A Cost Minimization Analysis of Ready-to-Administer Prefilled Sterilized Syringes in a Dutch Hospital

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ABSTRACT

Purpose: Preparation errors occur frequently during conventional preparation of parenteral medication in the clinical environment, causing patient harm and costs for the national health care system. The use of ready-to-administer prefilled sterilized syringes (PFSSs) produced by the hospital pharmacy can reduce preparation errors and the risk of bacteremia from contamination of the intravenous medication. The aim of this research is to compare the total costs of the conventional preparation method (CPM) with the PFSS method.

Methods: In this cost-minimization analysis, costs related to the preparation of the medication, bacteremia from contamination, adverse drug events as a result of preparation medication errors, and wastage of syringes were taken into account. Annual costs in a general Dutch hospital were consistently calculated. Three scenarios were analyzed: (1) all preparations as CPM (864,246 administrations per year), (2) all preparations as PFSSs, and (3) 50% as PFSSs and 50% as CPM. Deterministic and probabilistic sensitivity analyses were performed.

Findings: The first scenario found higher annual costs at €14.0 million (US$16.0 million) compared with the second scenario (€4.1 million, US$4.7 million). The most realistic situation (third scenario) found savings of €4.9 million (US$5.6 million) compared with the first scenario. Sensitivity analyses revealed that cost savings of PFSSs were strongly influenced by decreased risk of medication errors and contamination of intravenous medication. Extrapolating these results nationwide indicated potential savings of >€300 million (US$342 million) if only PFSSs were used.

Implications: The use of PFSSs prepared in the hospital pharmacy yielded cost savings compared with the CPM on the ward in the Dutch hospital. (*Clin Ther*. 2019;41:1139–1150) © 2019 Published by Elsevier Inc.

Key words: cost minimization analysis, hospital, preparation, ready to administer, syringe.

INTRODUCTION

Medication errors are common in the hospital setting, especially during the preparation and administration of parenteral medication.[1,2] Studies have found various error rates of one-third to even 48% during the preparations of parenteral medication.[1,3–5] Such medication errors may lead to adverse drug events (ADEs), causing serious harm, such as permanent disabilities or even death, and involve high costs for the health care system.[6,7] Furthermore, high rates of extrinsic contamination, caused by, for example, in-use manipulation of parenteral medication, were reported in several hospitals, even in hospitals with good nursing standards.[8–12] Contamination can cause potentially severe bacteremia in patients Macias et al[8] reported an incidence of bacteremia of 2%

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(95% CI, 1%−3%) in contaminated parenteral medication produced in the clinical environment.[8]

Many different solutions have been suggested to improve the safety profile of parenteral medication in hospitals. Providing ready-to-administer medication prepared in the pharmacy department has been suggested frequently.[13,14] This is implemented in hospitals across Europe.[15,16] A new development in this area is ready-to-administer prefilled sterilized syringes (PFSSs) produced by the pharmacy. PFSSs are produced on stock under good manufacturing practice conditions by the hospital pharmacy using (semi)-automatic filling and closing machines whereby quality and safety parameters are embedded in the whole process of manufacturing.[17] The use of PFSS products eliminates the preparation step on the ward, thereby preventing medication errors.[13] Another advantage of PFSS use is its preserved sterility up to the moment of administration. In addition, when prepared in advance, wastage of parenteral medication can be mostly avoided.[18] Medications that are suitable to deliver as PFSSs should fulfill the following criteria: administered as a fixed-dose concentration, suitable for injection or infusion with a pump, and having a small volume (≤50 mL) (examples include midazolam, morphine, and norepinephrine).

Many countries struggle with the problem of optimizing the process of tolerable parenteral medication in hospitals. Different guidelines across countries outline how preparation of parenteral medication in the clinical environment should be performed.[19] Recently, the Council of Europe published a resolution about preparation of medication that encourages the supply of PFSSs by the pharmacy.[20] Moving the activities of preparation of medication from the clinical environment to the pharmacy requires investments in pharmacy equipment but will result in efficacy, better quality, and reduction in preparation medication errors in the hospital.[19,20]

In this study, we compare the costs of production of ready-to-administer PFSSs by the pharmacy to the conventional preparation method (CPM) for intravenous medication by nurses in the clinical environment. Direct medical costs as a result of medication errors, contaminated medications, and wastage of medication were evaluated to determine the economic impact of the introduction of the production of PFSSs by the hospital pharmacy.

MATERIALS AND METHODS

An economic model was developed in Excel for Windows version 2010 (Microsoft Corp, Redmond, Washington) to estimate the costs and savings of PFSSs produced by the hospital pharmacy versus conventional preparation of parenteral medication by nurses. The study was conducted in the Isala Hospital (Zwolle, the Netherlands), which is among the leading clinical teaching hospitals in the Netherlands, with a capacity of >1100 hospital beds and the ability to provide highly specialized care.

Model inputs were mainly retrieved from this specific Dutch hospital, and additional data were preferably collected from the national and international literature. The pharmacy information system was used to obtain information about the medication administrations in the hospitals. Only delivery details were used. These data did not include any patient data. In the analysis, only direct medical costs were taken into account. The cost perspective is that of hospitals and hospital budgets. All costs are reported in 2017 Euros and equivalencies in US dollars.

Model Structure

We designed a decision tree−type economic model in which 2 alternatives for parenteral preparations were considered: CPM by nurses in the clinical environment or supply of PFSSs by the hospital pharmacy (Figure 1). The scope of the model was limited to 1 year. With this decision tree, we analyzed 3 scenarios. In scenario 1, all parenteral administrations were prepared by nurses in the clinical environment (eg, ward, operating room). In scenario 2, all parenteral administrations were prepared as ready-to-administer PFSSs by the hospital pharmacy. Scenario 3 is a combination of scenarios 1 and 2. In scenario 3, 50% of the administrations were produced as PFSSs and 50% were prepared according to the CPM. This will probably be the most realistic scenario because of maximum capacity of the production of PFSSs at the pharmacy and because of chemical and physical limitations of the production of medication (eg, instability of antibiotics).

Model Parameters

All parenteral administrations of 1 year (2015) were included in the analysis. This number was extracted from the hospital pharmacy database with all

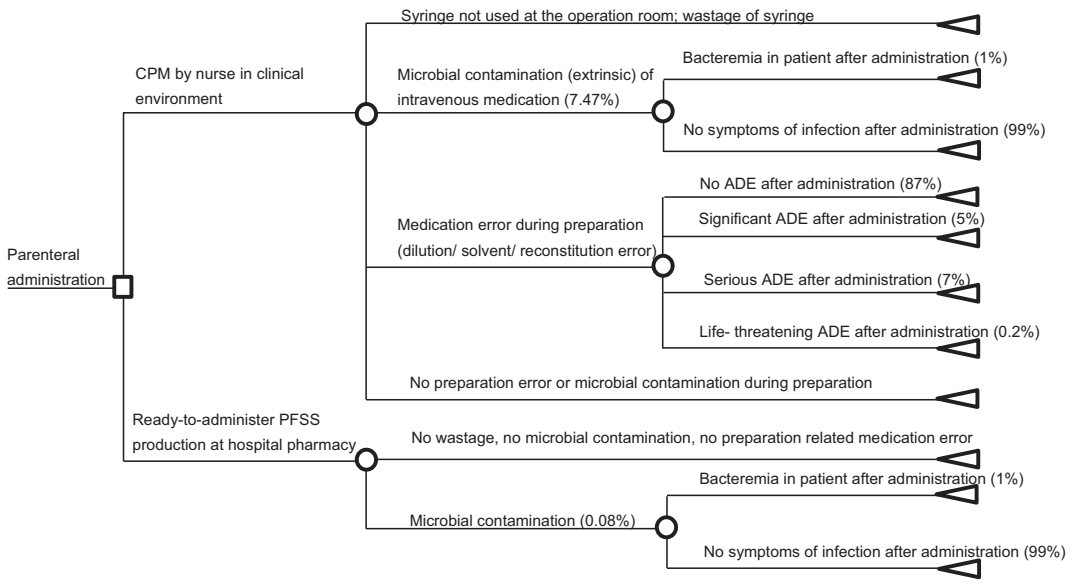

Figure 1. Decision tree parenteral administration.

medication orders by selecting the route of administration during 2015. Cytostatic drugs, ready-to-administer parenteral products (infusions, syringes) supplied by industry, high-risk drug products (eg, concentrated electrolytes, methotrexate), and total parenteral nutrition were excluded because they were not suitable for PFSS production or were already produced by the pharmacy. In 2015, a total of 864,246 parenteral medications were prepared in the clinical environment of the hospital. A further analysis of these 864,246 parenteral medication administrations was performed to determine which part was suitable to deliver as a PFSS. The criteria were as follows: administration as fixed dose, suitable for large-scale production, and suitable for injection (volume) or infusion pump. Approximately 200,000 administrations were discarded because they were not suitable for large-scale production because of the chemical or physical properties of the medication (eg, instability of antibiotics). Twenty-five active pharmaceutical ingredients, all of which fulfilled the criteria, accounted for >300,000 administrations (eg, midazolam, metoclopramide, morphine, norepinephrine). Further selection of suitable active pharmaceutical ingredients found that at least 50% of the parenteral administrations were considered to be possibly delivered as PFSSs. Notably, this percentage was specifically analyzed in an additional scenario.

In scenario 1, nurses prepared all 864,246 parenteral medications in the clinical environment using the CPM. In our model, we included the probability of wastage, microbiological contamination, and medication errors during preparation of the drug, as defined below. In scenario 2, all 864,246 parenteral drugs were produced as PFSSs in the hospital pharmacy, and we assumed that no medication errors occur during production and only minimal microbial contamination to be possible. In scenario 3, 50% of the medications were supplied as PFSSs and 50% of the parenteral medications were prepared according to the CPM, with the same probabilities as in scenario 1.

DEFINITIONS

Wastage

When using PFSSs, no wastage was found. Because of direct use of the PFSSs, no manipulation is necessary and the PFSS can be reused for the next procedure. Wastage in the operating room was measured in the hospital. For every operation, a standard set of medication for treatment (according to the type of

operation and patient) and a set of emergency medication are available for direct use when necessary. The set of emergency medication remains mostly unused and is discarded because of the short expiry of parenteral medication when prepared in the operating room. Every 8 h a new medication set is prepared by an operating assistant. A mean of 6 of 9 emergency medication sets were wasted every day.

Microbial Contamination

Contamination rates of parenteral medication were extracted from a meta-analysis comparing parenteral products prepared in a clinical environment (ward, operating room) using the CPM and pharmaceutical environment (pharmacy department). This was 7.47% for the CPM and 0.08% for PFSSs.[12] Macias et al[8] reported an incidence of bacteremia of 2% (95% CI, 1%−3%) in patients after administration of contaminated parenteral medication. In our model, we conservatively set the incidence of bacteremia to 1% because of the possible high impact of this parameter on the results. Treatment costs of bacteremia are based on 2 days in a critical care unit and 3 days in the ward in a general hospital.[21]

Medication Error

Medication errors during preparation of parenteral drugs occur frequently. In a systematic review by McDowell at al,[13] the incidence of medication errors was categorized in stages during the process of preparation and administration of intravenous medication. PFSSs could avoid certain errors in 2 stages of the process: obtaining incorrect diluent and incorrect reconstitution of medication and diluent. Providing preprepared syringes reduce the overall error rate from 0.22 (95% CI, 0.14−0.31) to 0.17 (95% CI, 0.09−0.27).[13] On the basis of these results a 5% reduction in medication error rate is calculated for supplying PFSSs versus the CPM in the deterministic analysis. Outcomes of errors were modeled based on the results of a study in 2 hospitals in the United Kingdom on incidence and severity of medication errors during preparation and administration (430 observations).[4] They reported that 5% of all medication errors during the preparation step resulted in potentially minor and significant ADEs, 7% resulted in potentially moderate and serious ADEs, and 0.2% in potentially severe and life-threatening ADEs. The total amount of harmful errors is approximately 13%.[4] This finding is similar to the 10% medication error rate causing harm as reported by Paradis et al.[22] We used data from the study by Hug et al[23] on the excess length of stay in community hospitals as a result of ADEs. An increase in ADE severity was associated with an increase in length of stay and costs. For significant ADEs, the excess length of stay was 2.77 days; for serious ADEs, 3.47 days; and for life-threatening ADEs, 5.54 days.[23]

Costs

Costs were mostly based on actual hospital data from 2015 to 2017. Table I summarizes the different costs used in the cost analysis. Some costs were calculated using reference prices provided by the cost manual of the guideline of economic evaluations in health care.[21]

The production of PFSSs at the pharmacy were manufactured according to good manufacturing practice guidelines with an (semi)-automatic filling and closing machine, which can fill 2-, 5-, 10-, and 50-mL syringes. This machine can produce up to 3500 syringes per hour. The filled syringes will be sterilized. After sterilization the syringes were labeled with an (semi)-automatic labeling machine. To all production equipment, 10% depreciation charges were indexed annually.[21] The PFSS product cost consisted of packaging material and pharmacy staff, including laboratory costs for analysis of the medication for quality control purposes. For both the CPM and PFSS methods, no medication cost or raw material costs were included in the analysis because of the wide range of medications included in our study. Annual costs related to the waste of unused prepared drugs in case of emergency were calculated independently of the total amount of parenteral drugs in the hospital. Total costs of wastage included staff costs (preparation time was recorded at the operating room), drug products costs, and instrumental and packaging costs (similar to CPM packaging costs). With the use of these cost components, the total annual wastage costs at the operating room were calculated.

Statistical Analysis

Next to the base-case analysis for the 3 scenarios, deterministic sensitivity analyses were performed on key parameters for testing the sensitivity of model

Table I. Summary and description of costs per unit (VAT included).

Description of Costs	Costs per Unit, €	Remarks and References
Bacteremia event	3792	2 days at the critical care unit, 3 days on the ward,[21],*
Significant ADE due to a medication error	1258	Excess length of stay in hospital: 2.77 days on the ward[21,23]
Serious ADE due to a medication error	1575	Excess length of stay in hospital: 3.47 days on the ward[21,23]
Life-threatening ADE due to a medication error	6731	Excess length of stay in hospital: 5.54 days at critical care unit[21,23]
Staff costs (nurse) for preparation of the CPM	3.54	Mean preparation time for CPM per unit is 6.47 min†
Medical instrument and packaging costs per CPM administration	1.10	Including syringes, needles, gloves, disinfectant, sterile gauzes, labels, diluents, and sterile trays based on the hospital's actual purchasing prices
Annual wastage of drug products at the operating room	99,682	Costs of medical instruments and packaging, staff costs for preparation time of the unused prepared drugs, and costs of the drug products
Annual syringe filling and labeling machine costs	56,621	Depreciation (10% annual) and maintenance costs (yearly) of the syringe filling machine, syringe labeler, and inspection cabinets[21]
Annual validation costs	34,668	Initial validation costs of the syringe filling machine are spread over 10 years[21]
PFSS product, 5 mL	3.49	Cost price (VAT included) of an average PFSS product, which is made up of the production costs (packaging materials, pharmacy personnel) and laboratory analysis costs (overhead), partly based on the hospital's actual purchasing prices (raw material and storage costs were not included)
PFSS product, 10 mL	4.90	
PFSS product, 50 mL	8.08	
Mean PFSS cost	4.63	The 5-mL PFSS contributes 60%, the 10-mL PFSS contributes 30%, and the 50-mL contributes 10% to the total amount of PFSS products

ADE = adverse drug event; CPM = conventional preparation method; PFSS = prefilled sterilized syringe; VAT = value added tax.

* Critical care nursing day at a general hospital costs €1215 per day, and a nursing day on the ward costs €454 per day.[21]

† Mean nurse wage is €31.41 per hour in the Netherlands, 2017.[21]

outcomes to these parameters. For the uncertainty of the parameters, 95% CIs or a range of ±10% for a parameter with unknown uncertainty was used. The effects of changes in these parameters on the costs of each scenario are presented in tornado diagrams.

To examine the influence of the uncertainty in input parameters on the uncertainty of the outcomes, a probabilistic sensitivity analysis was performed. For all parameters with uncertainty, a probability distribution was assigned. From these distributions, a value was randomly drawn and the outcomes were reestimated; this process was repeated thousand times, yielding a distribution of outcomes that reflect the uncertainty of the deterministic outcomes. The ranges used to create the parameters' probability distributions were based on the 95% CIs or assuming a range of ±10% for a parameter with unknown uncertainty. For the probability distributions,

BetaPert distributions were used. The BetaPert distribution is a probability distribution that can be defined by a minimum, a most likely, and a maximum value. Hereby, the point estimate was converted into the most likely value using the lower and upper bound of the 95% CI or the bounds based on the ±10% of the point estimate, using the following formula: Most Likely Value = (6 × Point Estimate − Minimum Value − Maximum Value) × 1/4.

All model input parameters are summarized in Table II.

RESULTS

The net annual costs of the different scenarios are given in Table III. Using conventional preparation method by nurses (scenario 1) yielded a total cost of €14.0 million (US$16.0 million) in 1 year, mainly because of costs attributable to medication errors and bacteremia. The use of PFSSs exclusively (scenario 2) resulted in much lower total costs (€4.1 million, US$4.7 million) and according to the CPM resulted in €9.9 million (US$11.3 million) savings in favor of supplying only PFSSs. The cost of drug products is almost the same in scenarios 1 and 2. In scenario 1, the costs were mainly attributable to the salary of the nursing staff (calculated as the number of administrations multiplied by the preparation time of the nurse). In scenario 2, the costs were mainly attributable to the unit cost of the PFSSs multiplied by the number of administrations by the packaging materials of the PFSSs. Scenario 3 represents probably the more realistic scenario in the hospital in which 50% of the parenteral drugs are prepared as PFSSs and the other part according to the CPM. Scenario 3 yielded a total cost of €9.1 million (US$10.4 million). Compared with scenario 1 (CPM exclusively), scenario 3 gains a net savings of €4.9 million (US$5.6 million), which is mainly the result of a decrease in the number of medication errors and cases of bacteremia. Costs of drug products in scenario 3 are higher than in

Table II. Model input parameters, including base case, DSA values, and PSA distributions.

Parameter	Base Case	DSA, %	PSA, %
Parenteral administrations at Isala Hospital, No. (range)	864,246	−10 to +10	−10 to +10
Significant medication errors, % (95% CI)	4.65	2.79 to 6.74	2.79 to 6.74
Moderate medication errors, % (95% CI)	6.28	3.95 to 8.84	3.95 to 8.84
Life-threatening medication errors, % (95% CI)	0.23	0 to 0.7	0 to 0.7
Mean PFSS cost, € (range)	4.63	−10 to +10	−10 to +10
Equipment costs (total per year), € (range)	56,621.33	−10 to +10	−10 to +10
Syringe filling machine	36,481.50		
Syringe labeler machine	13,806.83		
Inspection cabinets	331.63		
Maintenance	5970.00		
Initial validation costs for PFSS (annual), € (range)	34,668.2	−10 to +10	−10 to +10
Staff costs for nurses for CPM (hourly), € (range)	31.41	−10 to +10	−10 to +10
Incidence contamination CPM, % (95% CI)	7.47	5.16 to 9.78	5.16 to 9.78
Incidence contamination PFSS, % (95% CI)	0.0785%	−0.023 to 0.181	−0.023 to 0.181
Contaminated syringes causing a bacteremia event, % (range)	1	−10 to +10	−10 to +10
Costs bacteremia event, € (range)	3792.0	−10 to +10	−10 to +10

CPM = conventional preparation method; DSA = deterministic sensitivity analysis; PFSS = prefilled sterilized syringe; PSA = probablistic sensitivity analysis.

Table III. Net annual costs of scenarios, including differences based on 864,246 parenteral administrations in 1 year.

Description of Costs	Scenario 1 (All CPM)	Scenario 2 (All PFSSs)	Scenario 3 (50% PFSSs and 50% CPM)	Difference Between Scenario 2 and Scenario 1	Difference Between Scenario 3 and Scenario 1
Cost of drug products (packaging, instruments, staff wages, and machines), €	4,021,177	4,096,024	4,104,245	74,847	83,068
Cost of medication errors, €	7,478,048	0	3,739,024	−7,478,048	−3,739,024
Cost of bacteremia (due to contamination), €	2,447,219	25,726	1,236,472	−2,421,493	−1,210,746
Cost related to wastage of drugs at operating rooms, €	99,682	0	49,841	−99,682	−49,841
Total costs, €	14,046,126	4,121,750	9,129,583	−9,924,375	−4,916,543
Cost per product, €	16.25	4.77	10.56		

CPM = conventional preparation method; PFSS = prefilled sterilized syringe.

scenario 1 (€83,068, US$94,677) because of the significant contribution of constant costs such as the syringe filling machine and validation costs (for PFSS production). Increasing the proportion of PFSS products further will decrease total costs, mainly because of a decrease in medication errors and cases of bacteremia, which are the main contributors in the cost savings of PFSSs.

Deterministic Sensitivity Analysis

In Figures 2 and 3, the tornado simulations show the variables with the greatest effect on the results for the different scenarios. The sensitivity analysis found that scenario 1 always generates more costs than scenarios 2 and 3, when model parameters were subject to ±10% variation. An increased incidence of medication errors contribute significantly to increased costs for the CPM. Unit costs of PFSSs significantly influence the total costs of scenarios 2 and 3. These factors have some influence on the outcome, but scenarios 2 and 3 remain cost savings compared with scenario 1 (CPM). The limit (<€0) is not even approached in both comparisons.

Probabilistic Sensitivity Analysis

Figure 4 shows the results of the probabilistic sensitivity analysis. Although the deterministic base-case values indicate that both PFSS scenarios are cost saving, the PSA found that the uncertainty of these results is rather large. For scenario 1 vs scenario 2, the results of the simulations range from €10.6 million (US$12.1 million) to €33.6 million (US$38.3 million), and for scenario of 1 vs scenario 3, the range is €5.2 million (US$5.9 million) to €16.8 million (US$19.1 million). However, this uncertainty analysis also found that PFSSs are cost saving, with a probability of 90% and a >50% likelihood of saving up to €5 million (US$5.7 million).

When the amount of PFSSs is low, the PFSS scenario is more expensive because of investment in equipment for the automatic filling process. Figure 4 also implies that it is possible that scenarios 2 and 3 actually would cost more than scenario 1 because of the overlap in CIs of the medication error rate for the CPM (95% CI, 0.09−0.27) and PFSS (95% CI, 0.14−0.31) scenarios.[13]

Figure 5 shows the boxplots (with whiskers to minimum and maximum) of the costs for the different scenarios from the probabilistic sensitivity analysis. The median costs of scenarios 1, 2, and 3 were €13.3 (US$15.2), €4.1 (US$4.7), and €8.8 (US$10.0), respectively, with a high spread in costs for scenario 1. This finding is mostly caused by the medication errors during preparation that are present in scenario 1 and not in scenario 2.

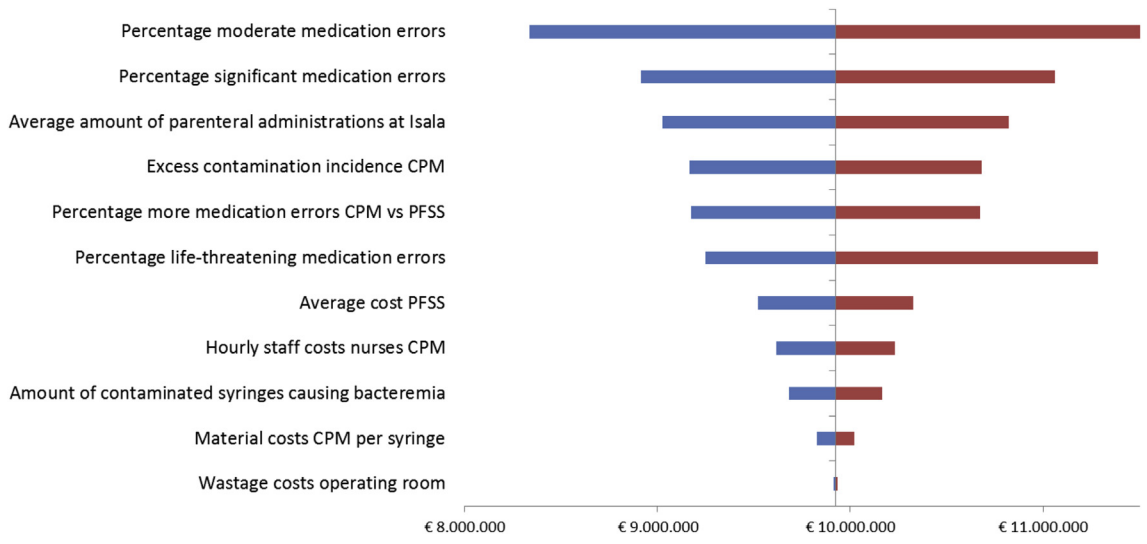

Figure 2. Tornado diagram scenario 1 (all CPM) versus scenario 2 (all PFSS).

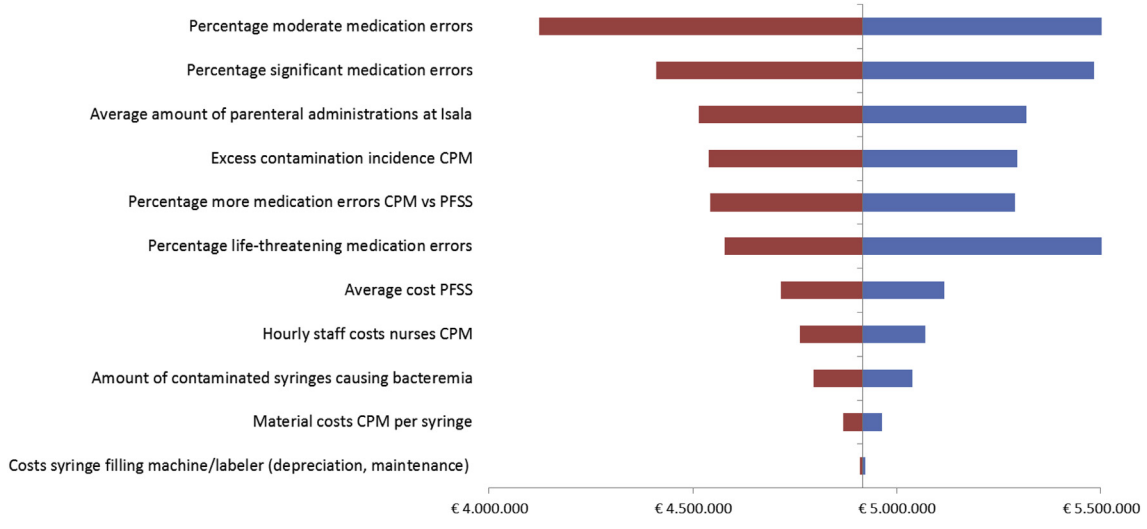

Figure 3. Tornado diagram scenario 1 (all CPM) versus scenario 3 (50% CPM, 50% PFSS.

DISCUSSION

This cost minimization analysis provides insight into the costs and benefits of the production and use of ready-to-administer PFSSs compared with the CPM of parenteral medication. In all examined scenarios, PFSS use resulted in decreased total costs. The cost savings of PFSSs are mainly driven by the reduction in medication errors and contaminations, which are substantial parts of the costs of the CPM. Examples of intravenous medication errors are wrong reconstitution and miscalculation of dose, resulting in an overdose that can be life-threatening for several

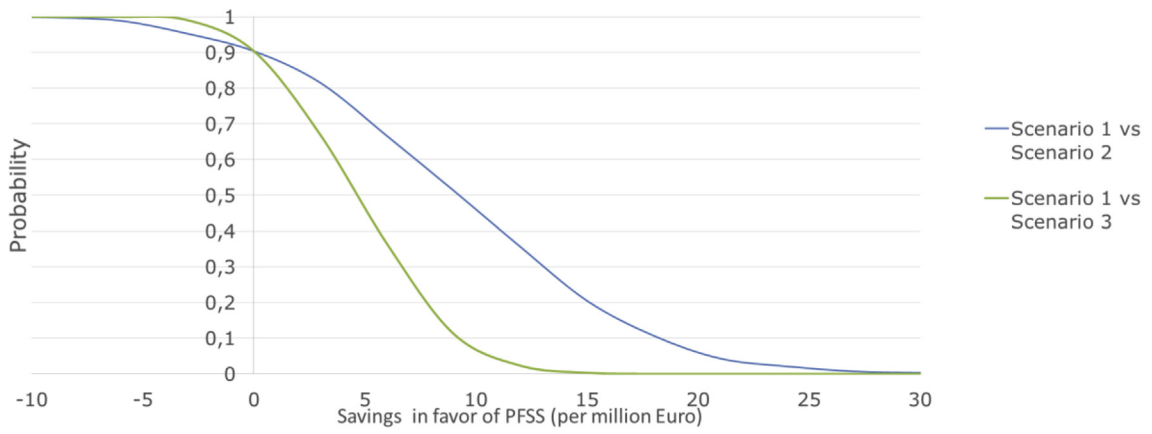

Figure 4. Probabilistic sensitivity analysis of different scenarios in million Euros for Isala hospital.

medications (eg, hemorrhage with heparin overdose).[4] These complications have major effects on the costs. Removing the reconstitution step by providing preprepared syringes would reduce the overall error rate and cause less contamination of intravenous medications.[12,13] Our study is in line with the work of Benhamou et al[24] and Rosselli et al[25] analyzing the budget impact of specific medications. Benhamou et al[24] found a minimum of €2,781,182 net savings in introducing atropine PFSSs in the operating room.

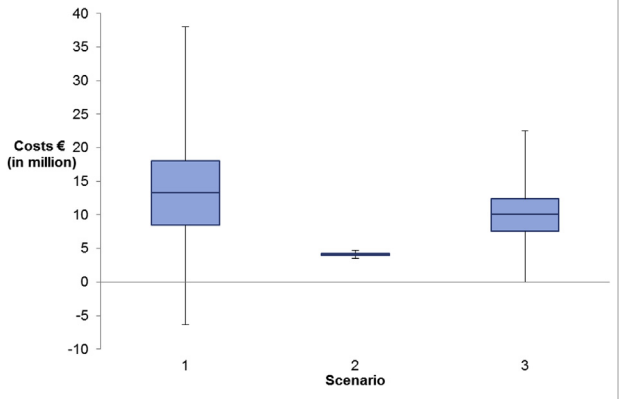

Figure 5. Boxplot (quartiles) with whiskers from minimum to maximum of Monte Carlo simulation of costs of different scenarios in million euro for Isala hospital.

The net savings were mainly attributable to eliminating wastage and reducing medication errors. In their analysis, a 77% reduction in medication errors was established and a €1,167,323 saving on wastage.[24] Rosselli et al[25] compared 4 different drug administration systems for dopamine and a $47,000 savings when ready-to-administer medications were used. Both studies found high cost savings possible with one specific medication, which may suggest that our analysis is conservative.

For the reference hospital, scenario 3 is set as the most realistic scenario because of the maximum capacity of the production of PFSSs at the pharmacy (one filling machine) and because of chemical and physical limitations of the production of medication (eg, instability of antibiotics). In addition, it is not possible to administer every parenteral medication by a syringe. When a larger volume is needed, an infusion bag is the preferred product. According to these limitations, nurses should always be capable to prepare parenteral medication in the clinical environment. Hospitals can perform a risk assessment to decide which products should be prepared in the pharmacy and which products can be prepared in clinical environment (eg, low risk of errors during reconstitution) with appropriate risk-reducing measures.[19] Moving from the CPM to PFSSs could also have an impact on other factors, such as increased transportation, lower storage costs, benefits from specialization and economics of scale, difference

in skill mix required, and associated salary costs. These factors are not included in our analysis but could have an impact on the outcome and could also be different among countries or health care systems.

In our analysis, the production of PFSSs is performed by the hospital pharmacy. Another approach could be delivery of PFSSs by the pharmaceutical industry. Currently, not many of these products are commercially available. One of the reasons for this could be that most of the medications are generics and commercially less attractive because high investments have to be made to change the product line in addition to low margins on the products.

The major challenge for hospitals using PFSSs would be to realize the savings when introducing PFSSs. The hospitals have to make investments in starting up the production of PFSSs while the savings will be in reductions of complications because of medication errors and contaminations. Obviously, these savings are not fixed expenses for the hospital. A consideration could be to make it a quality improvement project in collaboration with health insurance companies.

The economic evaluation has some limitations. Clinical situations and costs are simplified in the model with respect to the actual situation. Some costs were not included in the analysis. For example, we did not include the costs of the raw materials, such as medications and solvents, into the model because of the wide range of medications included in our study. Inclusion of raw material costs will probably result in increased cost savings of PFSSs compared with the CPM because the PFSS method uses material bought in bulk, whereas the CPM uses commercial products (ampoules, infusions). We used data obtained from one hospital combined with data from literature studies, preferably systematic reviews, which may limit the generalizability of the model. However, sensitivity analysis indicate that the cost-saving effects of PFSSs versus the CPM were stable across all investigated parameters. This finding suggests that implementation of the PFSS method in similar hospitals leads to significant cost savings and can improve patient tolerability. For the deterministic sensitivity analysis, the uncertainty was not available for all parameters. Possibly structural uncertainty could have a higher impact than the uncertainty found in the deterministic sensitivity analysis.

When using this model for other countries, certain model input parameters should be reconsidered, for example, labor costs. Furthermore, differences in health care systems and initiatives of supplying medications to the wards by the pharmacy, such as Centralised Intravenous Admixture Services or Satellite pharmacies, could give different outcomes.[15,25]

Extrapolation of our results nationwide by multiplying the total parenteral administrations in Isala to national data in the Netherlands indicates potential savings of >€300 million (US$342 million) when only PFSSs were used. When calculated per 100,000 administrations, >€1.15 million (US$1.3 million) can be saved. PFSSs are an important step to improve the safety profile of parenteral medication alongside other initiatives, such as good prescribing,[26] safe labeling,[27] and technologies to improve the administration of medications, for example, a barcode administration system.[28,29]

CONCLUSION

In this cost minimization analysis, the use of PFSSs compared with the CPM leads to significant cost savings in the hospital budget. These savings result from reductions in the number of medication errors and contaminations of parenteral medications. We suggest wider implementation of this service.

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CONFLICTS OF INTEREST

The authors have indicated that they have no conflicts of interest regarding the content of this article.

APPENDIX A. SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.1016/j.clinthera.2019.04.024.

REFERENCES

1. Keers RN, Williams SD, Cooke J, Ashcroft DM. Prevalence and nature of medication administration errors in health care settings: a systematic review of direct observational evidence. *Ann Pharmacother*. 2013;47:237–256.
2. Berdot S, Gillaizeau F, Caruba T, Prognon P, Durieux P, Sabatier B. Drug administration errors in hospital inpatients: a systematic review. *PLoS One*. 2013;8, e68856.
3. Taxis K, Barber N. Incidence and severity of intravenous drug errors in a German hospital. *Eur J Clin Pharmacol*. 2004;59:815–817.
4. Taxis K, Barber N. Ethnographic study of incidence and severity of intravenous drug errors. *BMJ*. 2003;326:684.
5. Parshuram CS, To T, Seto W, Trope A, Koren G, Laupacis A. Systematic evaluation of errors occurring during the preparation of intravenous medication. *CMAJ*. 2008;178:42–48.
6. Leendertse AJ, Egberts AC, Stoker LJ, van den Bemt PM, HARM Study Group. Frequency of and risk factors for preventable medication-related hospital admissions in The Netherlands. *Arch Intern Med*. 2008;168:1890–1896.
7. Bates DW, Spell N, Cullen DJ, et al. The costs of adverse drug events in hospitalized patients. adverse drug events prevention study group. *JAMA*. 1997;277:307–311.
8. Macias AE, Huertas M, Ponce de LS, et al. Contamination of intravenous fluids: a continuing cause of hospital bacteremia. *Am J Infect Control*. 2010;38:217–221.
9. Macias AE, de LS, Huertas M, et al. Endemic infusate contamination and related bacteremia. *Am J Infect Control*. 2008;3:48–53.
10. Van GJ, Foudraine NA, Nooteboom F, Crombach WHJ, Oldenhof NJJ, Van DH. Unexpected high risk of contamination with staphylococci species attributable to standard preparation of syringes for continuous intravenous drug administration in a simulation model in intensive care units. *Crit Care Med*. 2002;30:833–836.
11. Austin PD, Hand KS, Elia M. Systematic review and meta-analysis of the risk of microbial contamination of parenteral doses prepared under aseptic techniques in clinical and pharmaceutical environments: an update. *J Hosp Infect*. 2015;91:306–318.
12. Larmené-Beld K, Frijlink H, Taxis K. A systematic review of microbial contamination of parenteral medication prepared in a clinical versus pharmaceutical environment. *Eur J Clin Pharmacol*. 2019;75:609–617.
13. McDowell SE, Mt-Isa S, Ashby D, Ferner RE. Where errors occur in the preparation and administration of intravenous medicines: a systematic review and bayesian analysis. *Qual Saf Health Care*. 2010;19:341–345.
14. Berdot S, Roudot M, Schramm C, Katsahian S, Durieux P, Sabatier B. Interventions to reduce nurses' medication administration errors in inpatient settings: a systematic review and meta-analysis. *Int J Nurs Stud*. 2016;53:342–350.
15. Scheepers HPA, Beaney AM, Le Brun PPH, et al. Aseptic preparation of parenteral medicinal products in healthcare establishments in europe. *Eur J Hosp Pharm Sci Pract*. 2016;23:50–53.
16. Scheepers H, Neerup Handlos V, Walser S, Schutjens M, Neef C. Impact of the council of europe resolution on quality and safety assurance requirements for medicinal products prepared in pharmacies for the special needs of patients. *Eur J Hosp Pharm Sci Pract*. 2017;24:218–223.
17. European Commission. EudraLex - volume 4 - good manufacturing practice (GMP) guidelines. http://ec.europa.eu/health/documents/eudralex/vol-4_en. Accessed July 23, 2017.
18. Weinger MB. Drug wastage contributes significantly to the cost of routine anesthesia care. *J Clin Anesth*. 2001;13:491–497.
19. Committee of Ministers, Council of Europe. *Resolution CM/Res(2016)2 on Good Reconstitution Practices in Health Care Establishments for Medicinal Products for Parenteral Use*. Adopted by the Committee of Ministers on 1 June 2016 at the 1258th meeting of the Ministers' Deputies; 2016. https://www.edqm.eu/sites/default/files/resolution_cm_res_2016_2_good_reconstitution_practices_in_health_care_establishments_for_medicinal_products_for_parenteral_use_.pdf. Accessed October 2, 2017.
20. Committee of Ministers, Council of Europe. *Resolution CM/ResAP(2011)1 on quality and safety assurance requirements for medicinal products prepared in pharmacies for the special needs of patients*. Adopted by the Committee of Ministers on 1 June 2016 at the 1258th meeting of the Ministers' Deputies; 2016. https://www.edqm.eu/sites/default/files/resolution_cm_res_2016_1_quality_and_safety_assurance_requirements_for_medicinal_products_prepared_in_pharmacies.pdf. Accessed October 2, 2017.
21. Hakkaart-van Roijen L, Van der Linden N, Bouwmans C, Kanters T, Tan S. *Kostenhandleiding. methodologie van kostenonderzoek en referentieprijzen voor economische evaluaties in de gezondheidszorg*. National Health Care Institute; 29 Feb 2016. https://www.zorginstituutnederland.nl/publicaties/publicatie/2016/02/29/richtlijn-voor-het-uitvoeren-van-economische-evaluaties-in-de-gezondheidszorg. Accessed August , 2017.

22. Paradis AR, Stewart VT, Bayley KB, Brown A, Bennett AJ. Excess cost and length of stay associated with voluntary patient safety event reports in hospitals. *Am J Med Qual*. 2009;24:53—60.
23. Hug BL, Keohane C, Seger DL, Yoon C, Bates DW. The costs of adverse drug events in community hospitals. *Jt Comm J Qual Patient Saf*. 2012;38:120—126.
24. Benhamou D, Piriou V, De Vaumas C, et al. Ready-to-use pre-filled syringes of atropine for anaesthesia care in French hospitals - a budget impact analysis. *Anaesth Crit Care Pain Med*. 2017;36:115—121.
25. Rosselli D, Rueda JD, Silva MD, Salcedo J. Economic evaluation of four drug administration systems in intensive care units in Colombia. *Value Health Reg Issues*. 2014;5:20—24.
26. Koppel R, Metlay JP, Cohen A, et al. Role of computerized physician order entry systems in facilitating medication errors. *JAMA*. 2005;293:1197—1203.
27. Larmene-Beld KHM, Alting EK, Taxis K. A systematic literature review on strategies to avoid look-alike errors of labels. *Eur J Clin Pharmacol*. 2018;74:985—993.
28. Keers RN, Williams SD, Cooke J, Ashcroft DM. Causes of medication administration errors in hospitals: a systematic review of quantitative and qualitative evidence. *Drug Saf*. 2013;36:1045—1067.
29. Poon EG, Keohane CA, Yoon CS, et al. Effect of bar-code technology on the safety of medication administration. *N Engl J Med*. 2010;362:1698—1707.
29. Poon EG, Keohane CA, Yoon CS, et al. Effect of bar-code technology on the safety of medication administration. *N Engl J Med*. 2010;362:1698—1707.

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