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## Variable accuracy, precision, and consistency of compounded famciclovir formulated for management of feline herpesvirus-1 in cats

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### Abstract

**Objective:** To evaluate compounded famciclovir suspensions for accuracy, precision, and consistency in drug content.

**Procedures:** Two compounded famciclovir concentrations were evaluated (250 and 400 mg/mL, 30 preparations total from nine 503A compounding pharmacies) with U.S. Food and Drug Administration (FDA)-approved famciclovir tablets as control. Drug quantification via high-performance liquid chromatography (with famciclovir reference standard and pramipexole internal standard) was performed at 0, 14, and 28 days with concentrations of 90%–110% of labeled dose considered acceptable (US Pharmacopoeia standards).

**Results:** FDA-approved tablets from three different manufacturers were found to be accurate and precise with acceptable drug content. A significantly greater mean deviation from labeled content was noted for 400 mg/mL suspensions (–52.9%) compared to 250 mg/mL suspensions (–18.0%). When assessing time points separately, 15/63 (24%) samples of 250 mg/mL and 0/27 (0%) samples of 400 mg/mL suspensions met the acceptance standards. Coefficients of variation (CV) in drug content among pharmacy batches ranged from 0.5% to 29%, with 5/10 formulations having significantly lower CV% compared to control (decreased precision). Similarly, drug content changed over time (0–28 days) in all compounded formulations, with both downward and upward trends observed (variable consistency).

**Conclusions:** Most compounded famciclovir formulations were inaccurate, imprecise, and inconsistent. FDA-approved famciclovir tablets may be preferred over compounded famciclovir formulations for the management of feline herpesvirus-1. If compounded famciclovir is used in practice, a concentration of 250 mg/mL is preferred over 400 mg/mL given the lower accuracy of the higher concentration.

### Keywords

antiviral, compounded medications, famciclovir, FHV-1, high-performance liquid chromatography, penciclovir

### Disciplines

Ophthalmology | Small or Companion Animal Medicine | Veterinary Toxicology and Pharmacology

### Comments

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## ORIGINAL REPORT

# Variable accuracy, precision, and consistency of compounded famciclovir formulated for management of feline herpesvirus-1 in cats

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**Conclusions:** Most compounded famciclovir formulations were inaccurate, imprecise, and inconsistent. FDA-approved famciclovir tablets may be preferred over compounded famciclovir formulations for the management of feline herpesvirus-1. If compounded famciclovir is used in practice, a concentration of 250 mg/mL is preferred over 400 mg/mL given the lower accuracy of the higher concentration.

## KEYWORDS

antiviral, compounded medications, famciclovir, FHV-1, high-performance liquid chromatography, penciclovir

## 1 | INTRODUCTION

Famciclovir is an oral antiviral medication originally developed in humans to manage herpes simplex virus. In the past two decades, numerous veterinary studies have shown that famciclovir is also effective to treat feline herpesvirus-1 (FHV-1)<sup>1,2</sup> and is safe to use in cats.<sup>1-5</sup> Famciclovir limits primary herpetic disease, reduces reactivation and severity of recrudescence, and decreases viral shedding in cats.<sup>1,2</sup> A dose of 90 mg/kg per os twice daily is recommended for treating herpetic lesions of the ocular surface in cats—established based on pharmacokinetic/pharmacodynamic modelling<sup>5</sup> and clinical studies.<sup>1,6</sup> Indeed, this higher dose was shown to reach therapeutic concentrations in tear film<sup>5</sup> and also provided faster resolution of herpetic signs when compared to 40 mg/kg.<sup>1</sup> This 90 mg/kg dose would require a typical adult cat weighing approximately 5 kg to receive up to 450 mg (~18 mm length for a 500 mg tablet) of famciclovir twice daily.

Compliance studies consistently show that feline patients are up to five times more accepting of liquid than tablet formulations.<sup>7-9</sup> Thus, compounding liquid formulations of famciclovir is an appealing option for clinicians and owners, providing an alternative to tablets that could increase patient compliance, reduce patient stress related to drug administration, and improve clinical outcomes. However, information about the reliability of compounded famciclovir is critically lacking. Inaccurate dosing with compounded formulations—shown for several drugs in veterinary medicine<sup>10-12</sup>—could have deleterious consequences for cats treated with famciclovir. Subtherapeutic dosing of famciclovir could prolong disease duration, viral shedding, and animal suffering. Doses above the therapeutic range could increase the risk of side effects (eg, gastrointestinal upset) or systemic toxicity (eg, kidney injury).<sup>1,5</sup>

The purpose of this study was to evaluate compounded famciclovir suspensions for accuracy and precision of drug content at 0, 14, and 28 days, and compare the results with U.S. Food and Drug Administration (FDA)-approved famciclovir (control). Given previous studies,<sup>10-12</sup> unlike control tablets, we hypothesized that drug content of compounded formulations would have highly variable concentrations within and between compounding pharmacies (ie, low precision) and that drug content would fall out of the accepted range of 90%–110% (ie, low accuracy) set by the US Pharmacopeia,<sup>13</sup> regardless of the initial drug concentration (250 or 400 mg/mL).

## 2 | MATERIAL AND METHODS

### 2.1 | Famciclovir formulations

Famciclovir suspensions were obtained from nine 503A compounding pharmacy facilities based throughout the

United States, either veterinary-specific ( $n = 5$ ) or veterinary and human-focused ( $n = 4$ ), selected based on the authors' personal experience (ie, common pharmacies used by general practitioners and veterinary ophthalmologists), the ability for products to be shipped to the investigators' state (though all pharmacies had multi-state shipping capabilities, the extent of which varied by pharmacy), and the availability of famciclovir in one or more concentrations. The study investigated the two most common concentrations available at the selected pharmacies, 250 and 400 mg/mL, allowing for assessment of potential concentration-related differences in compounding accuracy and precision. Of note, the formulations provided by the compounding pharmacies differed from the one described in the USP Compounding Compendium (100 mg/mL in Oral Plus and Ora Sweet), meaning that the compounding pharmacies did not follow the USP standard for compounded famciclovir which has been tested and verified to meet compendial standards.<sup>14</sup> Six pharmacies (A, B, C, D, E, F) provided the 250 mg/mL concentration only, one pharmacy (G) provided both 250 and 400 mg/mL concentrations, and two pharmacies (H, I) provided the 400 mg/mL concentration only.

A total of 30 orders were placed throughout the study for 'in clinic use', as reported in previous work assessing compounded formulations,<sup>10,12</sup> requesting a certificate of analysis when available. This total was comprised of  $n = 3$  orders for each formulation at each pharmacy (ie, three different lots), with orders placed  $\geq 14$  days but  $\leq 21$  days apart to increase the likelihood preparations were made from different batches. At receipt, several product details were noted including the type of oil-based vehicle, beyond-use date, and physical characteristics, and then, samples were stored following pharmacies' recommendations until analysis (within 7 days): room temperature ( $n = 27$ ) or refrigeration after opening ( $n = 3$ ).

FDA-approved famciclovir tablets (Apotex Corp) were used as a control. Two other manufacturers of generic famciclovir (NorthstarRX LLC and Camber Pharmaceuticals) were also tested to assess for potential differences in the accuracy or precision of FDA-approved formulations. Of note, generic tablets rather than brand-name famciclovir (Famvir; Novartis) were used in this study as the latter is no longer commercially available. A new bottle of each brand of famciclovir tablets was purchased immediately before the experiment, with manufacture dates of 06/2017 (Apotex Corp), 09/2017 (Northstar RX LLC), and 01/2018 (Camber Pharmaceuticals) and expiration dates of 06/2020 (Apotex Corp), 09/2020 (Northstar RX LLC), and 01/2021 (Camber Pharmaceuticals). Tablets were stored at room temperature (15–30°C) per the manufacturer recommendation, and analysis was performed >12 months prior to the earliest expiration date of any manufacturer, and thus, the authors speculated the stability and consistency of drug content was appropriate;

however, these parameters were not specifically assessed in the current study for these FDA-approved tablets.

## 2.2 | Sample preparation and analysis

The physical characteristics of the FDA-approved tablets including general appearance (color, presence/absence of physical defects) and weight were noted prior to analysis. All compounded suspensions were evaluated for the following physical characteristics the day of shipment receipt from compounding pharmacies:

- Color of the suspension: Graded on a scale of 1–3, with 1 = white, 2 = cream, 3 = yellow.<sup>10</sup>
- Clarity of the suspension: Graded on a scale of 1–3, with 1 = transparent, 2 = semi-translucent, 3 = opaque.<sup>10</sup>
- pH of the suspension: Recorded in 1:10 diluted preparations (in methanol) using a pH meter (Accumet<sup>®</sup> Basic AB15, Fischer Scientific).
- Extent of settling in 24 h: Calculated as the ratio of settled particles' height (in mm) by the suspension liquid's height (in mm) and reported as %.<sup>10</sup>
- Ease of removal via syringe: Graded on a scale of 1–3, with 1 = smooth flow, no clogging, 2 = occasional interruption to flow with clogging, 3 = frequent interruption to flow with clogging.

Drug content was then analyzed with high-performance liquid chromatography (HPLC) within 7 days of receipt; the first day of analysis is noted as Day 0 in the rest of this work.

Suspensions were stored according to pharmacies' recommendation, and drug content analysis was repeated by the same investigator (LOL) at Day 14 and Day 28, an overall duration based on the average treatment course of famciclovir in clinical patients<sup>1</sup> and the beyond-use date provided by the pharmacies ( $\geq 30$  days).

### 2.2.1 | Compounded suspensions

After manually shaking each formulation for 45 s, three aliquots of 0.5 mL were transferred to separate 50-mL centrifuge tubes. The amount of famciclovir was standardized to 20  $\mu\text{g}/\text{mL}$  in each vial by serial dilutions as follows: (i) 24.5 mL methanol added to each tube, followed by vortex mixing (5 min) and sonication (10 min); (ii) a 1 mL aliquot of the first dilution was mixed with 24 mL of methanol, followed by vortex mixing (2 min) and filtration (0.45  $\mu\text{m}$  filter); (iii) 1 mL aliquot of the second dilution was mixed with 4 mL or 7 mL (for 250 and 400 mg/mL samples, respectively) of mobile phase—composed of 50 mM monobasic

phosphate buffer and methanol (50% v/v mixture) adjusted to pH 3.05 with orthophosphoric acid—followed by vortex mixing (2 min); (iv) 1 mL aliquot mixed with 1 mL of the internal standard pramipexole (Sigma-Aldrich)—prepared as 10  $\mu\text{g}/\text{mL}$  solution in the mobile phase—followed by vortex mixing (45 s).

### 2.2.2 | FDA-approved tablets

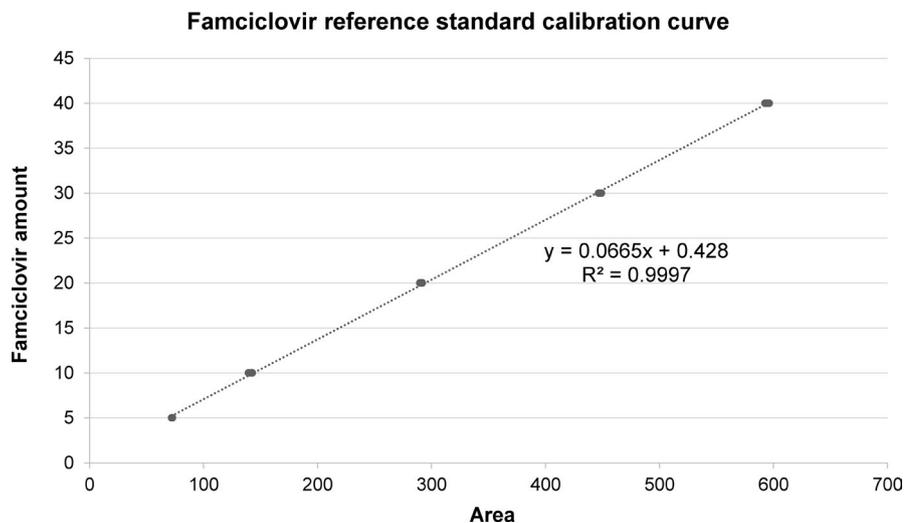
Three arbitrarily selected tablets (250 mg each) were analyzed with each run and served as a control. Each tablet, assessed to be whole and intact, was weighed on a milligram scale and crushed with a mortar and pestle, and the following steps were completed in triplicate: (i) 10 mg of famciclovir powder was mixed with 25 mL deionized water, followed by vortex mixing (3 min) and sonication (10 min); (ii) 1 mL aliquot mixed with 9 mL deionized water, followed by vortex mixing (3 min) and filtration (0.45  $\mu\text{m}$  filter); (iii) 1 mL aliquot mixed with 1 mL of the internal standard pramipexole (Sigma-Aldrich)—prepared as 10  $\mu\text{g}/\text{mL}$  solution in the mobile phase—followed by vortex mixing (45 s).

### 2.2.3 | Solutions for standard curve

Analytical reference standards for famciclovir (USP reference standard) and pramipexole (Sigma-Aldrich) were obtained, kept refrigerated at 4°C, and protected from light until use. Stock solutions of reference famciclovir (100  $\mu\text{g}/\text{mL}$ ) and pramipexole internal standard (100  $\mu\text{g}/\text{mL}$ ) were prepared daily using deionized water as the solvent, and the following solutions were obtained by dilution with mobile phase, vortex mixing (3 min) between successive dilutions and terminal filtration (0.45  $\mu\text{m}$  filter): pramipexole (5  $\mu\text{g}/\text{mL}$ ) with famciclovir 5  $\mu\text{g}/\text{mL}$ , 10  $\mu\text{g}/\text{mL}$ , 20  $\mu\text{g}/\text{mL}$ , 30  $\mu\text{g}/\text{mL}$ , or 40  $\mu\text{g}/\text{mL}$ .

### 2.2.4 | High-performance liquid chromatography

Famciclovir content was assessed by testing three aliquots for each sample, using UV detection at 309 nm and a previously validated reverse-phase HPLC method<sup>15</sup> with slight modifications due to differences in instrumentation capabilities to detect the drug, as well as UV detection at 263 nm to detect the internal standard. Mobile phase A consisted of 50 mM monobasic phosphate buffer and methanol (50% v/v mixture) adjusted to pH 3.05 with orthophosphoric acid (prepared fresh daily), while mobile phase B was methanol. HPLC analysis was performed at a flow rate of 0.7 ml/min with an isocratic mixture of 40% mobile phase A with 60%



**FIGURE 1** Calibration curve for famciclovir reference standard (5, 10, 20, 30, and 40 µg/mL). Famciclovir amount in µg/mL is on the y-axis, and the area under the peak is on the x-axis.  $R^2 = .9997$

mobile phase B. The analytical column was maintained at 40°C. Before analysis of the samples, the HPLC column (Symmetry C18, 250 x 4.0 mm i.d., 5 µm particle size, Waters Corporation) was conditioned for 30 min and equilibrated for 30 min, and then, blank samples and internal standard were injected in the column to monitor for carryover and shifts in retention time and changes in chromatographic quality. Study samples were then analyzed (20 µL; 1 injection/sample). The extraction efficacy of famciclovir from an oil base was determined by spiking three oil samples with known concentrations (20 mg/mL) of reference standard famciclovir. Mean ± standard deviation (range) extraction efficacy was found to be 86.1 ± 1.9 (84–87.4)%. To reduce dilution bias, the variability in drug concentrations quantified in the triplicate samples was determined after each run, and samples were re-run if the variability was found to be greater than 20%; this process was required in less than 10% of samples tested.

### 2.2.5 | Calculation of famciclovir concentration

The concentration of famciclovir was determined by calculating the ratio of the area under the peak of the internal standard (pramipexole) to the area under the peak of the sample. Linear regression with a weighting factor of 1/X was used for calibration curves, all of which had correlation coefficients ≥0.99, as demonstrated in Figure 1.

## 2.3 | Data analysis

The Shapiro-Wilk test was used to assess data for normality. Student's *t* tests were used to assess differences in drug content (accuracy) and coefficients of variation (precision) between generic famciclovir and each compounding pharmacy, as well as differences in the percent deviation from labeled

drug content between 250 and 400 mg/mL suspensions. A one-way ANOVA and post hoc Tukey test were used to compare drug content at three time points (D0, D14, and D28) for any given lot of each compounding pharmacy (consistency), as well as drug content quantified among three generic formulations of famciclovir. Statistical analysis was conducted with SigmaPlot version 14.0 (SYSTAT), and values of  $p < .05$  were considered statistically significant.

## 3 | RESULTS

### 3.1 | Compounded famciclovir suspensions

Though requested, certificates of analysis were not obtained from any compounding pharmacy as they were not made available to clients or could only be provided with the additional cost of sample analysis. Data were normally distributed ( $p \geq .085$ ) so results are presented as mean ± standard deviation.

#### 3.1.1 | Physical characteristics

Physical characteristics of famciclovir suspensions were highly variable among compounding pharmacies but were generally similar among lots from the same pharmacy (Table 1). Syringe removal of the 250 mg/mL suspensions from bottles was always subjectively easy (without clogging), while removal of 400 mg/mL suspensions from bottles was difficult with occasional to frequent clogging of syringes due to accumulation of sediment. Although not objectively evaluated, there was a noticeable contrast in the homogeneity and amount of particulate matter between the 250 and 400 mg/mL suspensions, with 400 mg/mL having a greater number of particles of larger size and a greater heterogeneity.

**TABLE 1** Physical characteristics studied of compounded famciclovir suspensions (250 and 400 mg/mL) obtained from nine compounding pharmacies on three different occasions (lots)

Concentration	Pharmacy	Lot	pH	Color	Clarity	Settling % in 24 hours	Ease of removal via syringe	Oil Base	Beyond- use date
250 mg/mL	A	1	6.14	1	3	60	1	Fixed	90 days
		2	6.03	1	3	61	1		
		3	6.52	1	3	64	1		
	B	1	5.74	1	3	56	1	Sesame	180 days
		2	6.41	1	3	51	1		
		3	6.33	1	3	50	1		
	C	1	6.05	3	3	90	1	Corn	100 days
		2	6.24	3	3	85	1		
		3	6.96	3	3	90	1		
	D	1	6.25	1	3	62	1	Almond	180 days
		2	6.12	1–2	3	67	1		
		3	6.61	1–2	3	64	1		
	E	1	6.66	1	3	80	1	Almond	150 days
		2	6.56	1	3	81	1		
		3	7.13	1	3	76	1		
	F	1	7.63	1	3	86	1	Almond	30 days
		2	6.94	1	3	90	1		
		3	7.21	1	3	89	1		
G	1	6.06	2	3	87	1	Vegetable	60 days	
	2	6.12	2	3	85	1			
	3	7.07	2	3	84	1			
400 mg/mL	G	1	5.94	1	3	70	2	Fixed	90 days
		2	6.08	1	3	73	2		
		3	7.11	1	3	70	2		
	H	1	6.34	1	3	86	2	Almond	180 days
		2	6.43	1–2	3	86	2		
		3	6.75	1	3	88	2		
	I	1	6.28	1	3	76	3	Almond	60 days
		2	6.27	1	3	70	3		
		3	6.74	1	3	77	3		

Letters designate the pharmacies (A–I) and numbers indicate the lot tested. Color was graded on a scale of 1–3 (1 = white, 2 = cream, 3 = yellow). Clarity was graded on a scale of 1–3 (1 = transparent, 2 = semi-transparent, 3 = opaque). Settling percentage in 24 h was calculated as the ratio of settled particles' height (in mm) by the suspension liquid's height (in mm). Ease of removal via syringe was graded on a scale of 1–3 (1 = smooth flow, no clogging, 2 = occasional interruption to flow with clogging, 3 = frequent interruption to flow with clogging).

### 3.1.2 | Accuracy

Drug content quantified in 250 and 400 mg/mL famciclovir suspensions are depicted in Figures 2 and 3, respectively. All compounded suspensions tested in the present study had a drug content that was significantly lower ( $p \leq .032$ ) compared to famciclovir tablets (control), a finding that was more pronounced for 400 mg/mL suspensions (Figure 3) than 250 mg/mL suspensions (Figure 2). For 400 mg/mL, acceptable concentrations per the US Pharmacopoeia standards

(360–440 mg/mL) were achieved by generic famciclovir tablets (mean 418 mg/mL) but none of the compounding pharmacies: 196 mg/mL (pharmacy G), 172 mg/mL (pharmacy H), and 182 mg/mL (pharmacy I). For 250 mg/mL, acceptable concentrations (225–275 mg/mL) were achieved by generic famciclovir tablets (mean 254 mg/mL), pharmacy A (229 mg/mL), and pharmacy C (225 mg/mL). Acceptable concentrations were not achieved by pharmacy B (182 mg/mL), pharmacy D (198 mg/mL), pharmacy E (215 mg/mL), pharmacy F (184 mg/mL), nor pharmacy G (197 mg/mL).

All compounded suspensions tested in the present study had an overall drug content that was significantly lower ( $p \leq .032$ ) compared to famciclovir tablets (control), a finding that was more pronounced for 400 mg/mL suspensions than 250 mg/mL (Figures 2 and 3). Importantly, all lots examined had an average drug content (D0, D14, and D28 combined) that was outside of the acceptance criteria established by the USP ( $\pm 10\%$ ), with a wide range of  $-70\%$  to  $+14\%$  from labeled drug content, except for lots 1 and 3 from pharmacy C, lot 1 from pharmacy F and lot 3 from pharmacy E. Mean percent from the labeled content was significantly greater ( $p < .001$ ) for 400 mg/mL suspensions ( $-52.9\%$ ) than 250 mg/mL suspensions ( $-18.0\%$ ). When assessing time points separately, only 15/63 (24%) samples of 250 mg/mL and 0/27 (0%) samples of 400 mg/mL suspensions fell within the USP standards (Table 2).

### 3.1.3 | Consistency

Consistency in compounded preparations, expressed as CV% in drug content at Days 0, 14, and 28, is summarized in Table 2 and Figure 4.

Here, the term 'consistency' was selected over 'stability' as drug content did not show a downward trend (ie, drug degradation) over time in most samples. In fact, results were highly variable from one pharmacy or one lot to another. Drug content significantly decreased from D0 to D14 and D28 in some cases, as demonstrated by lot 3 of pharmacy D ( $p \leq .021$ , Figure 4A) and lot 2 of pharmacy I ( $p = .005$ , Figure 4B). In contrast, drug content significantly increased from D0 to D14 and D28 in lot 2 of pharmacy C ( $p \leq .005$ , Figure 4C) or varied up and down in lot 2 of pharmacy D ( $p \leq .016$ , Figure 4D).

### 3.1.4 | Precision

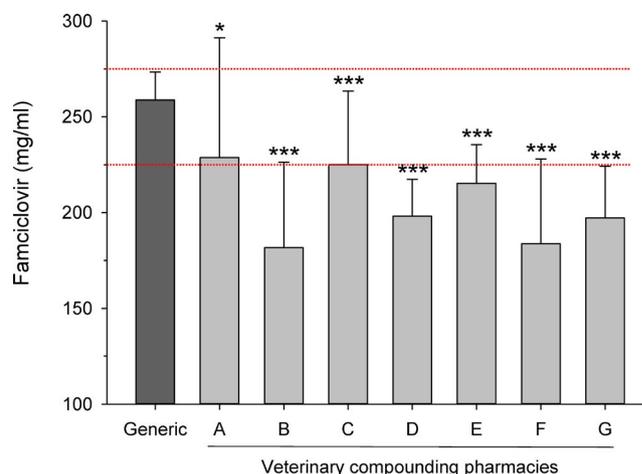
Precision in compounded preparations, expressed as coefficients of variation (CV%) in drug content at Day 0 for the three lots obtained for each suspension, is summarized in Table 3, Figure 5 (250 mg/mL), and Figure 6 (400 mg/mL).

Precision was significantly lower (ie, higher CV%) than the control in 4/7 pharmacies that provided 250 mg/mL suspensions ( $p \leq .026$ , Figure 5), and 1/3 pharmacies that provided 400 mg/mL suspensions ( $p = .044$ , Figure 6).

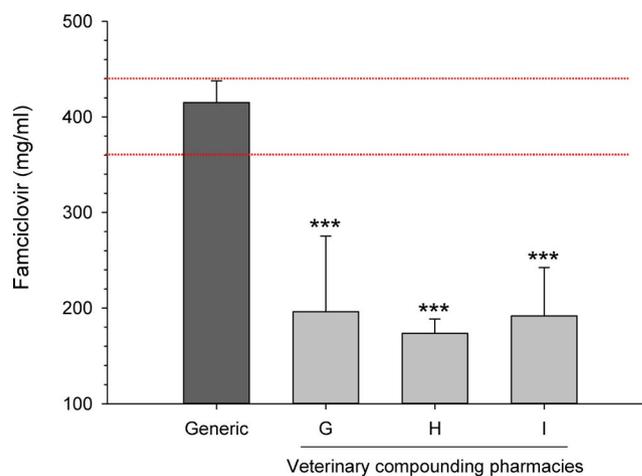
## 3.2 | FDA-approved famciclovir tablets

### 3.2.1 | Physical characteristics

FDA-approved tablets were consistent in color and appearance. No gross defects were noted. Weights were



**FIGURE 2** Mean + standard deviation of drug content detected in multiple aliquots of generic famciclovir tablets and formulations of 250 mg/mL famciclovir suspensions (Days 0, 14, and 28) obtained from seven different compounding pharmacies (A–G). Drug content that falls within 225–275 mg/mL (90%–110%) is deemed acceptable per the US Pharmacopoeia standards (dashed red lines). Asterisks depict statistical differences in drug content between generic famciclovir (positive control) and compounding pharmacies: \* $p < .05$ , \*\*\* $p < .001$



**FIGURE 3** Mean + standard deviation of drug content detected in multiple aliquots of generic famciclovir tablets and three formulations of 400 mg/mL suspensions (Days 0, 14, and 28) obtained from three different compounding pharmacies (G–I). Drug content that falls within 360–440 mg/mL (90%–110%) is deemed acceptable per the USP standards (dashed red lines). Asterisks (\*\*\*) depict statistical differences ( $p < .001$ ) in drug content between generic famciclovir (positive control) and compounding pharmacies

consistent within each manufacturer, with a maximum product weight variability (from mean weight on receipt) of 1.1%, 2.5%, and 4.9% for manufacturer A (control), B, and C, respectively.

**TABLE 2** Drug content (mean  $\pm$  standard variation, in mg/mL) and percentage difference (drug content vs. labeled content, in %) for each lot and each time point (Days 0, 14, 28) of compounded famciclovir suspensions obtained from nine compounding pharmacies

Concentration	Pharmacy	Lot	D0	% Difference	D14	% Difference	D28	% Difference	<i>p</i> value
250 mg/mL	A	1	216 $\pm$ 40	-13	203 $\pm$ 15	-18	184 $\pm$ 7	-26	.344
		2	301 $\pm$ 24	+20	291 $\pm$ 4	+16	273 $\pm$ 13	+9	.177
		3	169 $\pm$ 6*	-32	145 $\pm$ 3	-42 <sup>†</sup>	163 $\pm$ 2	-34	<.001
	B	1	176 $\pm$ 73	-29	135 $\pm$ 18	-46	98 $\pm$ 17	-60	.179
		2	212 $\pm$ 14	-15	200 $\pm$ 38	-20	175 $\pm$ 11	-30	.250
		3	157 $\pm$ 8	-37	150 $\pm$ 12	-40	153 $\pm$ 40	-38	.950
	C	1	236 $\pm$ 15	-5	266 $\pm$ 8	-6	261 $\pm$ 32	+4	.241
		2	182 $\pm$ 10* <sup>‡</sup>	-27	250 $\pm$ 26	0	286 $\pm$ 5	+14	<.001
		3	258 $\pm$ 32	+3	267 $\pm$ 7	+6	212 $\pm$ 32	-15	.084
	D	1	213 $\pm$ 4	-14	203 $\pm$ 29	-18	234 $\pm$ 36	-6	.409
		2	189 $\pm$ 13* <sup>‡</sup>	-24	223 $\pm$ 1 <sup>†</sup>	-10	165 $\pm$ 2	-34	<.001
		3	192 $\pm$ 28 <sup>‡</sup>	-23	165 $\pm$ 5 <sup>†</sup>	-34	114 $\pm$ 2	-54	.003
	E	1	192 $\pm$ 7* <sup>‡</sup>	-23	232 $\pm$ 16	-7	219 $\pm$ 5	-12	.010
		2	220 $\pm$ 12	-12	183 $\pm$ 30	-26	216 $\pm$ 10	-13	.100
		3	233 $\pm$ 13	-6	266 $\pm$ 7 <sup>†</sup>	+6	213 $\pm$ 19	-14	.009
	F	1	233 $\pm$ 15	-6	238 $\pm$ 6	-4	210 $\pm$ 53	-16	.548
		2	151 $\pm$ 5*	-39	117 $\pm$ 12 <sup>†</sup>	-53	157 $\pm$ 3	-37	.002
		3	167 $\pm$ 44*	-33	248 $\pm$ 16	<-1	196 $\pm$ 16	-21	.036
G	1	170 $\pm$ 4	-32	171 $\pm$ 14	-31	172 $\pm$ 5	-31	.966	
	2	223 $\pm$ 27*	-10	164 $\pm$ 12 <sup>†</sup>	-34	161 $\pm$ 17	-35	.013	
	3	198 $\pm$ 7*	-20	276 $\pm$ 8 <sup>†</sup>	-10	199 $\pm$ 16	-20	<.050	
400 mg/mL	G	1	168 $\pm$ 41	-58	100 $\pm$ 13	-75	117 $\pm$ 13	-70	.117
		2	287 $\pm$ 46	-28	228 $\pm$ 21 <sup>†</sup>	-43	184 $\pm$ 25	-54	.025
		3	132 $\pm$ 38	-67	110 $\pm$ 13	-72	103 $\pm$ 28	-74	.470
	H	1	174 $\pm$ 9	-56	130 $\pm$ 37	-67	177 $\pm$ 18	-55	.106
		2	173 $\pm$ 28	-56	204 $\pm$ 12	-49	164 $\pm$ 29	-59	.198
		3	173 $\pm$ 2	-56	155 $\pm$ 20 <sup>†</sup>	-61	128 $\pm$ 17	-68	.037
	I	1	143 $\pm$ 30	-64	155 $\pm$ 10	-61	221 $\pm$ 45	-44	.050
		2	245 $\pm$ 39	-38	180 $\pm$ 19 <sup>†</sup>	-55	136 $\pm$ 10	-66	.006
		3	185 $\pm$ 6 <sup>‡</sup>	-53	202 $\pm$ 15 <sup>†</sup>	-49	135 $\pm$ 9	-66	<.001

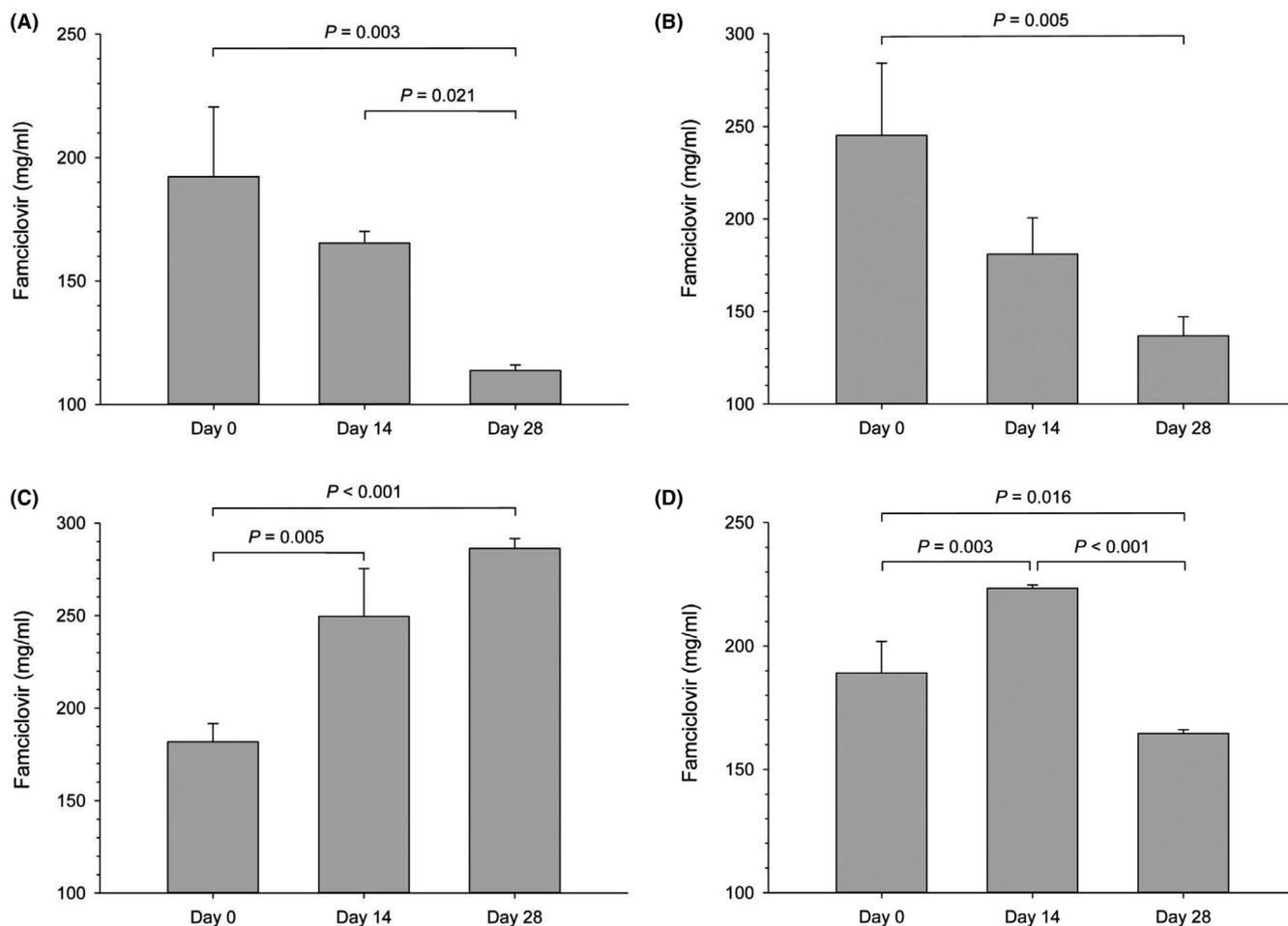
The accuracy of preparations (drug content within  $\pm$  10% of the labeled content) is depicted by dark gray shading. The consistency of preparations (drug quantified at three time points) is depicted by results of the one-way ANOVA (*p* value at last column) and post hoc Tukey test. Differences in drug content between D0-D14, D14-D28, and D0-D28 are depicted by an asterisk (\*), a cross (<sup>†</sup>), or a double cross (<sup>‡</sup>), respectively.

### 3.2.2 | Accuracy and precision

Drug content in all famciclovir tablets fell within the accepted range (90%–110%) set by USP standards. No significant differences (*p* = .551) were noted in famciclovir content among the three generic formulations tested in the present study (250 mg tablets), with a mean  $\pm$  standard deviation drug content of 258  $\pm$  6 mg (manufacturer A, control), 247  $\pm$  19 mg (manufacturer B) and 256  $\pm$  23 mg (manufacturer C). Mean precision for the three manufacturers was 2%, 10%, and 12%, respectively, a finding that was not statistically significant (*p* = .148).

## 4 | DISCUSSION

The majority of compounded famciclovir suspensions evaluated in the present study were deemed inaccurate, that is, containing a drug content outside of 90%–110% standards set by USP. This finding was noted for both 250 mg/mL (48/63 samples, 76%) and 400 mg/mL (27/27 samples, 100%) suspensions. In contrast, none of the generic famciclovir tablets were inaccurate (0/42 samples, 0%), highlighting the difference between FDA-approved medications—prepared under good manufacturing principles and undergoing stringent



**FIGURE 4** Mean + standard deviation of famciclovir drug content detected in multiple aliquots of different lots from selected compounding pharmacies (a = lot 3, pharmacy D; b = lot 2, pharmacy I; c = lot 2, pharmacy C; d = lot 2, pharmacy D). These examples were chosen to demonstrate the varying trends in drug content changes seen over the three time points (Day 0, Day 14, and Day 28). Statistical differences ( $p < .05$ ) among time points are depicted by  $p$  values in each graph

analyses to assess drug content, stability, and safety—and compounded formulations of drugs, that do not have to adhere to such regulations to assure quality.<sup>16</sup> In fact, poor accuracy in compounded formulations has been reported in veterinary medicine, as exemplified by studies on compounded doxycycline,<sup>12</sup> cyclosporine,<sup>10</sup> and famciclovir.<sup>17</sup> For the latter, a recently published study evaluated drug content in different formulations of famciclovir (chews, treats, pastes, suspensions, tablets) compounded from a single pharmacy; as a comparison, our study focused on a single type of formulation (oil suspension) but from multiple compounding pharmacies. Both studies showed significant variation and deviation in measured drug content from labeled drug content, a finding confirmed in various compounded formulations and multiple compounding pharmacies. Further, our study showed that most compounded famciclovir suspensions were imprecise, unlike generic tablets, meaning that samples originating from the same compounding pharmacy often had highly variable drug content (CV up to 65%). However, a portion of this variability may be attributable to

the method of analysis with HPLC, a process that was overall simpler for famciclovir tablets than for famciclovir suspensions. With that in mind, and accounting for the wide range of therapeutic dosing when targeting vascularized tissue (40–90 mg/kg), it is likely that selected compounded formulations provide a good alternative for managing herpetic cats that are otherwise difficult to medicate with famciclovir tablets. Nonetheless, veterinarians and owners should be aware that drug concentrations could differ from the labeled content and recognize that the bioequivalence of such formulations has not been tested to date.

Another goal of the study was to mimic the at-home scenario of owners treating cats with a compounded famciclovir suspension. Suspensions were stored according to the manufacturer's recommendations, shaken for 45 s before sampling, and tested for drug content for up to 28 days, a typical duration of treatment for feline herpesvirus-1 per the authors' experience. For most compounded suspensions, we noted that drug content was inconsistent among D0, D14, and D28 time points, with both downward and upward trends

**TABLE 3** The precision (coefficient of variation [CV]) for each individual lot (within lot) is illustrated

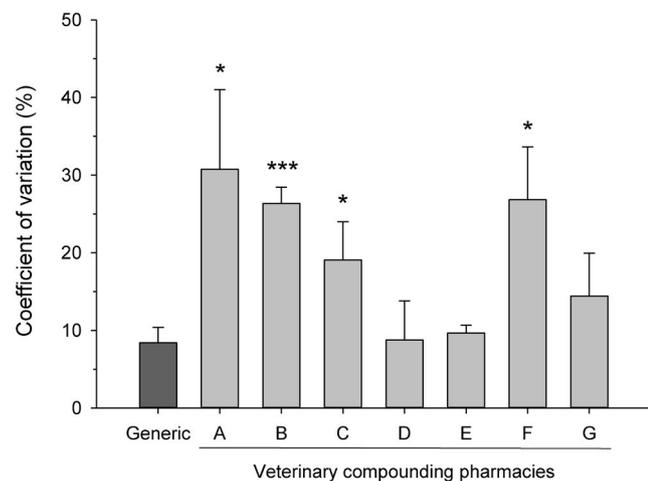
Concentration	Pharmacy	Lot	CV % within lot	<i>p</i> value
250 mg/mL	A	1	8	.021*
		2	5	
		3	8	
	B	1	28	<.001*
		2	10	
		3	2	
	C	1	6	.026*
		2	22	
		3	12	
	D	1	7	.912
		2	15	
		3	25	
	E	1	9	.389
		2	10	
		3	11	
F	1	7	.011*	
	2	15		
	3	20		
G	1	0.5	.152	
	2	19		
	3	20		
400 mg/mL	G	1	27	.044*
		2	22	
		3	13	
	H	1	16	.759
		2	12	
		3	15	
	I	1	24	.150
		2	29	
		3	20	

The *p* value shown is from comparing the precision of the lot with generic famciclovir (positive control) by a Student's *t* test.

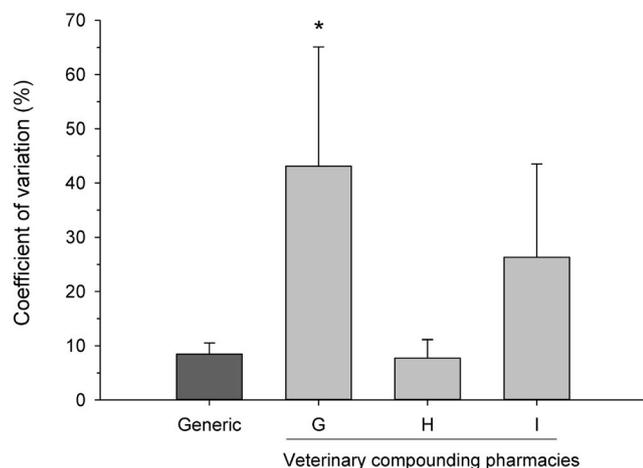
\*Indicates statistical significance.

detected. This variability may be related to the heterogeneous distribution of drug particles in the oil-based vehicle used for compounding, highlighting that cats might receive a variable dose of famciclovir from one administration to another despite vigorous shaking of the bottle for 45 s prior to use. We performed vigorous shaking of each formulation before sampling for HPLC, a process shown to reduce variability in dosing for ophthalmic suspensions of prednisolone acetate<sup>18</sup> but shaking may not be sufficient for oily formulations of famciclovir. However, variability due to the HPLC method could also contribute to these results, at least in part, and may be responsible for the variation of concentrations seen over time. Of note, drug recovery using the present HPLC method was considered adequate with a mean recovery of

86%. Although recovery was not 100%, final famciclovir concentrations were not adjusted as the recovery experiment only evaluated a single concentration and a single oil type, and the compounded formulations were directly compared to positive control samples (generic famciclovir) that were processed in a similar fashion. Nonetheless, imperfect drug recovery may have been sufficient to cause a formulation to fall outside the stringent acceptance criteria set. For 250 mg/mL, it is possible that a greater number of formulations would have met the USP acceptance criteria if the recovery rate of famciclovir from oil suspensions was closer to 100%, for example, Pharmacy A, Lot 1, Day 0 which differed by only 4% from the acceptance criteria. In contrast, none of the 400 mg/mL suspensions would have met the acceptance criteria (even



**FIGURE 5** Mean + standard deviation coefficient of variation in drug content of three lots of generic famciclovir tablets and seven formulations of 250 mg/mL famciclovir suspensions obtained from different compounding pharmacies (A–G). Asterisks depict statistical differences in coefficient of variation (%) between generic famciclovir (positive control) and compounding pharmacies: \* $p < .05$ , \*\*\* $p < .001$



**FIGURE 6** Mean + standard deviation coefficient of variation in drug content of three lots of generic famciclovir tablets and three formulations of 400 mg/mL famciclovir suspensions obtained from different compounding pharmacies (G–I). An asterisk (\*) depicts statistical differences ( $p < .05$ ) in coefficient of variation (%) between generic famciclovir (positive control) and compounding pharmacies

with 100% extraction rate) as the percent deviation from the target concentration was much greater with 400 mg/mL compared to 250 mg/mL suspensions (52.9% vs. 18%).

The reason why compounded suspensions of famciclovir were inaccurate is unknown. Potential explanations include technical errors during the compounding process (eg, mathematical error), ingredients used, storage conditions, methods of preparation, and variability or errors in the HPLC processing technique. Although not objectively evaluated, the authors

believe that powdered famciclovir is poorly soluble in the oil suspensions used by compounding pharmacies, as we often noted numerous large-sized particles in the preparations we received. This concept is supported by the low lipophilicity reported for famciclovir.<sup>19</sup> This would explain why the accuracy of 250 mg/mL suspensions was overall better than 400 mg/mL suspensions (more drug, similar volume). In fact, a 250 mg/mL suspension was the most accurate formulation evaluated in the present study (pharmacy C), with a drug content falling within 90%–110% in 6/9 samples. Interestingly, this was the only formulation that did not have particles visible to the naked eye, and it was the only formulation compounded in corn oil. Further research is needed to determine the best vehicle for compounded formulations of famciclovir. The USP Compounding Compendium guidelines do provide a formulation for liquid famciclovir—100 mg/mL in Ora Plus and Ora Sweet, which has been verified to meet the compendial standards.<sup>14</sup> We suspect this formulation is not followed when compounding famciclovir for cats, as this formula provides a sweet suspension, for which the flavor and low concentration are unlikely to be clinically useful in treating most cats.

Regardless of the underlying cause, variable accuracy, precision, and consistency of compounded famciclovir could have deleterious effects when the formulations are used in clinical patients. Subtherapeutic dosing of famciclovir could prolong disease duration, viral shedding, and animal suffering. In fact, oral administration of an ineffective medication (due to subtherapeutic concentrations) could actually exacerbate the replication of FHV-1 due to the stress induced by drug administration in cats, and thereby worsen the associated clinical signs.<sup>6</sup> Despite these shortcomings, some clinicians argue that herpetic disease improves in selected cats that receive compounded famciclovir (personal communications with authors). This anecdotal evidence could have two potential explanations. First, clinical improvement could occur in spite of therapeutic intervention as the clinical signs associated with FHV-1 are generally self-limiting. Second, a lower drug content may not achieve the desired 90 mg/kg but could still reach a dose that approaches 40 mg/kg. For instance, 1 ml containing 200 mg of a 250 mg/ml famciclovir suspension (ie, 80% of labeled drug content) would equate to 40 mg/kg for an average 5 kg cat. While 40 mg/kg results in penciclovir concentrations above the minimal inhibitory concentration of FHV-1 in plasma, thereby slowing replication of FHV-1 in vascularized tissues (conjunctiva, eyelids), this dose does not provide sufficient concentrations of penciclovir in tears (therefore ineffective for the avascular cornea), and the clinical improvement noted with 40 mg/kg is often slower and less pronounced compared to 90 mg/kg.<sup>1</sup> Importantly, the example described above (200 mg ~ 40 mg/kg) assumes that the bioavailability of compounded famciclovir is similar to FDA-approved formulations. While the bioequivalence of the formulations was not tested in the present study, other reports in veterinary

medicine have shown reduced bioequivalence of compounded medications,<sup>20,21</sup> as compounding a drug can alter the particle size, form inactive precipitates and modify the pH, thus affecting the drug content, stability, absorption, and bioavailability.<sup>16,20</sup> Of note, all formulations evaluated in this paper were obtained from pharmacy facilities classified as 503A at the time of data collection. 503A pharmacies compound medications following a prescription for a specific patient and thus are not permitted to compound larger batches for in office use.<sup>22</sup> 503A pharmacies must follow USP quality standards and state board of pharmacy regulations but are not required to perform analyses to assure quality. Since data collection was completed, two of the nine pharmacies have added a new, separate facility (with a different name) to their parent company as a 503B compounding pharmacy. 503B compounding pharmacies are outsourcing facilities that are permitted to manufacture large batches of drugs with or without prescriptions to be sold to healthcare facilities for in office use.<sup>22</sup> These pharmacies are held to a higher regulatory standard and must validate every step of the compounding process according to current Good Manufacturing Practice regulation enforced by the FDA, including testing multiple batches of a new compounded product for drug content and stability prior to market release. Therefore, it is likely that drug levels would be more accurate and precise in 503B vs. 503A compounding pharmacies, a speculation that could be assessed in future studies, though the bioequivalence of such formulations remains unknown and would require in vivo studies in cats.

The present work evaluated a relatively large number of compounding pharmacies ( $n = 9$ ) compared to other published veterinary studies ( $\leq 6$ ).<sup>10,11,12,20</sup> The selection encompassed compounding pharmacies that are most commonly used by general practitioners and veterinary ophthalmologists (authors' personal experience); however, there is a chance that a pharmacy that was not tested here would have consistently provided accurate and precise formulations of famciclovir. Regarding HPLC methodology, several steps were taken to reduce variability in drug quantification including the use of internal standard, running samples in triplicates, and repeating analysis if variation among the 3 aliquots was over 20%; however, the greater complexity of testing an oily formulation vs. crushed tablets likely explains a portion of the high variability observed for compounded suspensions in the present study.

## 5 | CONCLUSION

The majority of compounded famciclovir formulations tested in the present study were inaccurate, imprecise, and inconsistent. FDA-approved famciclovir tablets may be preferred over compounded famciclovir formulations for the management of feline herpesvirus-1. If compounded famciclovir is used in practice,

a concentration of 250 mg/mL is preferred over 400 mg/mL given the lower accuracy of the higher concentration.

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## CONFLICT OF INTERESTS

The authors declare no conflicts of interest.

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