

## UC Davis

### UC Davis Previously Published Works

**Title**

Frequency and Severity of Neutropenia Associated with Food and Drug Administration Approved and Compounded Formulations of Lomustine in Dogs with Cancer

**Permalink**

<https://escholarship.org/uc/item/1k30m24d>

**Journal**

Journal of Veterinary Internal Medicine, 30(1)

**ISSN**

0891-6640

**Authors**

Burton, JH  
Stanley, SD  
Knych, HK  
[et al.](#)

**Publication Date**

2016

**DOI**

10.1111/jvim.13805

Peer reviewed

## Frequency and Severity of Neutropenia Associated with Food and Drug Administration Approved and Compounded Formulations of Lomustine in Dogs with Cancer

J.H. Burton, S.D. Stanley, H.K. Knych, C.O. Rodriguez, K.A. Skorupski, and R.B. Rebhun

**Background:** Compounded lomustine is used commonly in veterinary patients. However, the potential variability in these formulations is unknown and concern exists that compounded formulations of drugs may differ in potency from Food and Drug Administration (FDA)-approved products.

**Hypothesis/Objectives:** The initial objective of this study was to evaluate the frequency and severity of neutropenia in dogs treated with compounded or FDA-approved formulations of lomustine. Subsequent analyses aimed to determine the potency of lomustine obtained from several compounding pharmacies.

**Animals:** Thirty-seven dogs treated with FDA-approved or compounded lomustine.

**Methods:** Dogs that received compounded or FDA-approved lomustine and had pretreatment and nadir CBCs performed were eligible for inclusion. Variables assessed included lomustine dose, neutrophil counts, and severity of neutropenia. Lomustine 5 mg capsules from 5 compounding sources were tested for potency using high-pressure liquid chromatography (HPLC) with ultraviolet (UV) detection.

**Results:** Twenty-one dogs received FDA-approved lomustine and 16 dogs were treated with lomustine prescribed from a single compounding pharmacy. All dogs treated with FDA-approved lomustine were neutropenic after treatment; 15 dogs (71%) developed grade 3 or higher neutropenia. Four dogs (25%) given compounded lomustine became neutropenic, with 2 dogs (12.5%) developing grade 3 neutropenia. The potency of lomustine from 5 compounding pharmacies ranged from 50 to 115% of the labeled concentration, with 1 sample within  $\pm 10\%$  of the labeled concentration.

**Conclusions and Clinical Importance:** These data support broader investigation into the potency and consistency of compounded chemotherapy drugs and highlight the potential need for greater oversight of these products.

**Key words:** Canine; CCNU; Chemotherapy.

Compounding is the customized preparation of drugs that are not commercially available in the desired formulation or strength.<sup>1</sup> Compounding of veterinary drugs is widely performed and is occasionally a necessity because of the lack of available Food and Drug Administration (FDA)-approved drugs for animals. In veterinary oncology, compounded drugs may be used to more safely dose small dogs and cats with products that have a narrow therapeutic index. Compounding also may be needed when shortages of commercially available drugs occur. A number of compounding pharmacies exist to meet the needs of veterinarians, but there is concern as to whether compounded agents are as efficacious and of similar quality

*From the Department of Surgical and Radiological Sciences, University of California (Burton, Rodriguez, Skorupski, Rebhun); and the Department of Molecular Biosciences, University of California, Davis, CA (Stanley, Knych).*

*This work was completed at the School of Veterinary Medicine at the University of California, Davis.*

*This was presented in abstract form at the Veterinary Cancer Society meeting, October, 2014, St. Louis, MO.*

*Corresponding author: Dr J.H. Burton, Department of Surgical and Radiological Sciences, University of California, Davis, 1 Shields Avenue, Davis, CA 95616; e-mail: jhburton@ucdavis.edu*

*Submitted July 31, 2015; Revised November 6, 2015; Accepted November 9, 2015.*

*Copyright © 2015 The Authors. Journal of Veterinary Internal Medicine published by Wiley Periodicals, Inc. on behalf of the American College of Veterinary Internal Medicine.*

*This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.*

DOI: 10.1111/jvim.13805

### Abbreviations:

BSA	body surface area
FDA	Food and Drug Administration
HPLC	high-pressure liquid chromatography
UV	ultraviolet
VCOG-CTCAE	Veterinary Cooperative Oncology Group - Common Terminology Criteria for Adverse Events

compared to FDA-approved products. Studies evaluating compounded omeprazole in horses, and compounded itraconazole, ciclosporin, and trilostane in dogs have indicated that compounded drugs are not always equivalent in potency with respect to the active pharmaceutical ingredient, and subsequent efficacy failures are more frequent as compared to the FDA-approved product.<sup>2–5</sup>

Lomustine, a chemotherapy agent with demonstrated efficacy against several malignancies in dogs, was unavailable for commercial purchase as of May 2013 because of the discontinuation of sale of the FDA-approved formulation.<sup>6</sup> As a result, lomustine was routinely prescribed through a compounding pharmacy by veterinary oncologists at our institution for patients requiring the drug as part of their anticancer treatment. As with many chemotherapeutics, lomustine has a narrow therapeutic index. Neutropenia frequently occurs after treatment with this drug and 2 previous studies evaluating the efficacy of lomustine against relapsed lymphoma and mast cell tumors in dogs identified that neutropenia was the dose-limiting toxicity, with median neutrophil counts of approximately 1,400/ $\mu\text{L}$  1 week after treatment.<sup>7,8</sup> During the 10 months that

compounded formulations of lomustine were being prescribed by clinicians at the University of California, Davis Veterinary Medical Teaching Hospital, clinical observation suggested that dogs experienced fewer neutropenic events compared to previous clinical experience with FDA-approved formulation of lomustine. To further investigate this clinical suspicion, the initial objective of this study was to evaluate the frequency and severity of neutropenia in dogs treated with an FDA-approved formulation of lomustine as compared to dogs treated with lomustine obtained from a single veterinary compounding pharmacy. A subsequent objective was to assess the initial potency of lomustine capsules obtained from 5 veterinary compounding pharmacies.

## Materials and Methods

### Case Selection and Record Review

Medical records from the University of California, Davis Veterinary Medical Teaching Hospital were reviewed from January 1, 2012 to February 28, 2014 for dogs given their first dose of lomustine, either a compounded or the FDA-approved formulation. Inclusion criteria included a known date of lomustine administration and CBC performed before dosing as well as a nadir CBC performed 6–10 days after the first dose.

Data regarding the following variables were abstracted from each dog's medical record: signalment, body weight, body surface area (BSA), cancer diagnosis, whether they had previously received other chemotherapy or were treatment naïve, lomustine dosage, date and dose of first lomustine administration. Both the intended and actual dosages of lomustine were recorded because these dosages generally vary for FDA-approved lomustine because capsules are only available in 10 mg and 40 mg strengths. Data collected regarding hematologic variables included dates of pretreatment and nadir CBC, number of days after lomustine administration the CBC was performed, and baseline and nadir neutrophil counts. The severity of neutropenia after lomustine treatment was determined using the Veterinary Cooperative Oncology Group – Common Terminology for Adverse Events (VCOG-CTCAE) v1.1.<sup>9</sup>

### Lomustine Potency Analysis

Analytical reference standard for lomustine<sup>a</sup> was obtained. Five veterinary compounding pharmacies were selected based on their advertisements in national veterinary publications and their ability to compound lomustine. Purchased compounded formulations of lomustine with labeled concentrations of 5.0 mg were analyzed for potency. Individual capsules were weighed and then opened to remove the lomustine, which was emptied onto a wax paper sheet, weighed, and transferred to an amber vial, which was wrapped with aluminum foil to further protect from light exposure. The empty capsule was then reweighed.

A reference standard solution of lomustine was prepared in 100% methanol at a concentration of 1.0 mg/mL; the standard reference material was purchased from certified vendors<sup>a</sup> and certificates of analysis that reported the quality and purity data were provided. Before analysis, calculations were made so the concentration of lomustine in each capsule could be determined when compared to the reference standard. For each capsule, an amount containing the calculated 5 mg was diluted with 5 mL of methanol: H<sub>2</sub>O (10:90 v/v) to make each test solution. Each 50 µL test sample aliquot was transferred containing the methanol: H<sub>2</sub>O (10:90 v/v) to solubilize lomustine for analysis. The process was repeated for duplicate sampling of each preparation. The duplicate aliquots of each prepara-

tion were analyzed using high-pressure liquid chromatography (HPLC) with ultraviolet (UV) detection<sup>b</sup> with a C<sub>18</sub> reverse-phase column (2.1 × 100 mm, 3 µ).<sup>c</sup> The mobile phase was composed of 50:50 acetonitrile: H<sub>2</sub>O with 0.1% formic acid with an isocratic technique used throughout the analysis at a flow rate of 0.5 mL/min. The column temperature was maintained at 30°C by column oven. The UV detector was set to collect the following wavelengths: 254, 230, 215, and 274 nm. The injection volume was 40 µL.

### Statistical Analysis

Continuous data were described using median and range and categorical data as frequencies and percentages. Differences among groups were assessed using the Mann–Whitney test for continuous data. For categorical data, Fisher's exact test was used for variables with 2 categories and the Chi-squared test for variables with >2 categories. A *P* value of <.05 was considered statistically significant. All statistical analyses were performed using commercially available software.<sup>d</sup>

## Results

Fifty-five dogs that received lomustine during the study time period were identified on electronic medical database search. Eighteen of these cases did not have a baseline or nadir CBC for review, resulting in 37 cases that met the criteria for inclusion into this study. Twenty-one dogs were treated with the FDA-approved formulation of lomustine from June 11, 2011 to May 8, 2013 and 16 dogs received a compounded formulation of lomustine from May 13, 2013 to February 21, 2014. The compounded lomustine was dispensed from a single veterinary compounding pharmacy for all dogs in this portion of the study. Information regarding patient signalment, tumor type and previous treatment are reported in Table 1. The median body weight and body surface area (BSA) for the group of dogs that received compounded lomustine were significantly less than those of dogs that received FDA-approved formulations of lomustine (Table 1; *P* = .02 for both variables).

Table 2 summarizes the planned and actual dosages of lomustine as well as baseline and nadir neutrophil counts. There was no statistical difference between the planned and actual lomustine dosages between the dogs that received FDA-approved or compounded formulations of lomustine. The baseline median neutrophil count before treatment was not significantly different between dogs that received FDA-approved formulations of lomustine (8,309/µL; range, 3,802–19,580/µL) and those treated with compounded lomustine (7,879/µL; range, 4,440–38,059/µL; *P* = .81). Nadir neutrophil counts were performed on day 6 (*n* = 1), day 7 (*n* = 21), day 8 (*n* = 11), day 9 (*n* = 2), and day 10 (*n* = 2) after CCNU administration; median nadir neutrophil counts were not statistically significant different between day 7, 8, 9, and 10 (*P* = .66). Neutropenia occurred in all 21 dogs (100%) treated with FDA-approved lomustine and the median neutrophil count 1 week post-treatment was 638/µL (range, 42–2,941/µL). Significantly fewer dogs (*n* = 4; 25%) treated with compounded lomustine developed neutropenia 1 week post-treatment with a median neutrophil count of 3,520/µL (range, 560–20,697/µL;

$P < .0001$ ). Three dogs (19%) treated with compounded lomustine had either no change ( $n = 1$ ) or an increase ( $n = 2$ ) in neutrophil count from baseline to nadir. The grade (severity) of neutropenia was assessed using the VCOG-CTCAE v1.1<sup>9</sup> for each dog and is presented in Table 3. Dogs were grouped according to the severity of the neutropenia (no neutropenia and grade 1–2 versus grade 3–5) and dogs treated with the FDA-approved formulation of lomustine were significantly more likely to

**Table 1.** Patient demographics, tumor type, and whether previous chemotherapy had been administered for dogs treated with either FDA-approved or compounded lomustine.

	Median (range) or Frequency (%)		<i>P</i> value
	FDA-Approved Lomustine (n = 21)	Compounded Lomustine (n = 16)	
Breed			
Labrador retriever	4 (19%)	4 (25%)	NA <sup>a</sup>
Bernese mountain dog	3 (14.3%)	0	
Golden retriever	2 (9.5%)	2 (12.5%)	
English bulldog	1 (4.8%)	2 (12.5%)	
Mixed breed	3 (14.3%)	4 (25%)	
Rottweiler	2 (9.5%)	0	
Other (1 each) <sup>b</sup>	6 (28.6%)	4 (25%)	
Age (years)	8.5 (3.6–12.2)	8.0 (0.7–12.0)	.44
Sex			
MC	10 (47.6%)	6 (37.5%)	1.0
M	1 (4.8%)	3 (18.8%)	
FS	9 (42.9%)	6 (37.5%)	
F	1 (4.8%)	1 (6.3%)	
Weight (kg)	35.8 (8.7–63.6)	27.2 (3.9–43.8)	.02
BSA <sup>c</sup> (m <sup>2</sup> )	1.08 (0.42–1.59)	0.9 (0.24–1.24)	.02
Tumor Type			
Lymphoma <sup>d</sup>	5 (23.8%)	7 (43.8%)	.44
Mast cell tumor	9 (42.9%)	5 (31.3%)	
Histocytic sarcoma	7 (33.3%)	4 (25%)	
Previous chemotherapy			
Yes	13 (61.9%)	10 (62.5%)	1.0
No	8 (38.1%)	6 (37.5%)	

<sup>a</sup>NA, not assessed.

<sup>b</sup>Other breeds included Beagle, Chihuahua, Standard Poodle, Vizsla, Basset hound, Boxer, Bull mastiff, Pit bull, Rhodesian ridgeback, Miniature Schnauzer.

<sup>c</sup>BSA, body surface area.

<sup>d</sup>Included relapsed/refractory or cutaneous lymphoma.

develop  $\geq$  grade 3 neutropenia ( $n = 15$ , 71%) as compared to dogs treated with compounded lomustine ( $n = 2$ , 12.5%;  $P < .001$ ).

### Compounded Lomustine Potency

Three 5.0 mg capsules of lomustine were obtained from the veterinary compounding pharmacy that was used to prescribe compounded lomustine to all dogs that received compounded formulations of the drug in this study. The capsules were analyzed within 10 days of receipt from the compounding pharmacy. The 3 capsules varied 7% among the weights of the lightest and the heaviest (231.4, 244.8, and 249.3 mg). When analyzed for potency using HPLC-UV, the capsules were determined to contain 50, 54, and 54% of the labeled concentration of 5.0 mg.

Three capsules of lomustine 5.0 mg were obtained from 4 additional veterinary compounding pharmacies as well as the pharmacy from which the initial samples were analyzed. When analyzed for potency, the samples were determined to contain between 67 and 115% of the labeled concentration of lomustine (Fig. 1). Only 1 veterinary compounding pharmacy provided samples that fell within  $\pm 10\%$  of the labeled concentration, which is the maximal variability in potency allowed for FDA-approved pharmaceutical products.

### Discussion

This study confirmed our clinical impression that the frequency and severity of neutropenia associated with lomustine administration was significantly decreased when compounded formulations of lomustine were used to treat cancer-bearing dogs. Additionally, significant variability in the potency of compounded lomustine from several sources was identified, with only 1 of the veterinary compounding pharmacies providing potency within  $\pm 10\%$  of the label-claimed concentration.

Myelosuppression, in particular neutropenia, is a common sequela after lomustine administration and is considered to be the dose-limiting toxicity for this drug. Two previous publications evaluating use of lomustine as treatment for dogs with mast cell tumors and relapsed lymphoma reported median nadir neutrophil counts of 1,452 cells/ $\mu\text{L}$ <sup>8</sup> and 1,400 cells/ $\mu\text{L}$ <sup>7</sup>, respectively. In these studies, occurrence of  $\geq$  grade 3 neutropenia was reported to be 41%<sup>8</sup> and 42%<sup>7</sup>, and both of these studies used a higher dosage of lomustine (90 mg/m<sup>2</sup>) than given to dogs in this study and evalu-

**Table 2.** Lomustine dosages (planned and actual) and baseline and nadir neutrophil counts for dogs that received either FDA-approved or compounded lomustine.

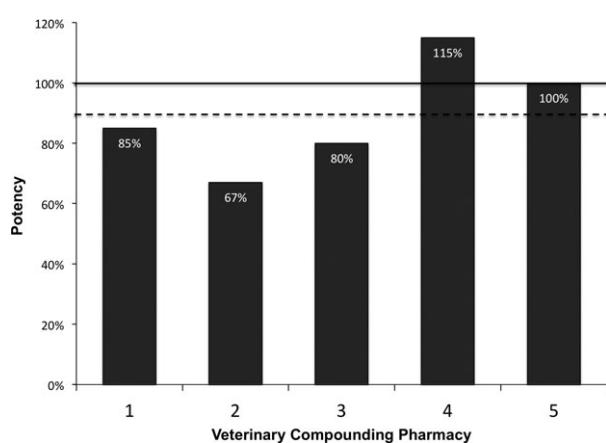
Variable	FDA-Approved Lomustine, n = 21 Median (range)	Compounded Lomustine n = 16 Median (range)	<i>P</i> value
Planned lomustine dosage (mg/m <sup>2</sup> )	71 (65–80)	73.5 (45.8–80)	.36
Actual lomustine dosage (mg/m <sup>2</sup> )	71.4 (61–77.8)	73.5 (45.8–80.6)	.21
Baseline neutrophil count (10 <sup>3</sup> cells/ $\mu\text{L}$ )	8.3 (3.8–19.6)	7.9 (4.4–38.1)	.81
Post-tx CBC (days)	7 (6–10)	7 (7–10)	.90
Nadir neutrophil count (10 <sup>3</sup> cells/ $\mu\text{L}$ )	0.64 (0.04–2.9)	3.5 (0.56–20.7)	<.0001

**Table 3.** Severity of neutropenia as determined by VCOG-CTCAE for dogs that received either commercially available lomustine or a compounded formulation of lomustine.

Severity of neutropenia	Neutrophil Count (cell/ $\mu$ L)	FDA-Approved Lomustine (n = 21)	Compounded Lomustine (n = 16)
None	WNL <sup>a</sup>	0	12 (75%)
Grade 1 (mild)	1,500 – LLN <sup>b</sup>	2 (9.5%)	1 (6.3%)
Grade 2 (moderate)	1,000–1,499	4 (19%)	1 (6.3%)
Grade 3 (severe)	500–999	5 (24%)	2 (12.5%)
Grade 4 (life-threatening)	<500	9 (43%)	0
Grade 5 (death)	–	1 (4.8%)	0

<sup>a</sup>WNL, within normal limits.

<sup>b</sup>LLN, lower limit of normal.



**Fig 1.** Bar graph of the percent potency of lomustine capsules with a labeled concentration of 5 mg obtained from 5 veterinary compounding pharmacies. The solid line indicates 100% of labeled concentration and the dashed line represents 90% of labeled concentration, which is the minimum potency allowed for FDA-approved products. The actual concentration of the samples obtained from the 5 compounding pharmacies ranged from 67 to 115% of the labeled concentration, with only 1 compounding pharmacy providing product that fell within  $\pm 10\%$  of the labeled concentration.

ated a CBC 7 days after lomustine treatment. Although the VCOG-CTCAE grading scheme had not been published at the time of publication of these earlier studies, both previous studies used the same criteria to define grade 2, 3, and 4 neutropenias as the current VCOG-CTCAE v1.1. This finding is further supported by a study in which 58–84% of dogs treated with lomustine 90 mg/m<sup>2</sup> with or without dexamethasone developed  $\geq$  grade 3 neutropenia, with median neutrophils counts ranging from 282 to 573 cells/ $\mu$ L at the nadir.<sup>10</sup> In another study, 57% of dogs that received lomustine developed neutropenia, with 21% being  $\geq$  grade 3, but the median dosage of lomustine used in that study was 57.9 mg/m<sup>2</sup> and ranged from 28.6 to 88.9 mg/m<sup>2</sup>, which may explain the decreased frequency of neutropenia in that study.<sup>11</sup> We observed a higher frequency of  $\geq$ grade 3 neutropenia in dogs treated with the FDA-approved lomustine in our study (71%). Evaluation of the nadir CBC over a range of days (6–10 days) may have led to a higher number of dogs diagnosed with neutropenia.

Because the majority of dogs had a CBC performed 7 days after treatment, however, we feel that this explanation is less likely. The timing of absolute nadirs in individual patients, however, is variable. Therefore, a single CBC nadir is unlikely to represent an individual dog's absolute nadir even when performed at the same time point as in other dogs. Nevertheless, allowing evaluation of a CBC between 6–10 days after treatment may, in part, explain reported differences in frequency and severity of neutropenia among historical studies and between historical studies and our findings.

Our study employed occurrence of a well-documented toxicity of a chemotherapy drug as a reflection of systemic exposure to lomustine and potential surrogate of antitumor activity of the drug. This approach was novel in that lomustine has a narrow therapeutic window accompanied by an established and accepted toxicity profile that can be easily monitored clinically. Our data raise concerns regarding the possibility of decreased efficacy of compounded lomustine formulations, but this outcome was not directly examined in our study. Ideally, to evaluate exposure and efficacy of the compounded versus FDA-approved formulation of the drug, pharmacokinetic evaluation and tumor response assessment would be primary outcome measures, but this approach was not feasible in our study because a variety of tumor types and stages of disease were included. Prospective studies evaluating compounded and FDA-approved formulations of chemotherapy drugs could be performed to further investigate activity, but ethical concerns must be taken into consideration in light of our findings to ensure that cancer-bearing dogs do not receive substandard treatment.

Our study was limited by issues inherent to most retrospective studies, including small sample sizes, lack of randomization into treatment groups, and collection of data from incomplete medical records. The median body weight and BSA of the dogs that received compounded lomustine were statistically lower than those of dogs that were treated with FDA-approved formulations, but the median dose of lomustine was not significantly different between the groups. Some concern exists that a higher number of dogs in the group that received compounded lomustine would be at increased risk for developing hematologic toxicities when using BSA to calculate dosage because of smaller patient size.<sup>12</sup> A standard alternative dosing scheme, however, is not routinely



employed for small dogs receiving lomustine. Differences in weight between the 2 groups might have been expected to result in a higher number of dogs that received compounded lomustine to develop neutropenia, but the opposite was observed in this study because dogs developed more frequent and severe neutropenia after treatment with FDA-approved lomustine.

We elected not to identify the compounding pharmacies from which lomustine was obtained for analysis in this study because it would be irresponsible to condemn or commend individual pharmacies based on a single sample tested at a single time point. In fact, our intention was not to identify ideal or substandard compounding pharmacies because there are many possible explanations for the observed variability. Furthermore, the potential benefits afforded by accurately compounded formulations in veterinary oncology are numerous and may include more precise dosing for smaller patients as well as optimization of low-dose chemotherapy protocols. Publication of these findings solely was intended to highlight potential inconsistencies that can occur with compounded formulations of chemotherapy drugs. Although we acknowledge that some compounding pharmacies indeed provide certificates of analysis (either standardly or upon request), we are unable to comment on the accuracy of these certificates as compared with our results without disclosing information regarding individual pharmacies. Nevertheless, the wide variability in the potency of lomustine at the present time is concerning. Although it is beyond the scope of our study to determine the source of variability among compounding pharmacies, our results should alert prescribing veterinarians to the potential hazards of prescribing compounded formulations of chemotherapy drugs.

In conclusion, our results support broader investigation into the potency and consistency of compounded chemotherapy drugs, particularly for agents expected to be well tolerated with a less predictable adverse event profile. These data also highlight the potential need for more oversight of these compounded products to ensure appropriate anticancer treatment for veterinary patients.

---

### Footnotes

<sup>a</sup> Sigma-Aldrich, St. Louis, MO

<sup>b</sup> Agilent 1100 Binary LC, Santa Clara, CA

<sup>c</sup> Advanced Chromatography Technologies, Ltd, Aderdeen, UK

<sup>d</sup> Prism GraphPad, version 6.0, La Jolla, CA

---

### Acknowledgments

*Grant support:* This work was supported by the Center for Companion Animal Health, School of Veterinary Medicine, University of California, Davis.

*Conflict of Interest Declaration:* Authors disclose no conflict of interest.

*Off-label Antimicrobial Declaration:* Authors declare no off-label use of antimicrobials.

### References

1. International Academy of Compounding Pharmacists [Internet]. IACP Compounding FAQs [about 1 screen]. Available from: <http://iacp.site-ym.com/?page=2> [Accessed 2014 May 5].
2. Cook AK, Nieuwoudt CD, Longhofer SL. Pharmaceutical evaluation of compounded trilostane products. *J Am Anim Hosp Assoc* 2012;48:228–233.
3. Umstead ME, Boothe DM, Cruz-Espindola C, et al. Accuracy and precision of compounded ciclosporin capsules and solution. *Vet Dermatol* 2012;23:431–e482.
4. Nieto JE, Spier S, Pipers FS, et al. Comparison of paste and suspension formulations of omeprazole in the healing of gastric ulcers in racehorses in active training. *J Am Vet Med Assoc* 2002;221:1139–1143.
5. Mawby DI, Whittemore JC, Genger S, et al. Bioequivalence of orally administered generic, compounded, and innovator-formulated itraconazole in healthy dogs. *J Vet Intern Med* 2014;28:72–77.
6. U.S. Food and Drug Administration [Internet]. U.S. Food and Drug Administration Resolved Drug Shortages [about 2 screens]. Available at: <http://www.fda.gov/Drugs/DrugSafety/DrugShortages/ucm050793.htm>. Accessed May 5, 2014.
7. Moore AS, London CA, Wood CA, et al. Lomustine (CCNU) for the treatment of resistant lymphoma in dogs. *J Vet Intern Med* 1999;13:395–398.
8. Rassnick KM, Moore AS, Williams LE, et al. Treatment of canine mast cell tumors with CCNU (Lomustine). *J Vet Intern Med* 1999;13:601–605.
9. Veterinary Cooperative Oncology Group - Common Terminology Criteria for Adverse Events (VCOG-CTCAE) following chemotherapy or biological antineoplastic therapy in dogs and cats v1.1. *Vet Comp Oncol* 2011.
10. Intile JL, Rassnick KM, Bailey DB, et al. Evaluation of dexamethasone as a chemoprotectant for CCNU-induced bone marrow suppression in dogs. *Vet Comp Oncol* 2009;7:69–77.
11. Heading KL, Brockley LK, Bennett PF. CCNU (lomustine) toxicity in dogs: A retrospective study (2002–07). *Aust Vet J* 2011;89:109–116.
12. Price GS, Frazier DL. Use of body surface area (BSA)-based dosages to calculate chemotherapeutic drug dose in dogs: I. Potential problems with current BSA formulae. *J Vet Intern Med* 1998;12:267–271.