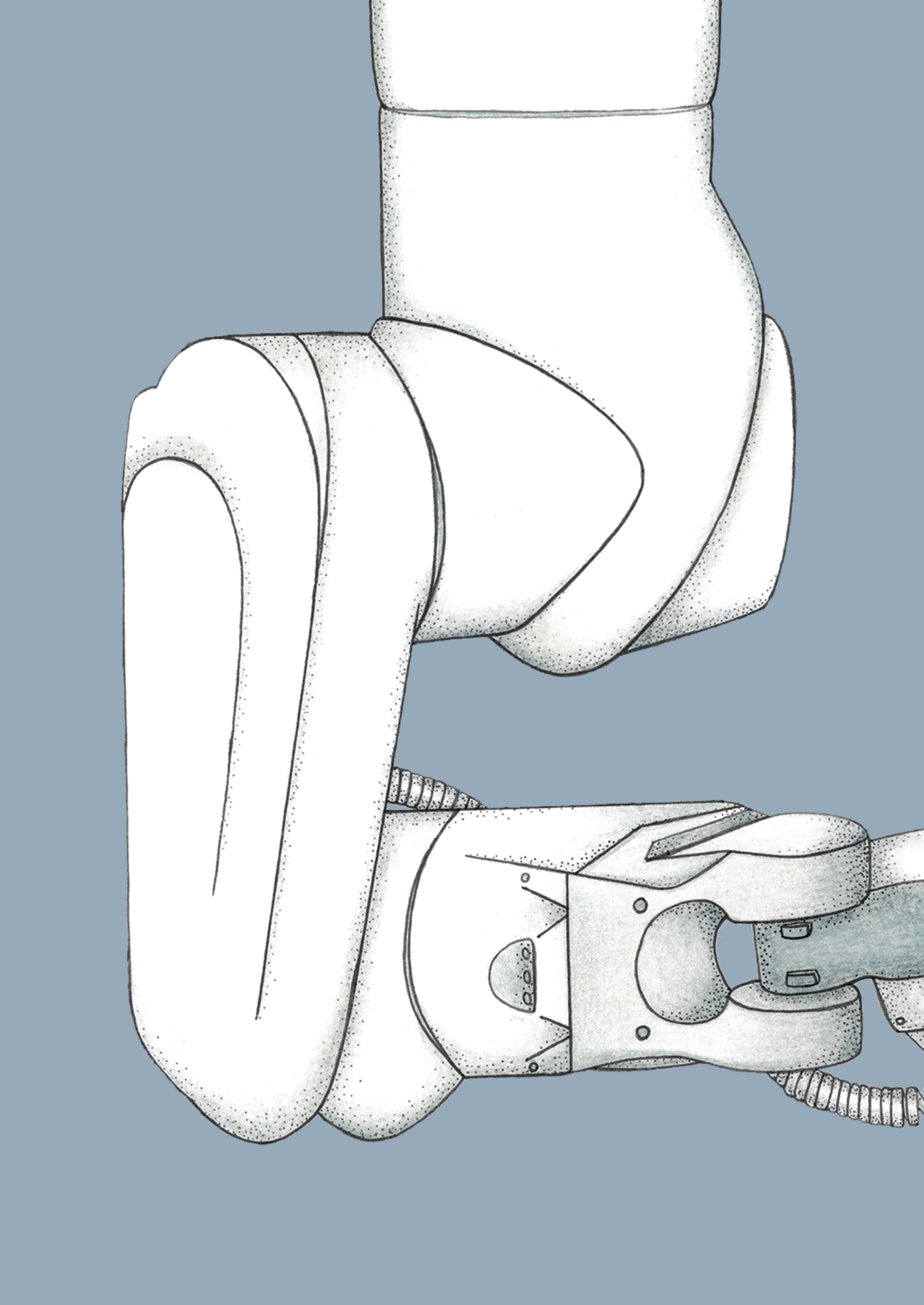
Robotic reconstitution of cytostatic drugs and monoclonal antibodies: transforming aseptic drug compounding in hospital pharmacies

Geersing, T.H.



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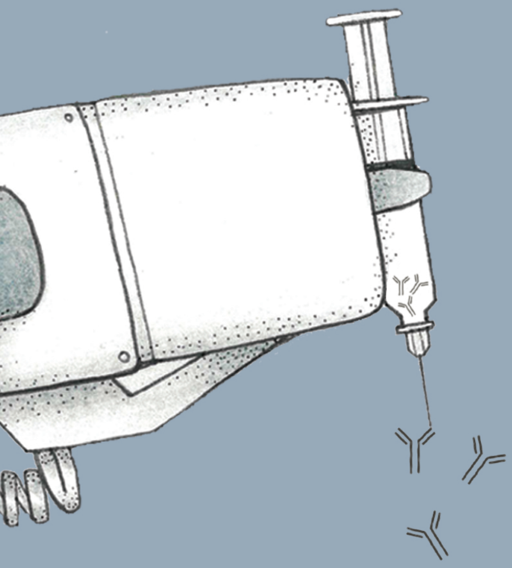
An economic evaluation of vial sharing of expensive drugs in automated compounding



Simone D. Baan*, Tjerk H. Geersing*,
Mirjam Crul, Eric J. F. Franssen, Marjolein G. Klous

*Both authors contributed equally

ABSTRACT

Background Manual compounding of expensive cytotoxic drugs often leads to drug wastage, due to residual product in vials not being used.

Aim To determine the cost savings that can be achieved by implementing an automated compounding process with a vial sharing strategy, instead of manually compounding drugs.

Method The drug wastage during automated compounding was compared with that of three simulation scenarios using manual compounding, in a general teaching hospital. All automatically compounded preparations of rituximab, pemetrexed, bevacizumab, and trastuzumab from September 2019 and up until February 2020 were included. A vial sharing strategy was implemented during the automated compounding process (scenario 1). In this scenario, all residual drugs could be reused for up to seven days. Two of the simulation scenarios for manual compounding were executed using a batch compounding strategy, for an entire working day (scenario 2), and twice a day (scenario 3). The third manual compounding simulation was executed without making use of a batch compounding strategy (scenario 4).

Results There was no drug wastage during automated compounding with vial sharing (scenario 1). The cost of drug wastage for 1001 preparations, over a period of six months for rituximab, pemetrexed, bevacizumab, and trastuzumab combined, were € 34,133 for scenario 2, € 46,688 for scenario 3, and € 88,255 for scenario 4. The estimated total cost savings between 2017, when the compounding robot was commissioned, and 2021, was more than € 280,000.

Conclusion Vial sharing of expensive drugs during automated compounding can prevent drug wastage, resulting in an economic and environmental advantage as opposed to manual compounding.

Intern International Journal of Clinical Pharmacy.2022;44(3):673–679.

INTRODUCTION

While the cost of cancer care is rising, manual compounding of expensive cytotoxic drugs often leads to drug wastage and higher costs, because residual drug in vials are not being used. Due to compounding of patient-specific dosages, and dose variations due to weight and body surface area, it is possible for residual drug to be left over in vials. The ever-increasing financial burden of cancer care ensures that stakeholders are constantly examining strategies for cost containment.[1] Many strategies to reduce health care costs are medium to long-term solutions where the impact on expenditure is unpredictable.[2] Low-cost measures, with a rapid effect on spending containment, and that can optimize human and economic resources, are highly desirable.

There are regulatory, safety, stability, and microbiological concerns regarding the re-use of drug vials (vial sharing) during manual compounding. The Good Manufacturing Practice guideline that outlines line clearance requirements, prohibits storing of vials with residual drug in the safety cabinet. However, storing these vials outside the class A environment introduces a risk of microbiological contamination.[3] Therefore, alternative strategies of compounding that reduce the waste of expensive drugs are highly needed.[4]

Several measures have been studied to reduce the amount of drug wastage. A list of these measures is provided in Table 1a. Dose rounding of the ordered dose leads to more convenient doses, which in turn leads to significant waste reduction, significant environmental gain and significant financial gain.[5-12] Another measure to reduce waste is batching of doses, whereby several doses of the same drug are made in one consecutive session. Residual drug can be used for the next preparation, thus avoiding drug wastage due to leftover drugs or overfilling. The waste reduction that can be achieved by batching of preparations will vary from one hospital to another, as it depends on the number of patients using a drug and the logistics of cytostatic drug compounding and administration. In addition to batching and dose rounding, the use of multi-dose vials and the selection of the most suitable vial can also reduce drug wastage. Nevertheless, Fasola et al. showed that despite all these measures, drug wastage is still abundant.[4,13] Automated compounding of cytotoxic drugs is becoming more common in hospitals all over the world, resulting in reduced compounding errors and also reducing the exposure of healthcare workers to hazardous drugs.[14,15] Compounding robots provide accurate and precise drug doses and may also allow for more cost-effective cytotoxic compounding compared to manual compounding.[16] In a cost volume analysis in 2014, the APOTECAchemo robot was found to be costeffective when compared to manual preparation, if more than 34,000 units per year were prepared.[17] A recent systematic review expressed a 'call to action' for publishing more data on the benefits of automated compounding using a robot.[14]

One of the benefits of automated compounding compared to manual compounding is the possibility to reduce drug wastage.[18] The study group demonstrated that vial sharing of single-use vials is microbiologically safe for up to seven days, when using the compounding robot.[18] The use of barcodes, including a use-by date for partially used vials, secures line clearance and eliminates the possibility of mixing up vials during compounding. Inadequate line clearance is one of the concerns related to vial sharing during manual compounding.[19,20] While the economic effects of dose rounding and batching were described in previous studies,[4,8,13] the added value of vial sharing with automated compounding has not been evaluated yet.

Aim

The aim of this study was to determine the cost savings that can be achieved by implementing an automated compounding process with a vial sharing strategy, instead of manually compounding drugs.

Ethics approval

Ethics approval for this type of study was not required according to Dutch legislation.

METHOD

Setting

In OLVG hospital, a general teaching hospital in Amsterdam, the Netherlands, cytotoxic drugs were compounded in a biological safety cabinet (BSC) and in a robotic system APOTECAchemo (Loccioni, Italy), which were placed in the same Grade C background. The annual workload consisted of 20,000 cytostatic preparations. Approximately 60% of these cytotoxic preparations were compounded with APOTECAchemo. The robotic system consists of a class B loading area and a class A compounding area. The pharmacy technician loaded the drug vials and required materials into the robotic system. Syringes with pre-assembled needles were used. Needles have a microbiological advantage over spikes as they only create a small opening in the vial after piercing.

Manual compounding was performed in a class A BSC and was not validated for vial sharing. Several measures were taken to reduce drug wastage during manual compounding, see also Table 1a. Drugs were batched when the same drug was compounded for several preparations during the same time-frame of the day. Furthermore, drug doses were rounded to a specific number of milligrams (mg), fixed doses were given when possible, and vial sizes were selected to best match the ordered dose. The doses of the selected drugs in this study were rounded to the nearest 50 mg.

Table 1 (a) Drug wastage avoiding strategies during preparation of oncolytic drugs. (b) Scenarios of automated and manual preparation of cytotoxic drugs used for cost analysis with an example of waste calculations

(a)

Strategy	Definition	Example
Dose rounding	Rounding of the prescribed dose, preferably to the nearest vial size of that particular drug.	Prescribed dose: 430 mg. Dose rounding to the nearest 50 mg. Rounded dose: 450 mg.
Batching	Preparing all doses of a particular drug in one go without removing any of the starting materials from the working zone.	Available vial sizes: 100 mg and 400 mg. Prescribed 3 doses of 450 mg; 1350 mg in total. Batching: 3 x 400 mg and 2 x 100 mg needed. No batching: 3 x 400 mg and 3 x 100 mg needed.
Use most convenient vial size	Using the most appropriate vials on the market with the amount of drug to be used as close as possible to the amount prescribed.	Available vial sizes: 100 mg and 400 mg. Prescribed dose: 450 mg. Use convenient vial size: 1x400 mg and 1x100 mg. No use of convenient vial size: 2x400 mg.
Vial sharing	Preparing each dose separately, saving the remainder of the last used vial for preparing the next dose of the same drug at a later time.	Available vial sizes: 400 mg. Prescribed dose: 450 mg. Use 2 x 400 mg. Use the residual (350 mg and possible overfilling) for the next dose of the same drug.

(b)

Scenario	**Automated or manual preparation**	**Time window in which vials can be batched/shared**	**Similar to**	Example waste calculation Using 100 mg vials. Compounding during one day, with two preparations in the morning (850 mg and 950 mg) and one in the afternoon (650 mg)
1	Automated	7 days	Robotic compounding OLVG hospital	Needed: 2450 mg Used: 25 vials (2500 mg) Residual: 50 mg, for use on the next day Total waste: 0 mg
2	Manual	1 working day		Needed: 2450 mg Used: 25 vials (2500 mg) Residual: 50 mg Total waste: 50 mg
3	Manual	Half a working day*	Manual compounding OLVG hospital	Needed: 1800 mg morning + 650 mg afternoon Used: 18 vials (1800 mg) + 7 vials (700 mg) Residual: 50 mg Total waste: 50 mg
4	Manual	No reuse of vials	Manual compounding academic cen-tre (one-stop shop)	Needed: 850 mg + 950 mg + 650 mg Used: 9 vials (900 mg) + 10 vials (1000 mg) + 7 vials (700 mg) Residual: 150 mg Total waste: 150 mg

* Preparations were batched twice a day: one compounding session in the morning (7:00 am till 12:30 pm) and one compounding session in the afternoon (12:30 pm till 6:00 pm).

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Design

Data were extracted from the robot's software database APOTECAmanager (Loccioni, Italy) for preparations made between September 2019 and February 2020. The following four drugs were selected based on their potential for substantial cost savings through vial sharing; rituximab, pemetrexed, bevacizumab, and trastuzumab. These drugs were compounded more than twice a week and were expensive (over € 1000 per preparation, calculated using the average Dutch pharmacy retail price of the originator and biosimilar/generic drugs, according to national price list (December 2020)). Furthermore, these drugs were not prescribed as fixed doses and vial sharing was considered possible for up to seven days after the first vial puncture. The possibility of vial sharing for up to seven days was microbiologically validated,[18] and the chemical stability after vial puncture was based on scientific literature.

During compounding days with APOTECAchemo, vials with residual drug were stored on dedicated racks within the preparation area of the robotic system, waiting to be reused for subsequent preparations. The residual drug vials that were not used by the end of the day were unloaded. The pharmacy technician covered the punctured stoppers with an IVA seal (Covidien, Dublin, Ireland) in the class B loading zone, to protect them from microbiological contamination. During unloading, the robot provided a label with an expiration date and a unique barcode. Residual vials were stored in a refrigerator outside the cleanroom. The robot software enabled optimal use of residual drugs by checking the availability (in- or outside the robot) and the expiry date of a residual drug vial before every new preparation.

The extracted compounding data from the robotic system were used for one real-life automated compounding scenario, and three real-life manual compounding scenarios (Table 1b). Scenario 1 represents the real-life scenario in OLVG hospital with automated compounding by a robot, where all residual drug was used for the next preparation (vial sharing). There was no waste of the selected drugs during automated compounding as the interval between two preparations of the same drug was never more than seven days. Scenario 3 closely resembles routine manual compounding in OLVG hospital; batch compounding takes place twice a day, in the morning (7:00 a.m. till 12:30 p.m.) and in the afternoon (12:30 p.m. till 6:00 p.m.). The amount of drug needed per batch of preparations was rounded up to the nearest available vial, and all drug residues were marked as waste. Scenarios 2 and 4 are simulated scenarios for other hospitals. In scenario 2, it was simulated that all preparations from an entire working day can be compounded in one batch. In scenario 4 there is no batching, or vial sharing, and the drug residual is discarded after each preparation. The fourth scenario is common in hospitals where patients only visit the hospital for both diagnostics and treatment at the same time, the so-called one-stop shops. This creates a situation in which, based on recent lab values, ad hoc compounding is required, making batch compounding no longer possible.

The example in Table 1b shows how the different compounding scenarios affect the amount of wastage. The drug was compounded three times on the same day with two doses (850 and 950 mg) in the morning and one dose (650 mg) in the afternoon, resulting in a total of 2450 mg needed for the combined preparations. The smallest available vial size of the drug contains 100 mg. In scenarios 1, 2, and 3 there will be 0, 50, and 50 mg of wastage respectively. In scenario 4, there is wastage of 150 mg; after every preparation, a 50 mg residual is discarded because there is no batching of preparations or reusing of residuals.

Cost analysis

Drug costs were based on the Dutch national drug price on 30-12-2020 (medicijnkosten.nl) of the vials with the smallest amount of drug in OLVG hospital. These are the average combined costs of the originator and biosimilar/generic drugs on the Dutch market. All prices used were pharmacy retail prices, excluding the confidential discount. In the four different scenarios (Table 1b), the quantity of drug needed for compounding all preparations was calculated, as well as the resulting quantity of drug wastage.

The cost savings per drug were obtained by subtracting the drug costs in the different manual scenarios from the drug costs in the robotic scenario. To calculate the percentages of wasted drug, these savings per drug were divided by the corresponding drug costs in the robotic scenario. The total cost savings was extrapolated to estimate the cost savings since the implementation of the compounding robot in OLVG hospital. Data were analysed by using Excel (Microsoft Office, 2016, Microsoft, Redmond, USA).

RESULTS

The total number and cost of compounded doses for rituximab, pemetrexed, bevacizumab, and trastuzumab are shown in Table 2. Over the selected six-month period, the four drugs, combined, resulted in 1001 preparations. The total drug costs for these preparations were € 1,919,981. Pemetrexed has the highest average cost per preparation (€ 2400) and the highest total cost (€ 638,465), followed by rituximab. In addition, the smallest available vials of the selected drugs, and their corresponding prices are displayed in Table 2. These prices indicate the possible wastage per preparation.

Table 2 Number of preparations, vials and costs of cytotoxic drugs prepared from September 2019 to February 2020

Drug	Number of doses	Vials available in pharmacy (mg)	Price* of smallest vial size	Mg per preparation (median with inter-quartile range)	Average costs per preparation	Total drug costs during 6 months
Rituximab	317	100, 500	€ 228.99	700 (650-800)	€ 1600	€ 573,678
Pemetrexed	242	100, 500	€ 270.78	900 (850-988)	€ 2400	€ 638,465
Bevacizumab	204	100, 400	€ 303.47	500 (350-600)	€ 1500	€ 340,539
Trastuzumab	238	150, 420	€ 467.82	400 (350-500)	€ 1400	€ 367,300

*Calculated average Dutch pharmacy retail price of the originator and biosimilar/generic drugs according to national price list (December 2020).

The total cost per drug was the lowest in scenario 1, the real-life scenario in OLVG hospital, using automated compounding. There was no drug wastage seeing that all of the selected drugs were prepared frequently enough – within seven days – for the residuals to be reused. The residual of the last preparation of the last study day was not counted as waste, because it was used the day after. The total drug wastage in scenarios 2–4 was equal to the additional drug costs in these scenarios in comparison to scenario 1.

Fig. 1 illustrates the wastage per drug, or the additional costs compared to automated compounding. The wastage is shown in Euro and as a percentage of the total cost of the specific drug. The highest drug wastage was with trastuzumab in scenario 4, € 43,212, which translates to 13.1% wastage. The wastage of the four drugs combined for the six-month period were € 0 for scenario 1, € 34,133 for scenario 2, € 46,688 for scenario 3, and € 88,255 for scenario 4.

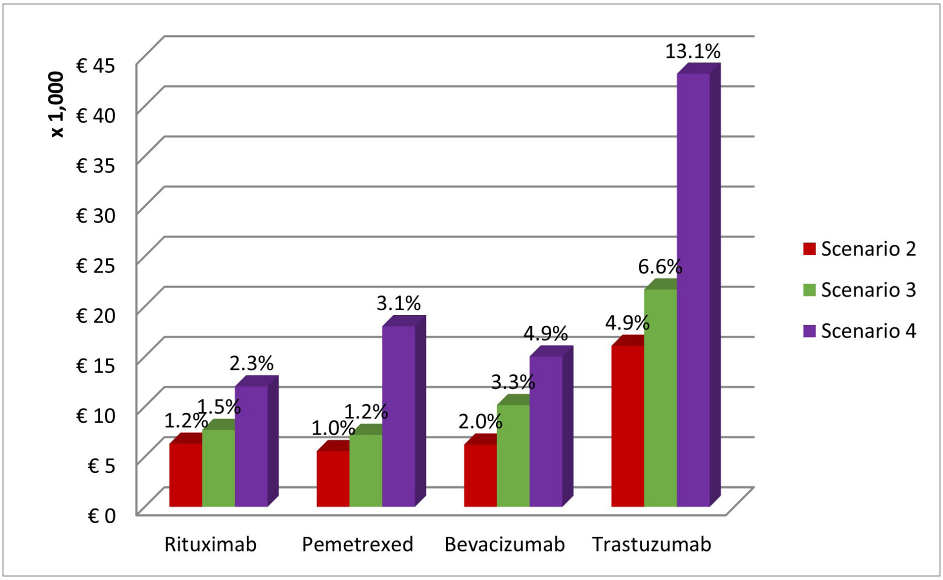

Fig. 1 Waste in manual compounding compared to automated compounding. Drug waste in Euro (Dutch pharmacy retail price) on the left, and percentage (above the bars) per drug, per scenario from September 2019 up until February 2020. Automated compounding: vial sharing for 7 days. Scenario 2: manual compounding, vials batched during 1 working day. Scenario 3: manual compounding, vials batched from 7:00 am – 12:30 pm and 12:30 pm – 6:00 pm. Scenario 4: manual compounding, no vial sharing, or batching.

Scenario 3, which closely resembles the actual manual chemotherapy compounding process in OLVG hospital, showed drug wastage of € 7,672 for rituximab (1.5%), € 7,182 for pemetrexed (1.2%), € 10,151 for bevacizumab (3.3%), and € 21,684 for trastuzumab (6.6%) (Fig. 1). The extrapolated total annual cost savings were more than € 93,375. When these cost savings are extrapolated over a three-year period, which is the same amount of time that the robot has been implemented in the hospital, a total saving of more than € 280,125 is realised. More substantial cost savings could be achieved if a vial sharing strategy was implemented for other more expensive drugs, for example, carfilzomib, ipilimumab, and panitumumab.

DISCUSSION

This is the first study to show that automated compounding of expensive drugs with vial sharing provides significant economic benefits over conventional manual compounding. In OLVG hospital, € 93,375 was saved annually by reusing rituximab, pemetrexed, bevacizumab, and trastuzumab. Sharing these drug vials may lead to annual savings of € 176,000 in hospitals that do not already use batch compounding.

Vial sharing for up to seven days, using a compounding robot saved between 1.2% (pemetrexed) and 6.6% (trastuzumab) of the total drug costs. These percentages represent low total drug wastage and efficient working procedures with expensive drugs in the manual scenario due to dose rounding, batching, and choosing the most suitable vial size. The highest percentage of drug wastage for trastuzumab is well explained. The smallest available vial of trastuzumab contained more drug (150 mg) when compared to the other drugs that were tested (100 mg), while all doses were rounded to 50 mg.

The robotic software enabled optimal use of residual drugs by continuously updating the digital drug storage bank, including the availability of residual drugs and their expiry dates. Respaud et al. also provided drug savings using a computerized drug storage bank.[21]

Studies on drug wastage during manual compounding with closed system transfer devices (CSTDs) use the same extension of the beyond-use date, for up to seven days, and also show relevant cost savings.[22,23] Siderov studied the cost savings of 10 monoclonal antibodies (more than 8,000 preparations) and achieved annual savings of more than € 30,000 per drug.[23] Despite the differences in the compounding methods and drugs used, this result is consistent with the cost savings in this study. Other CSTD studies performed in highincome countries showed considerable divergent drug wastage, ranging from 4% up to 57%.[13,22,24-26] Smith's study confirms that only expensive, frequently used drugs are well suited for vial sharing,[27] which confirms the drug selection criteria in our study.

Vial sharing during manual compounding presents challenges in microbiology, line clearance, drug stability, and in following regulations as described by national authorities. Medical spikes, common in the Netherlands, or CSTDs can be used when compounding cytotoxic drugs. However, leaving the spike or the CSTD in the vial could alter the stability of the drug due to unknown interactions with the material. With monoclonal antibodies, aggregate formation is possible, potentially leading to immunogenicity and adverse reactions for patients.[19,20] In addition, the spikes and CSTDs leave a hole in the rubber stopper of the vials if removed, resulting in a higher risk of microbial contamination. The use of needles during manual compounding of cytotoxic drugs is not recommended, due to the risk of needle-stick injuries and exposure to these drugs. During automated compounding with APOTECAchemo, syringes were loaded into the robot with capped needles and are discarded by the robot without human intervention. This is a safe method for the operators of the robot for reusing vials because there are no risks of needle-stick injuries.

An advantage of this study is that vial sharing during automated compounding was compared with different manual compounding scenarios. This allows other institutions to estimate the cost savings after implementing vial sharing in their setting. Institutions in which it is more difficult to plan and batch preparations together, for example one-stop-shops, will benefit more from vial sharing rather than institutions that already batch their preparations.

Clearly, there are limitations to the present study. Firstly, the data were retrospectively retrieved and the comparison between scenarios was calculated from the automated preparations to different scenarios, instead of comparing real-life, prospective data. Secondly, the extrapolation of the results over time could result in less accurate cost savings. Additionally, the cost savings that were identified, were found to be less accurate for countries other than the Netherlands, because the drug prices are different per country.[28] Therefore, extrapolating the results to pharmacies in different countries can result in a variation of the results.

For future research, it is recommended to prospectively compare both automated and manual compounding with reallife data instead of using simulated scenarios. Furthermore, the current study can be supplemented with a full cost analysis of automated and manual production of expensive drugs, including the time spent by the technicians and the cost of the disposable devices.

CONCLUSIONS

Vial sharing of expensive drugs during automated compounding can prevent drug wastage, making it economically and environmentally advantageous compared to manual compounding. The total cost savings depends on the current method of manual compounding, the price per vial, and the number of drug prescriptions in which vial sharing can be applied during compounding.

REFERENCES

1. Elkin EB, Bach PB. Cancer's next frontier: addressing high and increasing costs. *Jama* 2010; **303**(11): 1086-7.
2. Caplan AL. Will evidence ever be sufficient to resolve the challenge of cost containment? *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2011; **29**(15): 1946-8.
3. Eudralex GMP, annex 1, 2008. Manufacture of sterile medicinal products. https://ec.europa.eu/health/documents/eudralex/vol-4, Accessed date: 5 July 2021.
4. Fasola G, Aprile G, Marini L, Follador A, Mansutti M, Miscoria M. Drug waste minimization as an effective strategy of cost-containment in oncology. *BMC health services research* 2014; **14**: 57.
5. Afanasjeva J, Gruenberg K. Pharmacists as environmental stewards: Strategies for minimizing and managing drug waste. *Sustainable Chemistry and Pharmacy* 2019; **13**: 100164.
6. Au Y, Knoester P. Spillage dure medicatie kan drastisch minder. Maatregelen maken forse besparingen mogelijk. *Pharmaceutisch Weekblad* 2011; (4).
7. Francis SM, Heyliger A, Miyares MA, Viera M. Potential cost savings associated with dose rounding antineoplastic monoclonal agents. *J Oncol Pharm Pract* 2015; **21**(4): 280-4.
8. Lindsey S, Parsons LB, Figg LR, Rhodes J. Evaluation of the dosing strategies of biologic agents and the theoretical impact of dose rounding. *J Oncol Pharm Pract* 2018; **24**(1): 47-55.
9. Patel S, Le A. Rounding rituximab dose to nearest vial size. *J Oncol Pharm Pract* 2013; **19**(3): 218-21.
10. Smale EM, Egberts TCG, Heerdink ER, van den Bemt BJF, Bekker CL. Waste-minimising measures to achieve sustainable supply and use of medication. *Sustainable Chemistry and Pharmacy* 2021; **20**: 100400.
11. Winger BJ, Clements EA, DeYoung JL, et al. Cost savings from dose rounding of biologic anticancer agents in adults. *J Oncol Pharm Pract* 2011; **17**(3): 246-51.
12. De Graaf H, Haisma J. Verworpen vials. *Med Cont* 2006; (61): 748-50.
13. Fasola G, Aita M, Marini L, et al. Drug waste minimisation and cost-containment in Medical Oncology: two-year results of a feasibility study. *BMC health services research* 2008; **8**: 70.
14. Batson S, Mitchell SA, Lau D, et al. Automated compounding technology and workflow solutions for the preparation of chemotherapy: a systematic review. *European journal of hospital pharmacy : science and practice* 2020; **27**(6): 330-6.
15. Werumeus Buning A, Geersing TH, Crul M. The assessment of environmental and external cross-contamination in preparing ready-to-administer cytotoxic drugs: a comparison between a robotic system and conventional manual production. *Int J Pharm Pract* 2020; **28**(1): 66-74.
16. Geersing TH, Klous MG, Franssen EJF, van den Heuvel JJG, Crul M. Robotic compounding versus manual compounding of chemotherapy: Comparing dosing accuracy and precision. *Eur J Pharm Sci* 2020; **155**: 105536.
17. Masini C, Nanni O, Antaridi S, et al. Automated preparation of chemotherapy: quality improvement and economic sustainability. *Am J Health Syst Pharm* 2014; **71**(7): 579-85.
18. Geersing TH, Franssen EJF, Pilesi F, Crul M. Microbiological performance of a robotic system for aseptic compounding of cytostatic drugs. *Eur J Pharm Sci* 2019; **130**: 181-5.
19. Besheer A, Mahler HC, Matter-Schwald A, et al. Evaluation of Different Quality-Relevant Aspects of Closed System Transfer Devices (CSTDs). *Pharmaceutical research* 2020; **37**(4): 81.

20. Sreedhara A, Zamiri C, Goswami S, et al. Challenges of Using Closed System Transfer Devices With Biological Drug Products: An Industry Perspective. *Journal of pharmaceutical sciences* 2020; **109**(1): 22-9.
21. Respaud R, Tournamille JF, Saintenoy G, et al. Computer-assisted management of unconsumed drugs as a cost-containment strategy in oncology. *International journal of clinical pharmacy* 2014; **36**(5): 892-5.
22. Edwards MS, Solimando DA, Jr., Grollman FR, et al. Cost savings realized by use of the PhaSeal(®) closed-system transfer device for preparation of antineoplastic agents. *J Oncol Pharm Pract* 2013; **19**(4): 338-47.
23. Siderov J. Utility of PhaSeal, a closed-system drug transfer device, in facilitating vial sharing to reduce waste and assist in medication cost savings. *Journal of Pharmacy Practice and Research* 2019; **49**(5): 421-5.
24. Gopisankar MG, Wahlang J, Jagtap V, Sarkar C, Purnima Devi L, Harris C. Cancer chemotherapy drug wastage in a tertiary care hospital in India-A 3-month prospective and 1-year retrospective study. *British journal of clinical pharmacology* 2019; **85**(10): 2428-35.
25. Hess LM, Cui ZL, Li XI, Oton AB, Shortenhaus S, Watson IA. Drug wastage and costs to the health-care system in the care of patients with non-small cell lung cancer in the United States. *Journal of medical economics* 2018; **21**(8): 755-61.
26. Liran O, Prus J, Gordon N, Almog V, Gruenewald T, Goldstein DA. A real-world analysis of cancer drug wastage due to oversized vials. *Journal of the American Pharmacists Association : JAPhA* 2018; **58**(6): 643-6.
27. Smith RS. A 2-year retrospective review of vial sharing options for the compounding of cytotoxics. *European Journal of Hospital Pharmacy* 2015; **22**(3): 161-4.
28. Goldstein DA, Clark J, Tu Y, et al. A global comparison of the cost of patented cancer drugs in relation to global differences in wealth. *Oncotarget*. 2017;**8**:71548-55.