Stability of Generic Formulations of Bortezomib 1.0 and 2.5 mg/mL in Vials and Syringes Stored 4⁰C and Room Temperature (23⁰C)

Shirley Law, Lauren F. Charbonneau[1,2], John Iazzetta[2], William Perks[2], and Scott E. Walker[2,3]

[1]Odette Cancer Centre Department of Pharmacy, [2]Sunnybrook Health Sciences Centre Department of Pharmacy, and the [3]Faculty of Pharmacy, University of Toronto, Toronto, Ontario.

INTRODUCTION

Differences in published reports on the stability of various parenteral drugs considered pharmaceutically equivalent and an interpretation of the recent National Association of Pharmacy Regulatory Authorities (NAPRA) guidelines, has led some to conclude that each institution should conduct separate evaluations of the stability of each formulation used in their institution.

Studies evaluating the stability of reconstituted bortezomib (CJHP 2008 and 2014) demonstrated the stability of 1.0 and 2.5 mg/mL solutions of bortezomib for up to 42 days when stored at either 4⁰C or 25⁰C. The introduction of generic versions of bortezomib, beginning in 2015, raise questions of the stability of the generic formulations and the validity of extending stability from one brand to another.

Data for the TEVA, Actavis and Dr.Reddy's formulations have been available, but comparisons of the stability between manufacturers' formulations has not be rigorously tested.

OBJECTIVES

To evaluate the stability of Janssen, Teva, Actavis and Dr.Reddy's bortezomib formulations reconstituted to produce either 1.0 or 2.5mg/mL, during storage over at least 21-days at room temperature (23⁰C) and under refrigeration (4⁰C) in plastic syringes and manufacturer vials.

To interpret whether differences in stability, if any, between manufacturers would affect preparation, storage or assignment of Beyond Use Dates (BUD).

METHODS

Liquid Chromatographic Method

A validated stability-indicating liquid chromatographic system with UV detection was re-validated for each study. The system was shown to be capable of separating bortezomib from its degradation products (Figure 1).

Stability Study: Vials at 4⁰C and 25⁰C.

On study day 0, 3.5mg vials of bortezomib (Janssen, Teva, Actavis and Dr.Reddy's formulations) were prepared. Three units of each container were stored at 23⁰C and 3 at 4⁰C. Analysis of concentration and physical inspection were completed on each of the 8, 10 or 11 study days over a 21 or 42 day study period, in each study.

Data Reduction and Statistical Analysis

The primary end-point for this evaluation of differences in stability between manufacturers was the shortest time to achieve 90% of the initial concentration (with 95% confidence). Since this end-point is highly dependent on variability in the data, to ensure homogeneity, the standard deviation of regression observed for each concentration, container type, temperature and manufacturer combination was compared using analysis of variance and linear regression. An evaluation of the shortest time to achieve 90% of the initial concentration with 95% confidence (T-90[95%CI]) was completed using analysis of variance, where manufacturer, study duration, number of study days, concentration, temperature, container type and the standard deviation of regression were tested as factors. The five-percent level was used as the *a priori* cut-off for significance.

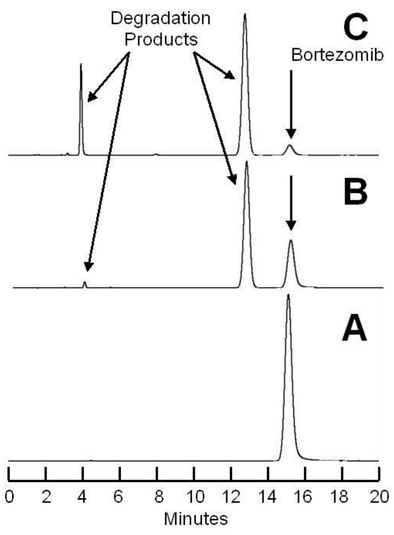

Figure 1. The liquid chromatographic system consisted of a mixture of 15% methanol and 85% 0.04 mol/L potassium phosphate monobasic buffer (pH of 7) which was pumped through 15 cm x 4.6 mm reverse-phase C18, 3-µm column (Supelcosil; Supelco, Toronto, Ontario) at 1.0 mL/min.
Chromatogram A represents a solution of 1.0 mg/mL bortezomib in water prior to the addition of sodium hypochlorite.
Chromatogram B was chromatographed immediately after the addition of 5uL of 0.3% sodium hypochlorite. 29% of the initial bortezomib was observed to remain.
Chromatogram C was chromatographed immediately after the addition of 5uL of 0.4% sodium hypochlorite. 12% of the initial bortezomib was observed to remain. Degradation products appear at 3.7 and 13.5 minutes. Additional products appeared at 4.3, 4.8, 8.7 and 29 minutes.

NONE of the authors of this poster have any personal or financial relationships with any commercial entities that may have a direct or indirect interest in the subject matter of this presentation.
The bortezomib used in these studies was donated by each manufacturer and the manufacturers' supported the work with a Research or Educational Grant.

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RESULTS

Assay Validation

All studies were completed using the same analytical method over a 9-year period. Analytical performance was similar in all studies. Average absolute deviation ranged from 1.91 – 2.99%, standard deviation of regression varied from 0.82 to 1.02% and analytical reproducibility, within a day (as measured by CV), ranged from 0.62% to 1.51%.

Concentration Results

All concentrations in all four studies exceeded 94.95% on all study days. The shortest time to achieve 90% of the initial concentration, with 95% confidence (T-90 [95%CI] in each study was 36.36 days for the Janssen formulation, 46.45 days for the Teva formulation, 25.72 days for the Actavis formulation and 32.30 days for the Dr.Reddy's formulation. (Table 1). In all studies this estimate exceeded the study duration.

To ensure homogeneity within the data set, the standard deviation of regression (which varied from 0.35% to 1.57%; Table 1) was evaluated for differences by ANOVA. ANOVA failed to detect significant differences in the standard deviation of regression due to the factors of manufacturer (p=0.931), temperature (p=0.854), concentration (p=0.241) or container (p=0.833). Furthermore, there was no correlation between the standard deviation of regression and the time to achieve 90% of the initial concentration - with 95% confidence (T-90[95%CI]) observed in the study (r=-0.030, n=30; p=0.706). The results indicate that the standard deviation of regression is, effectively, a random variable in the analysis.

In the evaluation of the T-90 [95%CI], analysis of variance failed to detect significant differences due to manufacturer (p=0.970), temperature (p=0.088), concentration (p=0.881), or container (p=0.465).

Table 1. Data summary of the Bortezomib Concentrations in all four Studies.

	Vial 4C 1mg/mL	Syringe 4C 1mg/mL	Vial RT 1mg/mL	Syringe RT 1mg/mL	Vial 4C 2.5mg/mL	Syringe 4C 2.5mg/mL	Vial RT 2.5mg/mL	Syringe RT 2.5mg/mL
Janssen[1]								
Shortest T-90[4] in days (95% CI)	93.84		174.49		51.48	50.07	37.26	36.36
Standard Deviation of Regression (Sy.x)[5]	1.099		0.941		0.874	0.763	0.660	0.745
Study Duration (days)	42		42		21	21	21	21
Study Days (Number of analysis days)	11		11		8	8	8	8
Teva[2]								
Shortest T-90[4] in days (95% CI)	62.15	87.60	46.45	83.65	60.27	125.74	100.88	55.56
Standard Deviation of Regression (Sy.x)[5]	1.334	1.074	1.573	1.048	1.063	0.688	0.354	0.999
Study Duration (days)	42	42	42	42	42	42	42	42
Study Days (Number of analysis days)	10	10	10	10	10	10	10	10
Actavis								
Shortest T-90[4] in days (95% CI)	71.26	91.43	33.59	32.59	67.79	35.42	30.21	25.72
Standard Deviation of Regression (Sy.x)[5]	0.704	0.774	0.447	0.81	0.908	0.828	1.277	1.090
Study Duration (days)	21	21	21	21	21	21	21	21
Study Days (Number of analysis days)	8	8	8	8	8	8	8	8
Dr.Reddy's[3]								
Shortest T-90[4] in days (95% CI)	37.21	92.41	31.41	34.00	62.59	47.92	40.96	32.30
Standard Deviation of Regression (Sy.x)[5]	1.003	0.906	0.847	0.966	0.440	0.610	0.549	1.045
Study Duration (days)	21	21	21	21	21	21	21	21
Study Days (Number of analysis days)	8	8	8	8	8	8	8	8

1. Data previously published; Walker et al. Can J Hosp Pharm 2008;61(1):14-20 and Walker SE et al Can J Hosp Pharm 2014; 67(2): 102-7.
2. Data previously presented, PPC 2016. Poster available at http://metrodis.org/SB_PPC.html
3. Data previously presented, International Hemato Onco conclave Sept 2017. Poster available at http://metrodis.org/SB_PPC.html
4. Time to achieve 90% of initial concentration (T-90) based on the degradation rate and is generally regarded as the Beyond Use Date.
5. Sy.x is the standard deviation of regression. This is equivalent to the inter-day variability (error) of the analytical method, expressed as a percent.

CONCLUSION

This study failed to detect differences in bortezomib stability due to manufacturer. Furthermore, the shortest time to achieve 90% of the initial concentration, with 95% confidence (T-90 [95%CI]) exceeds 25 days in all studied containers, at all temperatures, with all manufacturers and concentrations – all in excess of NAPRA HD 2016 guidelines. Therefore, since no meaningful difference in stability exists between manufacturers, an institution can confidently change bortezomib manufacturers without changing the bortezomib BUD.

Two head-to-head stability studies comparing different manufacturer's brands of vancomycin and a meta-analysis of cefazolin and vancomycin studies also failed to observe differences in stability as the result of manufacturer. Future research on manufacturer differences in stability should focus on drugs with a shorter expiry (e.g. azacitidine) or stable drugs where sterility tests are used to extended BUDs.