Influence of Manufacturers on Cefazolin & Vancomycin Stability

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BACKGROUND

NAPRA utilizes USP 797 to recommend standardized beyond use dates (BUD) for sterile compounds. Current USP 797 guidance allows institutions to extend the recommended BUD based on published stability data. However, upcoming changes propose a maximum BUD cut off for compounds due to variability in stability literature.

Table 1: USP 797 Beyond use date recommendations

a. Current BUD Guidance for Compounded Products

Risk level	Room Temp	Refrigerated	Frozen
Low	48 hours	14 days	45 days
Medium	30 hours	9 days	45 days
High	24 hours	3 days	45 days

b. Proposed BUD Cut offs for Compounded Products

		Room Temp	Refrigerated	Frozen
Made from ≥1 nonsterile components	No sterility testing	4 days	7 days	45 days
	With sterility testing	28 days	42 days	45 days
Made with only sterile components	No sterility testing	6 days	9 days	45 days
	With sterility testing	42 days	42 days	45 days

This variability has led some institutions to interpret the NAPRA guidance as requiring data for each brand of sterile preparation. However, a growing body of evidence suggests that there is no significant difference in stability between drug manufacturers. Two head-to-head studies among several vancomycin brands have found no difference in stability, and an unpublished study has found similar results with bortezomib.

Currently it is unknown if changes in cefazolin manufacturers contribute to variations in drug stability. As of 2017, 5 brands of cefazolin are marketed in Canada and 7 brands of intravenous vancomycin.

OBJECTIVES

To evaluate and confirm if variations in drug manufacturer contributes to variations in cefazolin and vancomycin admixture stability.

METHODS

We conducted a systematic review and meta-analysis of PubMed, Scopus and EMBASE from January 1950 to October 2017 for studies evaluating cefazolin stability. We utilized the search terms “cefazolin” AND “stability” and restricted our search according to our inclusion and exclusion criteria. We extracted information pertaining to study day, lab, manufacturer, temperature, container of storage, diluent and drug concentration in order to model their effects on percent of drug remaining.

Table 2: Inclusion and Exclusion Criteria

Inclusion	Exclusion
• Full text availability • Full data set disclosed • HPLC quantification • Reporting of all variables of interest	• Microbiological assay quantification • Uncommon diluent used (ie: dialysis, ophthalmic formulation) • Freezing and thawing samples

We performed multiple linear regression to model the factors contributing to percent of drug remaining. Nominal labels were given to the lab performing the study, temperature, diluent, and container. Study days and concentration (mg/mL) were reported in interval. We repeated this procedure with vancomycin as a control to provide face validity for our results. All statistical analysis was performed in IBM SPSS version 20.

RESULTS

We identified 3449 studies for cefazolin and 1552 studies for vancomycin. Duplicates were removed, and a total of 7 studies with 138 data points were recorded for cefazolin and 8 studies with 332 data points for vancomycin. Six and 8 different manufacturers were recorded for cefazolin and vancomycin respectively.

Table 3: Studies Included

a. Cefazolin

Reference	Manufacturer	Days
Gupta 1980	Eli Lilly	30
Bosso 1985	Smith Kline	2
Galanti 1996	Bristol-Myers	30
Xu 2002	Apothecon	30
Gupta 2003	Apothecon	22
Walker 2010	Novopharm	28
Donnelly 2011	Apotex	30

b. Vancomycin

Reference	Manufacturer	Days
Walker 1988	Eli Lilly	31
Khalfi 1996	Qualimed Lab	2
Galanti 1997	Eli Lilly	58
Gupta 1986	Eli Lilly	63
Allen 1997	Abbott	30
Walker 2010	Hospira	31
Lewis 2014	APP, Hospira, Pfizer	14
Huvelle 2016	Smith Kline, Mylan	57

Figure 2: Stability of Cefazolin Under Refrigeration

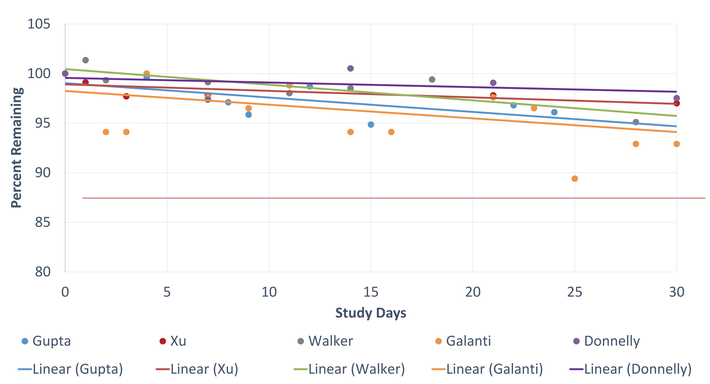

Table 4: Multiple Linear Regression on Percent of Drug Remaining

a. Cefazolin Multiple Linear Regression

	Coefficient	Std Error	T-value	P-value
Intercept	98.714	1.511	65.316	0.000
Study day	-0.193	0.034	-5.575	0.000
Lab	0.605	0.166	3.353	0.000
Manufacturer	0.198	0.201	0.984	0.327
Temperature	-4.018	0.685	-5.859	0.000
Container	1.191	0.570	2.091	0.038
Diluent	0.892	0.558	1.598	0.112
Concentration	-0.034	0.011	-3.148	0.002

b. Vancomycin Multiple Linear Regression

	Coefficient	Std Error	T-value	P-value
Intercept	101.457	1.304	77.778	0.000
Study day	-0.109	0.019	-5.776	0.000
Lab	1.099	0.183	5.979	0.000
Manufacturer	0.141	0.132	1.065	0.288
Temperature	-2.897	0.576	-5.029	0.000
Container	-0.508	0.964	-0.527	0.599
Diluent	-0.584	0.479	-1.219	0.224
Concentration	-0.166	0.0241	-6.872	0.000

Multiple linear regression for both drugs demonstrated that manufacturer, and diluent were not significant, while study day, temperature, lab, and concentration were significant factors in stability. Container was significant for cefazolin, but not for vancomycin. Significant p-values ($\alpha<0.05$) are highlighted in red. Cefazolin data demonstrated a collinearity between lab and manufacturer of 0.64; however, the VIF for manufacturer was 2.45.

CONCLUSIONS

Our study suggests that differences in manufacturers do not contribute to variability in stability of cefazolin. Our analysis of vancomycin was consistent with two prior published studies demonstrating an insignificant effect of manufacturer on stability results. The amended USP 797 guidelines allow a maximum BUD of 9 days for refrigerated compounded products without sterility testing or a maximum BUD of 45 days in frozen conditions. Therefore, minute variations in stability due to manufacturers may only be relevant for drugs with a BUD shorter than the NAPRA guidance. Future research on manufacturer differences should focus on these shorter expiry drugs.

There are several limitations that warrant discussion. We were unable to account for other factors such as exposure to light, freeze/thaw of batches or variations in laboratory equipment, as not all information was reported in the studies. There are a limited number of head-to-head trials, and published studies on this topic, which resulted in correlation between some factors in the model. Despite this, subsequent analysis of the model demonstrated only a minor impact of the correlation on the overall result.

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