Detecting the Impact of Changes in Platelet Demand following the Implementation of PRT Platelets in Canada

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Abstract: This paper describes tools to detect and estimate demand shifts for platelet products, through inventory monitoring, following the implementation of pathogen reduction (PR) technology at a pilot site in the Canadian Blood Services (CBS) network. A Statistical Process Control (SPC) framework was constructed to detect change points in inventory signals. A discrete event simulation is used to generate synthetic data for the inventory monitoring process. Both traditional forecasting and machine learning techniques were used to increase sensitivity to change detection and reduce time to detection by supplying the SPC algorithm with projected data. Experiments were run on data representative of changes in demand experienced at the pilot production site. It was found that larger shifts in demand had a higher probability of detection and a lower time to detection. Changes in demand, with an effect on the system larger than 10%, were almost always detected. Detection time varies greatly depending on the level of the demand shift. Typically, shifts greater than 25% have an average detection time of just over a week while shifts of less than 5% have an average detection time of up to 25 weeks.

1 INTRODUCTION

In all Canadian provinces, excepting Quebec, Canadian Blood Services is the sole agency responsible for managing the blood supply chain. CBS collects, produces, and distributes blood products to over 400 hospitals. Before being released for transfusion, products must be tested for the presence of transmissible diseases and/or bacterial contamination.

In this paper we consider two blood products, pooled and apheresis platelets, following the introduction of technology to reduce bacterial contamination. In Canada, a unit of pooled platelets is a combination of buffy coat platelets derived from five different donors, all of whom have the same blood type. Apheresis platelets are collected from a single donor. A single component is removed, while the remaining components are returned to the donor. Because platelets must be held at 37°C for maximum clinical efficacy, bacterial contamination, though rare, is possible. Thus, all platelet products, in Canada and elsewhere, have a regulated shelf-life. At the start of this study, platelets had a maximum shelf-life of 7 days.

At that time, platelet units in Canada were tested for bacterial contamination, using the BAC-T Alert® system, a non-destructive testing system that rapidly incubates an aliquot from production units. The risk of transfusing a bacterial contaminated unit was estimated at less than 1 in 1,000 with this technology. However, CBS introduced Pathogen Reduction Technology (PRT) for pooled platelet processing to reduce further the chance of transfusion related infections. PRT functions by combining a blood product with a light sensitive compound and exposing the mixture to ultraviolet light. The process causes mis-links in the DNA of pathogens in the blood product, preventing the organism from reproducing and effectively sterilizing the product (Estcourt et al., 2018).

While there are significant benefits to PRT treatment, it is known that treated units have a lower platelet count than untreated units (Estcourt, et al., 2017). Thus, there was potential that an increased number of units used would be required to achieve the same dose-response in patients who might have otherwise been transfused with non-PRT platelets. Additionally, there was uncertainty regarding the

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preference for a pathogen reduced platelet product amongst prescribing physicians.

1.1 Objective

This study provides a method for evaluating tools to detect and estimate demand shifts for platelet products following the implementation of PR technology at a pilot site in the CBS network.

2 LITERATURE REVIEW

Research on platelet management typically focuses on reducing waste and shortage. Often, this involves the selection of an appropriate platelet ordering policy and/or managing demand. Research in demand analysis can be categorized by method, including forecasting, simulation, and integrated Operations Research (OR) methods.

2.1 Forecasting Research

Forecasting methods improve inventory metrics by predicting demand. Forecasting methods have been used throughout the history of research on blood product inventory management, but recently there has been interest in forecasting as an application for machine learning methods.

Silva Filho (2012) used an ARIMA model to forecast demand across regional supply chain. A tool was created that could be used by managers in different regional blood centres. Lestari (Lestari, Anwar, Nugraha, & Azwar, 2017) used autoregressive methods to predict demand for different blood products, but found that a simple moving average performed best.

Khaldi (2017) applied Artificial Neural Networks (ANN) to forecast demand for products at a regional blood centre level. ARIMA models were used as a benchmark. The performance of the ANN models was found to far exceed that of the ARIMA models. However, ARIMA models produced results that were more interpretable for managers.

Shih (2019) compared time-series methods to machine learning. ARIMA, Exponential Smoothing Models, and Holt-Winters were compared with ANNs and Multiple Regression. Shih found that the time-series methods performed similarly, while Multiple Regression outperformed the Artificial Neural Network. When the time-series methods were compared to machine learning, the results were inconclusive, with different time series models and regressions performing better on some data sets.

2.2 Simulation Methods

Simulation is amongst the most popular technique for modelling and evaluating blood product inventory.

Atkinson (2012) used a hospital simulation to determine trade offs between cost and transfusion efficacy when demand is close to, or greater than, supply.

Asllani (2014) designed a decision support system which simulated the collections and demand for apheresis platelets in a regional blood centre. It was found that collecting fewer A+ apheresis platelets, and not collecting on weekends reduced waste by 7%.

Blake (2017) examined the inventory impact of increasing the shelf-life of platelets. Different ordering polices were required to reduce waste for each of the values of shelf-life, but significant improvements were found for all cases.

2.3 OR Methods

In addition to forecasting and simulation, several works related to platelet inventory management using techniques such as stochastic dynamic programming (SDP), approximate dynamic programming (ADP), and integer stochastic programming (ISP) can be found in the literature.

Haijema (2007) created a Markov decision process formulation for platelet ordering policies at the regional level. A simulation approach was used to search for the single best ordering policy. It was found that the simulation provided near optimal results in both the downsized and full-scale problems. Civelek (2015) follows much the same structure as Haijema (2007) and Van Dijk (2009) with the addition of a critical level protection policy.

Abdulwahab (2014) used both linear programming and approximate dynamic programming to develop a model of a single hospital and blood bank. The approach was able to find an optimal solution without downsizing. Similarly, Gunpinar (2015) used a stochastic integer programming model to model hospital level inventory to find an optimal solution.

Guan (2017) analyzed factors in platelet usage at the hospital level to determine factors influencing demand. These included units transfused in the previous days/weeks, census data, and complete blood count for inpatients.

2.4 Research Summary

Previous work on blood product inventory management has focussed on decision support with

the goal of reducing waste and shortage. Inventory monitoring is an important component of these models. However, it is performed with the assumption that the properties of demand do not have change points. Thus, there is a significant gap in the research on inventory monitoring itself, and the transient component of changes in the blood supply chain.

3 METHOD

In this study we employ Statistical Process Control (SPC) to monitor inventory at a CBS production centre following a change in product. A discrete event simulation is used to generate synthetic data for the inventory monitoring process, since data representative of possible demand changes did not exist. Forecasting methods, using both traditional and machine learning techniques, are employed to increase sensitivity to change detection and reduce time to detection by supplying expected future data points.

3.1 Control Charts

Standard control charting, was used to compare the values of points in a series, ordered by time, against established process properties.

In the problem case, both pooled and apheresis platelets are available to satisfy patient requirements. Apheresis units, which are more expensive than pooled platelets, are reserved for immunocompromised patients. Apheresis platelets may be substituted for pooled platelets, but pooled platelets are not substituted for apheresis demand. This complicates the problem, since pooled and apheresis platelets may be affected differently by changes in demand, and some changes will present more in one product than the other. To account for this, both the pooled and apheresis inventory streams were monitored in this project.

3.2 Data Generation

Since PRT platelets are a new product, no suitable data existed to evaluate change point detection methods. Thus, a discrete-event simulation was built to create inventory data representative of changes in demand. The simulation is comprised of three top-level components: collections, inventory, and demand. The relationships between the system elements are illustrated in Figure 1. Collections are created daily, according to a Poisson distribution, and placed in inventory. The shelf-life of collected units on arrival to inventory is decreased by some number of days to simulate the time required for production and testing processes. Demand is created daily, and inventory is allocated to fill it. Remaining inventory is aged one day or, if it has no remaining shelf-life, outdated. The process then repeats for some number of days.

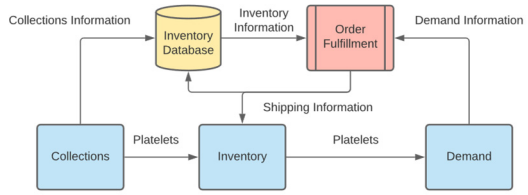

Figure 1: Inventory simulation framework. The simulation generates artificial data for the change point detection algorithm.

The simulation allocates inventory to fill demand using a matching heuristic based on the steps taken by CBS decision-makers when filling orders:

1. Exactly match apheresis inventory with apheresis demand, with priority given to units with lowest remaining shelf-life.
2. If there is unsatisfied demand for a specific apheresis unit, substitute a compatible apheresis unit, with priority given to units with the lowest remaining shelf-life.
3. Check the shelf-life of apheresis inventory. If there are any with a remaining shelf-life of 0 days, use them to fill compatible orders for pooled platelets.
4. Exactly match pooled inventory with pooled demand, with priority given to units with lowest remaining shelf-life.
5. If there is unsatisfied demand for pooled platelets which cannot be exactly matched, substitute a compatible pooled unit with priority given to units with the least remaining shelf-life.

Inventory is monitored continuously in the simulation and a feedback controller is included to maintain a stable inventory level. The controller reviews recent collections, including those in inventory, but not released for shipment, and determines the probability they will meet demand over a short planning horizon. If the probability is sufficiently low, collections are increased in the following weeks. There is, however, a limit to the effort the controller can exert, representing the level of adaptability of the system.

3.3 Enhancing Change Point Detection with Local Forecasting

The time required to detect changes in a time series is constrained by the rate of acquisition of new data. In this study, data is collected daily, but analyzed weekly to reduce noise due to day-to-day variation. To increase the speed and quality of detection, forecasting was used to supply the change point detection algorithm with additional (anticipated) data points. Linear Regression, ARIMA, Local Regression, Generalized Additive Models (GAM), and Random Forest methods were all evaluated.

4 DATA

The data used to populate the simulation comes from a sample from a CBS production site for the 2019 calendar year. Summary statistics for platelet inventory are shown below in Table 1.

Table 1: Daily inventory summary for the study region.

Blood Type	Product Type	Mean Daily Inventory, units	Daily Inventory Stand. Dev, units
A+	Pooled	56.99	16.02
A-	Pooled	4.98	3.28
B+	Pooled	11.14	4.80
B-	Pooled	0.28	0.55
AB+	Pooled	0.64	1.37
AB-	Pooled	0.00	0.00
O+	Pooled	60.63	20.10
O-	Pooled	13.11	7.19
A+	Apheresis	13.00	5.51
A-	Apheresis	2.88	2.31
B+	Apheresis	3.64	2.57
B-	Apheresis	0.189	0.56
AB+	Apheresis	1.82	1.67
AB-	Apheresis	0.14	0.49
O+	Apheresis	15.00	6.32
O-	Apheresis	1.03	1.08

Table 2 below displays the inventory summary for pooled and apheresis platelets.

Table 2: Daily inventory distribution.

Property	Pooled Inventory	Apheresis Inventory
Mean	147.8	37.7
Standard Deviation	28.4	9.2

5 EXPERIMENTS

5.1 Validation

The simulation model was validated by comparing simulation output to the parameters of the input data. The daily inventory was extracted from the input data. Daily inventory data was collected from the simulation by using a long-term run of 10,000 days. Results suggested that the simulation was able to represent, adequately, the system under study. (Results excluded for brevity.)

5.2 Synthetic Data

Two sets of data are generated by the simulation in this study. The first evaluates the false positive component of the detection accuracy metric, by creating data with the same statistical properties as the 2019 data.

The second set of evaluation data assesses the false negative component of the detection accuracy metric and the time to detection metric.

Changes in demand can be described by level, type of function, and the probability they will assume a value at a given time. See Table 3.

Table 3: Demand shift parameters.

F(t)	Magnitude
step	deterministic
linear	stochastic

Example changes in demand are depicted below in Figure 2. Note that linear changes in demand are implemented as a regular increase across a time period of four weeks.

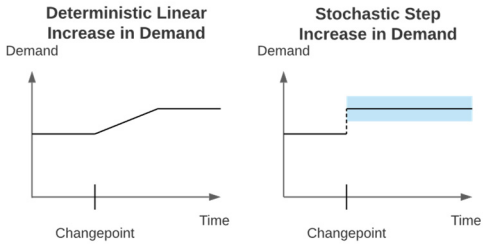

Figure 2: Examples of different possible changes in demand.

There are several ways in which demand may be affected by the introduction of PRT platelets, and while not all of them are necessarily equally likely, access to simulation makes testing worthwhile. As a

result of PRT platelets replacing BAC-T bacterial contamination detection there may be:

- An increase in pooled demand
- An increase in apheresis demand
- A transition of demand from pooled to apheresis

5.3 Evaluation of Forecasting Methods

As noted, local forecasting was used to improve the time to detection of a change by supplying the detection algorithm with assumed future data points. Forecasting methods, listed below, were tested on the base model data to determine their effect of the change point detection.

Table 4: Forecasting method performance and impact on false detection rate.

Method	Base Case MAPE, %	Base Case RMSE, units of platelets	Base Case False Detection Rate, %
No Forecasting	--	--	3.20
ARIMA	13.14	16.85	3.50
Linear Regressior	15.45	20.00	6.50
GAM – Local Regression	16.64	21.90	31.50
GAM - Splines	14.35	18.57	4.90

Two forecasting accuracy metrics were used to evaluate forecasting accuracy, along with false detection rate: Mean Absolute Percentage Error (MAPE) and Root Mean Squared Error (RMSE).

As can be seen in Table *4* the ARIMA model was found to perform best according to the forecasting accuracy metrics. Accordingly, for the case study, ARIMA methods were used to supply the change detection algorithm with additional data points.

5.4 Changes in Shelf-Life

After the implementation of PRT platelets, the regulatory shelf-life of pooled platelets was reduced from 7 days to 5 days for the period of time considered in the case study. To account for the change in approved shelf-life of PRT platelets the shelf-life of pooled platelets was decreased by two days in the simulation; apheresis platelets, which were not pathogen reduced, continued to have a 7-day shelf-life. Readers should note that subsequent to this study, the regulatory shelf-life of PRT platelets in Canada was extended to 7 days.

5.5 Overview of Experiments

Change point detection experiments in this study were divided into 3 categories: single factor, two factor, and 2^k factorial. The first category, single factor experiments, were used to investigate the effect of a single type of demand change on inventory. Two factor experiments follow the same structure but with two types of demand change present. Finally, the 2^k factorial experiments examine interaction among demand change factors.

6 RESULTS

6.1 Single Factor Experiments

To evaluate the performance of detection methods experiments were conducted on data with only a single factor change. An example is shown below in Figure 3 and Figure 4.

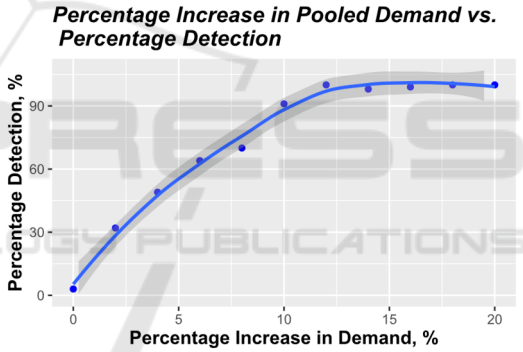

Figure 3: Change in demand and its effect on likelihood of detection.

Figure 3 depicts the percentage of detections when the level of increase in pooled demand is changed in a deterministic step. These results indicate that the chance of signal detection converges to 100% when demand increases exceed 10%. The grey shadow in the figure represents the confidence interval for detection.

Figure 4 shows the mean time to detection for the same single factor experiment. The mean time to detection decreases as the level of increase in pooled demand increases. The mean time to detection for a 2% increase is 23 weeks, while the mean time to detection for a 20% increase is 6 weeks.

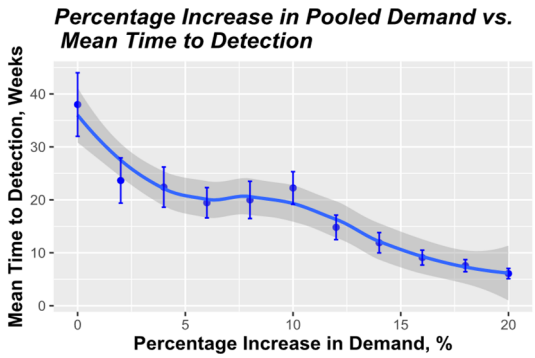

Figure 4: Change in demand and its effect on the time required to detect the change.

Two Factor Experiments:

A concern for the blood supplier was that an increase in the demand for pathogen-reduced pooled platelets, to make up for the lower per unit yield, might be accompanied by a migration of demand to apheresis platelets. Thus, a set of experiments was performed to examine the performance of detection methods to demand changes exhibiting these patterns.

The detection rates for these experiments are found in Figure 5. These results represent a step change in both pooled demand and shift to apheresis units. The contours indicate that the detection rate converges to 100% for demand shifts between 10% and 15%. It can also be observed that the effect of a migration from pooled to apheresis is detected, at lower levels, more often than the effect of an increase in demand for pooled platelets is detected.

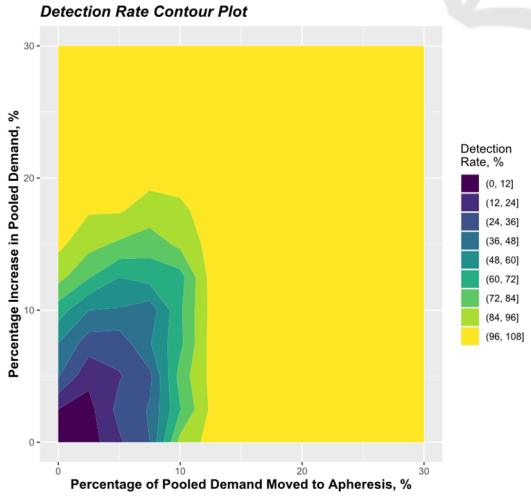

Figure 5: Contour plot of detection rate for change in pooled demand accompanied by a shift from pooled to apheresis units.

The mean time to detection for the multiple demand shift experiment is displayed in Figure *6*. While there are anomalies, the mean time to detection generally decreases as the magnitude of the demand shift increases. These results are similar to, but less favourable than, those detected during the single factor experiments.

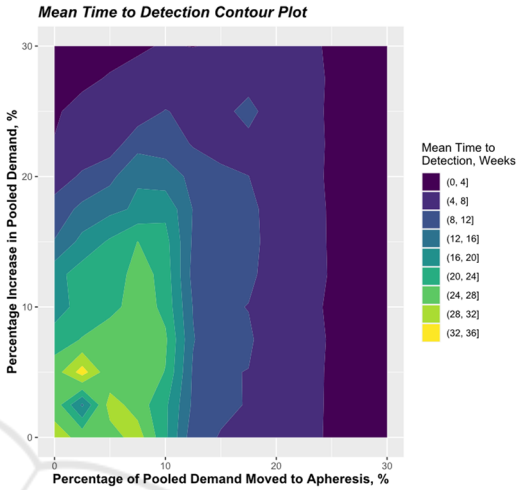

Figure 6: Contour plot of detection time for Contour plot of detection rate for change in pooled demand accompanied by a shift from pooled to apheresis units.

6.2 Multifactor Experiments

To ascertain the effect of different demand shift parameters on performance, and the interaction of factors, the change point detection algorithm was applied to data with multiple demand factors under the assumption of a 2^5-factorial experiment. See Table 5.

Table 5: Factor descriptions for 2^k experiments.

Factor				
1	2	3	4	5
An increase in pooled demand	An increase in apheresis demand	Transfer of pooled demand to apheresis	Step increase or linear increase	Deterministic or stochastic

The results of these experiments are displayed in Figure 7 and Figure 8. Patterns are evident when evaluating interactions of Factors 1-3 with Factors 4 (step vs. linear increase) and 5 (deterministic vs. stochastic step). In Figure 7, the red line indicates the mean percentage detections across experiments in that group. The chart shows that a linear change, as opposed to a step change, has a small negative effect

on both the probability of detection and time to detection. Interestingly, a stochastic change in demand is both more likely to be detected and is detected more quickly than a deterministic change. This may be because variance in an increasing demand trend leads to more extreme values in inventory that trigger detection rules in the SPC method.

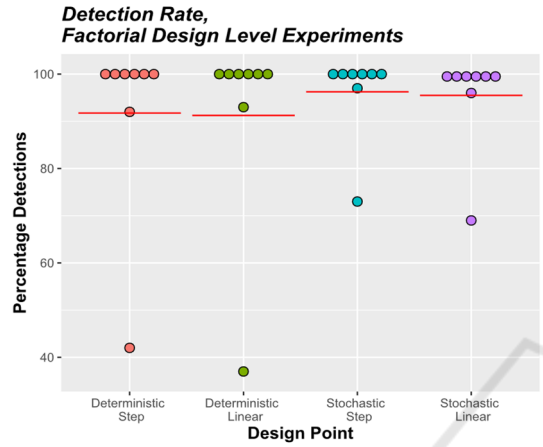

Figure 7: Detection rate for experiments factors 4 & 5: Step vs. linear change and stochastic vs. deterministic change.

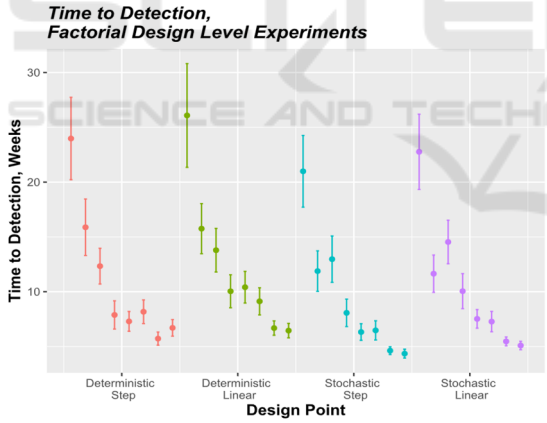

Figure 8: Mean time to detection for factorial level experiments grouped using factors 4 & 5 Step vs. linear change and stochastic vs. deterministic change.

The effect of a change in each factor on the results of the 2^5 factorial experiments are shown in Table 6. These indicate that the presence of all factors, except a linear change in demand (Factor 4), increase the detection rate and decrease time to detection. Factor 3, a shift of pooled demand to apheresis, has a significantly larger effect on detection time than the other factors. Since apheresis platelets make up only 32% of inventory, a small shift of demand from pooled has a large effect on apheresis inventory.

Table 6: The effect of 2k experiment factors on detection rate and time to detection.

Factor	Effect on Detection Rate, %	Effect on Detection Time, Weeks
1 - Pooled demand increase	10.25	-3.54
2 – Apheresis demand increase	12.13	-4.80
3 – Pooled demand to apheresis	12.625	-8.19
4 – Step vs. linear change	-0.625	1.19
5 – Stochastic vs. deterministic	4.375	-1.64

Evaluation of interaction effects proved that presence of more than one type of increase generally increases detection metrics. However, the presence of a transfer of demand from pooled platelets to apheresis platelets was found to have a small negative impact on detection performance. Interaction terms above 2nd order were found to be insignificant.

6.3 Summary

Simulation results, shown in Table 7 give an overview of estimated performance at different demand shift levels.

Table 7: Summary of detection performance.

Change to System, %	Mean Detection Rate, %	Mean Detection Time, Weeks	Detection Time CI, Weeks
1 to 5	72.8	25.12	14.43, 35.81
6 to 10	91.3	15.20	9.86, 20.54
11 to 15	98.4	8.83	5.19, 12.47
16 to 20	100.0	4.25	3.34, 5.16
21 to 25	100.0	1.38	1.26, 1.50
26 to 30	100.0	1.05	1.00, 1.10

Changes up to 5% change have a mean time to detection of 25 weeks, while changes above 25% have a mean time to detection of just over 1 week. The overall detection rate converges to 100% when the magnitude of change exceeds 10%.

7 CONCLUSION

Standard SPC is effective in detecting shifts in platelet demand. Results show that the key performance metrics of detection rate and detection time improve as the magnitude of the shift increases.

Forecast models were developed from established families of forecasting methods to supplement the SPC method. The models were evaluated using historical data, base case runs of the inventory simulation, as well as data representative of demand shifts. The best performing method, ARIMA, was incorporated into the SPC analysis to increase the speed of data acquisition by providing additional data points for the algorithm. Our model did not suggest better performance using machine learning for forecasting.

Changes in demand, with an effect on the system larger than 10%, were always detected in our study. Detection time varies greatly depending on the level of the demand shift. Typically, shifts greater than 25% have an average detection time of just over a week while shifts of less than 5% have an average detection time of 25 weeks.

The results of this paper were used by the blood agency to set parameters for monitoring the roll out of PRT platelets in Canada, supplementing their existing SPC methods.

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