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The accuracy and precision of insulin administration using human and veterinary pen-injectors and syringes for administration of insulin

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Abstract

Background: Many diabetic dogs and cats require small doses of insulin that must be administered accurately.

Objectives: To compare the accuracy and precision of insulin syringes and pen-injectors.

Animals: None.

Methods: To determine how accurately and precisely insulin doses are delivered, 0.5, 1, 2, 4, 8, and 16 U doses were dispensed 25 times from 5 SoloSTARs, 5 FlexPens, 5 KwikPens, 5 JuniorSTARs, 5 VetPens 0.5-8 U, 5 VetPens 1-16 U, and by 5 veterinarians using 30 U/0.3 mL and 40 U/mL insulin syringes. Each dose was weighed, using a precision balance, and the intended and delivered doses were compared.

Results: All pen-injectors delivered less insulin than the intended dose, underdosage being inversely proportional to insulin dose. The differences between the intended and the delivered dose were not significant using JuniorSTAR and VetPen 0.5-8 U at insulin doses of 0.5, 1, 2, and 4 U, using the 30 U/0.3 mL insulin syringe at the 4 U dose and using the 40 U/mL insulin syringe at the 4, 8, and 16 U doses. With all the devices, precision increased with increasing doses of insulin. The coefficient of variation was <8% for all 6 pen-injectors. Conversely, using 30 U/0.3 mL and 40 U/mL syringes at an insulin dosage of 0.5 U the coefficients of variation were 12.08% and 9.39%, respectively.

Conclusions and Clinical Importance: JuniorSTAR and VetPen 0.5-8 U were more accurate than the other devices when delivering ≤2 U doses, while the delivery of 8 and 16 U doses was more accurate using 40 U/mL syringes.

KEYWORDS
canine, cartridge, device, diabetes mellitus, feline, insulin, pen-injector, syringe

Abbreviation: CV, coefficient of variation.

1 | INTRODUCTION

Insulin therapy is the cornerstone of management for diabetic dogs and cats. The insulin products currently approved for veterinary use are Caninsulin/Vetsulin, and ProZinc. Both veterinary insulin types are less concentrated (40 U/mL) than human insulin products and, to avoid dosing errors, it is recommended to administer 40 U/mL insulin with 40 U syringes. Otherwise, almost all human insulin preparations have a concentration of 100 U/mL and must be administered using 100 U/mL syringes.

The availability of insulin preparations with different concentrations and which need to be administered with appropriately graduated insulin syringes could cause dosing errors that could be dangerous or even fatal for patients. In human medicine, where the variety of concentrations of insulin preparations is greater (insulin does or will come in concentrations of U100, U200, U300 and U500 and U400 is in clinical trials), such errors have been reported.[1,2] In addition, drawing insulin from its vial using the syringe can result in air bubbles causing dosing errors, sometimes sufficient to meet the definition of inaccuracy.[3] Finally, another important source of dosing error when using syringes is the administration technique.[4] It is the authors' opinion that even among veterinarians, nurses, pharmacists and owners of diabetic pets there is some confusion regarding the types of insulin syringes available and their correct use.

Much of the confusion and difficulty of measuring insulin using syringes could be eliminated by the use of insulin pen-injectors which have become readily available in human and veterinary medicine over the past few years. These devices are designed to be used by people with no formal medical training with the aim of measuring and delivering insulin doses in a simpler, less painful, and more accurate and precise way. The use of pen-injectors could provide both clinical benefits for diabetic animals and practical benefit for their owners. The preference for pen-injectors over syringes is uniform across all human studies, although the assessment is based on nonvalidated questionnaires,[5-11] and there is a consensus regarding the increased accuracy of pen-injectors at lower doses of insulin when compared with syringe.[12-15]

Diabetic dogs and cats occasionally require low doses of insulin, sometimes less than 5 U and rarely less than 1 U. At these doses, the tolerance for error is very small. Information regarding insulin overdoses in diabetic animals is relatively scarce,[16,17] and the difficulty of proving whether the overdose was due to insulin mishandling and administration errors or due to concomitant illnesses and transient remission must be considered. However, it is plausible that if low doses of insulin are not delivered accurately and precisely, episodes of hypoglycemia might occur, and blood glucose concentrations might fluctuate considerably. Hypoglycemic episodes are especially dangerous in pets which are unable to recognize or verbalize that they are experiencing hypoglycemia which could therefore go unnoticed until more serious signs arise.

To the best of the authors' knowledge, there are no veterinary studies concerning the accuracy and precision of these 2 methods of insulin delivery, except for an abstract in which the performance of 2 syringes (20 U/0.5 mL and 40 U/mL) were compared with those of VetPen 0.5-8 U and VetPen 1-16 U.[18] At very low doses (1 U), the authors found that syringes tend to overdeliver compared to pen-injectors; the latter were more precise and accurate for insulin doses ≤8 U, while both devices were comparable at 16 U doses.

The aim of this study was to compare the accuracy and precision of 6 pen-injectors and 2 insulin syringes. The authors hypothesized that low insulin doses would be measured less accurately than high insulin doses and that a pen-injector would be more accurate in delivering insulin than an insulin syringe.

2 | MATERIALS AND METHODS

The accuracy of the dose delivered was assessed using the precision gravimetric method. A preliminary evaluation was carried out in order to determine the correction coefficient which allowed converting the weight of insulin aliquots (expressed in mg) to the corresponding units. For this purpose, 50 μL of reverse osmosis water, 50 μL of insulin glargine (corresponding to 5 U) and 50 μL of porcine insulin zinc (corresponding to 2 U) were dispensed 10 times each by a single investigator (AB) using a Pipetman P100 laboratory pipette (Gilson, Mi lano, Italy) and were weighed using a Mettler HL 52 analytical balance (Mettler-Toledo S.p.A., Milano, Italy), with a resolution and a reproducibility of 0.00001 g. Each aliquot was placed into a polystyrene weighing container, and the measured value was immediately recorded. The balance was calibrated before each series of measurements using precision mass standards and was zeroed between weighings. Aliquots of water had a mean (±SD) weight of 50.00 (±0.15) mg, insulin glargine aliquots weighed 50.72 (±0.50) mg and porcine insulin zinc aliquots weighed 50.47 (±0.54) mg. The coefficient of variation (CV) for the method was <2% for both water and the 2 insulin preparations. The correction coefficient for converting the weight into units for insulin glargine (1.0143) was calculated by dividing the mean weight of 50 μL of insulin glargine by the mean weight of 50 μL of water. The correction coefficient for porcine insulin zinc (1.0093) was calculated as above and by additionally dividing the result by 2.5, due to the different concentrations of the 2 types of insulin (porcine insulin zinc is 2.5 times less concentrated than glargine). For all subsequent evaluations, the values measured with the balance were multiplied by the correction coefficient of insulin glargine for all the human insulins and by the correction coefficient of porcine insulin zinc for this type of insulin, in order to have all the results expressed in units.

To determine how accurately and precisely insulin doses were delivered, 0.5, 1, 2, 4, 8, and 16 U doses were dispensed 5 times by each pen-injector by a single investigator (AB) from 5 SoloSTARs (Sanofi S.p.A., Milano, IT) dispensing insulin glargine (Lantus, Sanofi S. p.A., Milano, IT), 5 FlexPens (Novo Nordisk S.p.A., Roma, IT) dispensing insulin detemir (Levemir, Novo Nordisk S.p.A., Roma, IT), 5 KwikPens (Ely Lilly and Co, Sesto Fiorentino, IT) dispensing insulin lispro (Humalog, Ely Lilly and Co, Sesto Fiorentino, IT), 5 JuniorSTARs (Sanofi S.p.A., Milano, IT) dispensing insulin glargine, 5 VetPens 0.5-8 U and 5 VetPens 1-16 U (MSD Italia S.r.l., Roma, IT) dispensing

TABLE 1 Mean (±SD) and range of delivered insulin doses for each device at each of the 6 doses tested (0.5, 1, 2, 4, 8, and 16 U)

Intended dose		SoloSTAR	FlexPen	KwikPen	JuniorSTAR	VetPen 0.5-8 U	VetPen 1-16 U	30 U/0.3 mL syringe	40 U/mL syringe
0.5 U	Mean (SD)	/	/	/	**0.48 (±0.04)**	**0.49 (±0.02)**	/	0.63 (±0.08)	0.65 (±0.06)
	Range	/	/	/	**0.42-0.57**	**0.45-0.51**	/	0.50-0.85	0.53-0.74
	P-value	/	/	/	**.2723**	**.8565**	/	<.0001	<.0001
1 U	Mean (SD)	0.96 (±0.06)	0.95 (±0.04)	0.93 (±0.07)	**0.98 (±0.05)**	**0.99 (±0.04)**	0.95 (±0.05)	1.10 (±0.06)	1.06 (±0.06)
	Range	0.82-1.07	0.89-1.04	0.81-1.06	**0.86-1.06**	**0.92-1.06**	0.82-1.02	0.98-1.24	0.94-1.15
	P-value	.0224	.0057	<.0001	**.4177**	**.9752**	.0030	<.0001	.0011
2 U	Mean (SD)	1.92 (±0.07)	1.94 (±0.09)	1.90 (±0.09)	**1.97 (±0.05)**	**1.97 (±0.06)**	1.93 (±0.06)	2.07 (±0.07)	2.06 (±0.07)
	Range	1.81-2.03	1.81-2.09	1.71-2.07	**1.89-2.07**	**1.87-2.09**	1.79-2.03	1.95-2.26	1.89-2.17
	P-value	.0007	.0122	<.0001	**.5959**	**.3501**	.0044	.0062	.0244
4 U	Mean (SD)	3.87 (±0.09)	3.89 (±0.11)	3.87 (±0.12)	**3.94 (±0.10)**	**3.94 (±0.04)**	3.88 (±0.07)	**3.94 (±0.08)**	**4.04 (±0.07)**
	Range	3.68-4.02	3.68-4.08	3.68-4.10	**3.75-4.22**	**3.87-4.01**	3.75-4.06	**3.81-4.20**	**3.88-4.14**
	P-value	<.0001	<.0001	<.0001	**.085**	**.056**	<.0001	**.0996**	**.36**
8 U	Mean (SD)	7.74 (±0.08)	7.85 (±0.09)	7.71 (±0.13)	7.90 (±0.10)	7.89 (±0.05)	7.86 (±0.12)	7.73 (±0.08)	**8.04 (±0.08)**
	Range	7.56-7.89	7.64-8.06	7.45-7.95	7.69-8.13	7.79-7.99	7.51-8.08	7.60-7.97	**7.89-8.15**
	P-value	<.0001	<.0001	<.0001	.0007	.0003	<.0001	<.0001	**.583**
16 U	Mean (SD)	15.50 (±0.17)	15.71 (±0.15)	15.49 (±0.19)	15.85 (±0.14)	/	15.87 (±0.12)	15.29 (±0.09)	**15.98 (±0.07)**
	Range	15.24-15.81	15.15-15.94	15.13-15.83	15.65-16.23	/	15.55-16.11	15.07-15.44	**15.78-6.08**
	P-value	<.0001	<.0001	<.0001	.0004	/	.0016	<.0001	**.9973**

Notes: P-values reflect the significance between delivered insulin doses for each device compared to intended dose. Bold indicates the absence of statistically significant differences from the intended dose.

porcine insulin zinc (Caninsulin, MSD Italia S.r.l., Roma, IT), and by 5 veterinarians (each dose was delivered by each veterinarian 5 times) using 30 U/0.3 mL insulin syringes (Pic Insumed 30G insulin syringe 30 U/0.3 mL, Artsana SpA, Grandate, IT) for insulin glargine and 40 U/mL insulin syringes (Caninsulin syringe 40 U/mL, MSD Italia S.r.l., Roma, IT) for porcine insulin zinc.

All the pen-injectors had 1-unit increment markings, except for JuniorSTAR and VetPen 0.5-8 U which had 0.5-unit increments. All the cartridges (in case of reusable pen-injectors) and the prefilled SoloSTAR, FlexPen and KwikPen were brought to room temperature for 2 hours before use. Prior to dosing, all the insulins were mixed by rolling and inverting the pen-injectors or shaking them, according to the manufacturer's recommendations. This is crucial for insulin suspensions, such as porcine insulin zinc, but is also advisable for solutions, such as glargine. When using a prefilled pen-injector or a new cartridge for the first time, an "air shot" with the pen tip facing upward was performed, and 5 U of insulin were discarded. This procedure had the purpose of eliminating the residual air inside the cartridge before measurements started. From each pen-injector, 0.5 (only for JuniorSTAR and VetPen 0.5-8 U), 1, 2, 4, 8, and 16 U (for all pens except VetPen 0.5-8 U) doses were delivered in random order 5 times from 5 pens and weighed as previously described by a single investigator (AB), who waited 5-10 seconds (according to the manufacturer's instructions) after depressing the plunger to ensure that the entire dialed dose was expelled.

Five veterinarians, who regularly administered insulin, used 30 U/0.3 mL insulin syringes for insulin glargine and 40 U/mL insulin syringes for porcine insulin zinc to draw up 0.5, 1, 2, 4, 8, and 16 U of both insulins in random order 5 times for each dose. The manufacturer marked the 30 U/0.3 mL insulin syringes in 0.5-unit increments whereas the 40 U/mL insulin syringes were marked in 1-unit increments. Individual doses were expelled and weighed as previously described by a single investigator (AB), and the veterinarians were unaware of the results.

Dose accuracy was defined as previously described[12-14] as the absolute percent difference from the intended dose and was expressed as percent error:

$$\text{Accuracy}\,(\%\text{error}) = [(\text{intended dose} - \text{delivered dose})/(\text{intended dose})] \times 100.$$

Dose precision was defined as previously described[12-14] as the absolute percent difference from the group sample mean and was expressed as the CV:

$$\text{Precision}\,(\text{CV}) = [(\text{SD of mean})/(\text{mean of delivered dose})] \times 100.$$

To assess whether the insulin cartridge was a possible source of error, the 2 pen-injectors that had the lowest CV during the previous experiment were selected for additional investigation. For the purposes of this analysis, 5 cartridges for each pen were used, and each cartridge was divided into first, second, third, and fourth quarters. After

MEAN PERCENTAGE ERROR (ACCURACY)

INTENDED DOSE	SoloSTAR®	FlexPen®	KwikPen™	JuniorSTAR® (glargine)	VetPen™ 0.5-8 U	VetPen™ 1-16 U	Syringe 30UI/0.3mL	Syringe 40UI/mL
0.5 U				-4.64%	-2.18%		+26.51%	+30.77%
1 U	-4.26%	-4.90%	-6.86%	-2.45%	-1.14%	-5.21%	+10.32%	+5.63%
2 U	-3.91%	-3.05%	-4.85%	-1.42%	-1.70%	-3.34%	+3.26%	+2.84%
4 U	-3.19%	-2.87%	-3.36%	-1.47%	-1.57%	-2.94%	-1.47%	+1.09%
8 U	-3.22%	-1.90%	-3.57%	-1.27%	-1.36%	-1.78%	-3.44%	+0.46%
16 U	-3.13%	-1.78%	-3.19%	-0.93%		-0.84%	-4.46%	-0.11%

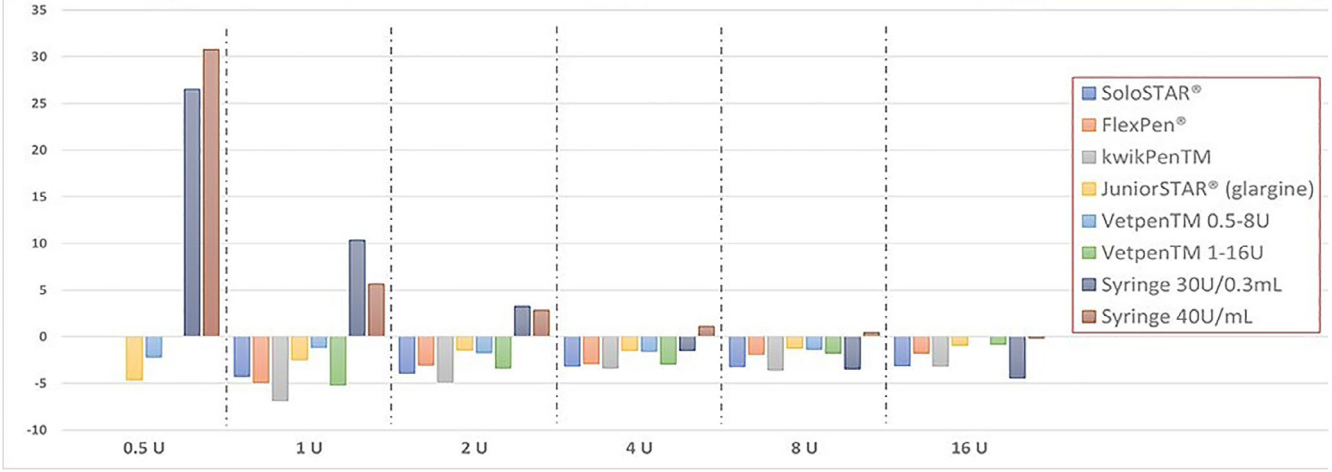

FIGURE 1 Mean percent error (accuracy) of each device at each of the doses tested (0.5, 1, 2, 4, 8, and 16 U). For each pen-injector, the mean of 25 random measurements of each dose tested of insulin was calculated. For each syringe, the mean of 25 random measurements (5 measurements for each of the 5 veterinarians) of each dose tested was calculated

TABLE 2 *P*-values for multiple comparison reflecting the differences between delivered insulin doses for each device compared to all other devices

	Intended dose	SoloSTAR	FlexPen	KwikPen	JuniorSTAR (glargine)	VetPen 0.5-8 U	VetPen 1-16 U	Syringe 30 UI/0.3mL	Syringe 40 UI/mL
SoloSTAR	0.5 U								
	1 U		.99	.75	.93	.42	.99	**<.0001**	**<.0001**
	2 U		.99	.97	.23	.42	.99	**<.0001**	**<.0001**
	4 U		.99	>.99	.12	.18	.99	.11	**<.0001**
	8 U		**.0033**	.96	**<.0001**	**<.0001**	**.0008**	.99	**<.0001**
	16 U		**<.0001**	>.99	**<.0001**		**<.0001**	**<.0001**	**<.0001**
FlexPen	0.5 U								
	1 U	.99		.93	.73	.2	>.99	**<.0001**	**<.0001**
	2 U	.99		.59	.72	.9	>.99	**<.0001**	**<.0001**
	4 U	.99		.99	.38	.48	>.99	.34	**<.0001**
	8 U	**.0033**		**<.0001**	.59	.73	>.99	**.0003**	**<.0001**
	16 U	**<.0001**		**<.0001**	.0099		**.0031**	**<.0001**	**<.0001**
KwikPen	0.5 U								
	1 U	.75	.93		.1	**.0068**	.97	**<.0001**	**<.0001**
	2 U	.97	.59		**.0145**	**.0406**	.78	**<.0001**	**<.0001**
	4 U	>.99	.99		.07	.1	.99	.06	**<.0001**
	8 U	.96	**<.0001**		**<.0001**	**<.0001**	**<.0001**	.99	**<.0001**
	16 U	>.99	**<.0001**		**<.0001**		**<.0001**	**<.0001**	**<.0001**
JuniorSTAR (glargine)	0.5 U					.85		**<.0001**	**<.0001**
	1 U	.93	.73	.1		.99	.61	**<.0001**	**<.0001**
	2 U	.23	.72	**.0145**		>.99	.53	**.0003**	**.0016**
	4 U	.12	.38	.07		>.99	.3	>.99	**.0024**
	8 U	**<.0001**	.59	**<.0001**		>.99	.82	**<.0001**	**<.0001**
	16 U	**<.0001**	**.0099**	**<.0001**			.99	**<.0001**	**.0134**
VetPen 0.5-8 U	0.5 U				.85			**<.0001**	**<.0001**
	1 U	.42	.2	**.0068**	.99		.13	**<.0001**	**.0006**
	2 U	.42	.9	**.0406**	>.99		.75	**<.0001**	**.0004**
	4 U	.18	.48	.1	>.99		.4	>.99	**.0013**
	8 U	**<.0001**	.73	**<.0001**	>.99		.92	**<.0001**	**<.0001**
	16 U								
VetPen 1-16 U	0.5 U								
	1 U	.99	>.99	.97	.61	.13		**<.0001**	**<.0001**
	2 U	.99	>.99	.78	.53	.75		**<.0001**	**<.0001**
	4 U	.99	>.99	.99	.3	.4		.27	**<.0001**
	8 U	**.0008**	>.99	**<.0001**	.82	.92		**<.0001**	**<.0001**
	16 U	**<.0001**	**.0031**	**<.0001**	.99			**<.0001**	**.0377**
Syringe 30 UI/0.3mL	0.5 U				**<.0001**	**<.0001**			.41
	1 U	**<.0001**	**<.0001**	**<.0001**	**<.0001**	**<.0001**	**<.0001**		**.0479**
	2 U	**<.0001**	**<.0001**	**<.0001**	**.0003**	**<.0001**	**<.0001**		.99
	4 U	.11	.34	.06	>.99	>.99	.27		**.0031**
	8 U	.99	**.0003**	.99	**<.0001**	**<.0001**	**<.0001**		**<.0001**
	16 U	**<.0001**	**<.0001**	**<.0001**	**<.0001**		**<.0001**		**<.0001**
Syringe 40 UI/mL	0.5 U				**<.0001**	**<.0001**		.41	
	1 U	**<.0001**	**<.0001**	**<.0001**	**<.0001**	**.0006**	**<.0001**	**.0479**	
	2 U	**<.0001**	**<.0001**	**<.0001**	**.0016**	**.0004**	**<.0001**	.99	

(Continues)

TABLE 2 (Continued)

	Intended dose	SoloSTAR	FlexPen	KwikPen	JuniorSTAR (glargine)	VetPen 0.5-8 U	VetPen 1-16 U	Syringe 30 UI/0.3mL	Syringe 40 UI/mL
	4 U	**<.0001**	**<.0001**	**<.0001**	**.0024**	**.0013**	**<.0001**	**.0031**	
	8 U	**<.0001**	**<.0001**	**<.0001**	**<.0001**	**<.0001**	**<.0001**	**<.0001**	
	16 U	**<.0001**	**<.0001**	**<.0001**	**.0134**		**.0377**	**<.0001**	

Notes: Bold highlights significant *P*-values.

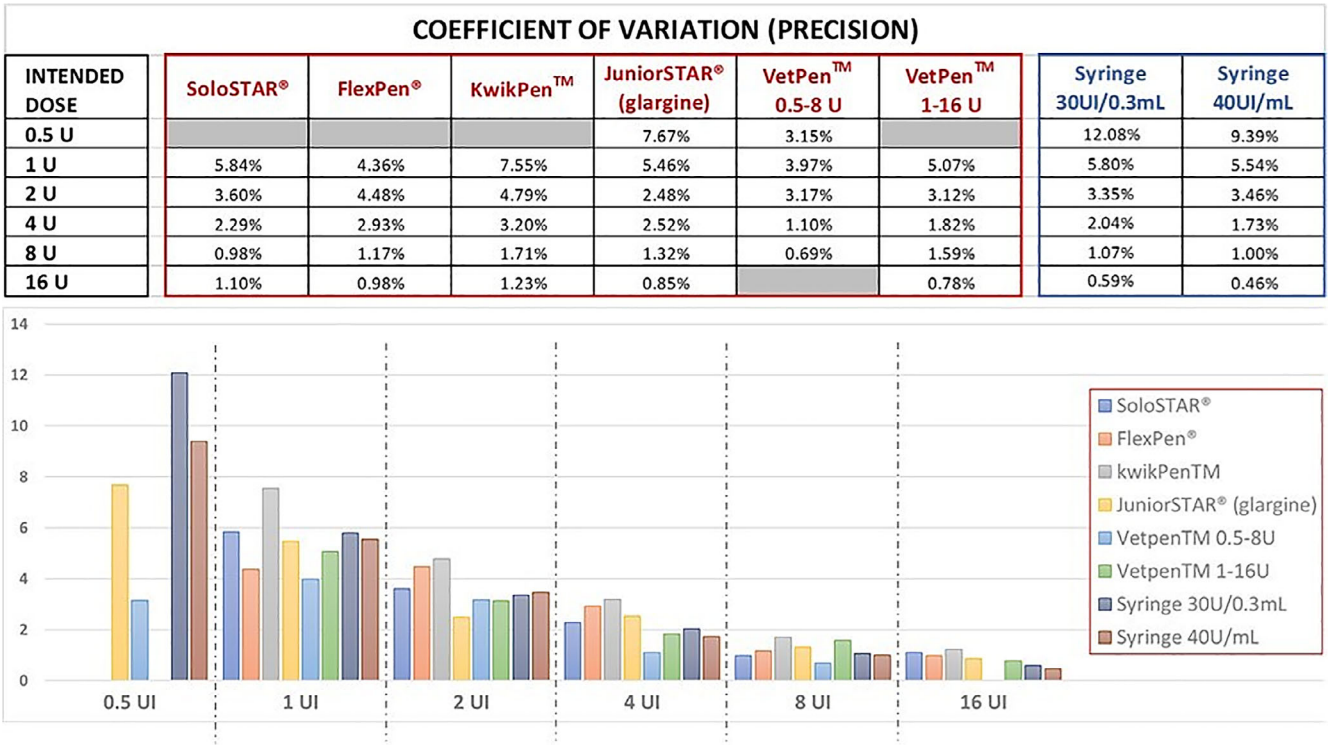

FIGURE 2 Coefficients of variation (precision) of each device at each of the doses tested (0.5, 1, 2, 4, 8, and 16 U). For each pen-injector, the mean of 25 random measurements of each dose tested of insulin was calculated. For each syringe, the mean of 25 random measurements (5 measurements for each of the 5 veterinarians) of each dose tested was calculated

appropriate air shots, 5 U of insulin were dispensed and weighed repeatedly 5 times from each of the quarters; the subsequent quarter was not begun until the residual insulin of the previous quarter had been dissipated.

2.1 | Statistical analysis

Data were normally distributed and results were expressed as means (±SD). To investigate whether there was a difference between the devices, a 2-way analysis of variance (ANOVA) including all 8 devices and the intended dose itself was used. Dunnett's multiple comparison method was used to determine which devices differed significantly from the intended dose. A Kruskal-Wallis test, including Dunn's multiple comparison, was used to investigate interoperator variability on the delivery of insulin doses using syringes. Finally, a separate ANOVA was used to evaluate the role of cartridges as a source of error. A *P*-value <.05 was considered significant.

3 | RESULTS

Table 1 shows the intended dose and the mean (±SD) and range of the delivered doses of insulin for each device at each of the 6 tested doses (0.5, 1, 2, 4, 8, and 16 U).

3.1 | Accuracy

At all doses tested, all the pen-injectors delivered less insulin than the intended dose, underdosage being inversely proportional to dose (mean percentage error from −6.86% to −0.84%; Figure 1).

TABLE 3 *P*-values for multiple comparison reflecting interoperator variability between delivered insulin doses using 30 U/0.3 mL syringes (with glargine insulin) and 40 U/mL syringes (with porcine insulin zinc) at each dose tested

	30 U/0.3 mL syringe (glargine insulin)						40 U/mL syringe (porcine insulin zinc)				
	Intended dose	Operator-1	Operator-2	Operator-3	Operator-4		Intended dose	Operator-1	Operator-2	Operator-3	Operator-4
Operator-2	0.5 U	>.99				Operator-2	0.5 U	>.99			
	1 U	>.99					1 U	.23			
	2 U	>.99					2 U	.0311			
	4 U	>.99					4 U	>.99			
	8 U	>.99					8 U	**.0395**			
	16 U	>.99					16 U	.58			
Operator-3	0.5 U	>.99	>.99			Operator-3	0.5 U	>.99	>.99		
	1 U	>.99	>.99				1 U	>.99	>.99		
	2 U	>.99	>.99				2 U	>.99	.88		
	4 U	>.99	>.99				4 U	>.99	>.99		
	8 U	>.99	>.99				8 U	>.99	>.99		
	16 U	>.99	>.99				16 U	>.99	>.99		
Operator-4	0.5 U	.93	>.99	>.99		Operator-4	0.5 U	.35	**.0393**	**.0067**	
	1 U	>.99	>.99	>.99			1 U	>.99	**.0081**	.49	
	2 U	>.99	>.99	>.99			2 U	>.99	**.0140**	>.99	
	4 U	.97	>.99	>.99			4 U	**.0235**	**.0023**	.22	
	8 U	>.99	>.99	>.99			8 U	>.99	**.0002**	.06	
	16 U	.07	.74	.35			16 U	>.99	**.0072**	.22	
Operator-5	0.5 U	>.99	>.99	.33	.18	Operator-5	0.5 U	.93	.14	**.0298**	>.99
	1 U	>.99	>.99	.74	>.99		1 U	.54	>.99	>.99	**.0266**
	2 U	>.99	>.99	>.99	>.99		2 U	**.0333**	>.99	.92	**.0151**
	4 U	>.99	.06	.43	**.0142**		4 U	>.99	.55	>.99	.77
	8 U	>.99	>.99	>.99	.92		8 U	>.99	.74	>.99	.15
	16 U	>.99	>.99	>.99	.19		16 U	>.99	>.99	>.99	.11

Notes: Bold highlights significant *P*-values.

TABLE 4 *P*-values reflecting the absence of statistically significant differences between the 5 U doses of insulin delivered from each quarter (5 measurements from each quarter) of 5 cartridges by the 2 pens with the lowest coefficient of variation (JuniorSTAR and VetPen 0.5-8 U)

	JuniorSTAR		
	2nd quarter	3rd quarter	4th quarter
1st quarter	.83	.49	.19
2nd quarter	/	.94	.64
3rd quarter	.94	/	.93
	VetPen 0.5-8 U		
	2nd quarter	3rd quarter	4th quarter
1st quarter	.91	.99	.8
2nd quarter	/	.98	>.99
3rd quarter	.98	/	.92

The differences between the intended and the delivered doses were not significant only using JuniorSTAR and VetPen 0.5-8 U at an insulin dosage of 0.5 (P = .2723 and P = .8565, respectively), 1 (P = .4177 and P = .9752, respectively), 2 (P = .5959 and P = .3501, respectively), and 4 U (P = .085 and P = .056, respectively). Using 30 U/0.3 mL insulin syringes, the delivered dose was significantly higher than the intended dose when attempting to deliver 0.5 (+26.51%; P < .0001), 1 (+10.32%; P < .0001) and 2 U (+3.26%; P = .0062), and significantly lower than the intended dose at 8 (−3.44%; P < .0001) and 16 U (−4.46%; P < .0001). Using 40 U/mL syringes, the delivered dose was significantly higher than the intended dose when attempting to deliver 0.5 (+30.77%; P < .0001), 1 (+5.63%; P = .0011), and 2 U (+2.84%; P = .0244). All the results for Dunnett's multiple comparison are summarized in Table 2.

3.2 | Precision

With all 6 pen-injectors and with both 30 U/0.3 mL and 40 U/mL insulin syringes, the precision increased with increasing doses of insulin (Figure 2). The CV was <8% for all 6 pen-injectors (from 7.67% to 0.69%). Conversely, using 30 U/0.3 mL and 40 U/mL syringes at an insulin dosage of 0.5 U the CVs were 12.08% and 9.39%, respectively; precision improved at insulin dosages ≥1 U (CV from 5.80% to 0.46%).

3.3 | Interoperator variability

Using 30 U/0.3 mL insulin syringe, the dose delivered by 1 operator was significantly different from that delivered by another operator in 1/60 comparisons (operator-4 vs operator-5 at the dose of 4 U; P = .0142; Table 3). Using the 40 U/mL insulin syringe the dose delivered by 1 operator was significantly different from that delivered by another operator in 14/60 comparisons (23%), of which 11 (78.6%) were at doses ≤4 U. In particular, between operator-2 and operator-4 the delivered dose was significantly different at each of the tested doses. All the results for multiple comparison are summarized in Table 3.

3.4 | Influence of cartridges

Of the 30 pen-injectors investigated, the 2 pens with the lowest CVs during the previous experiment were JuniorSTAR and VetPen 0.5-8 U. There were no statistically significant differences in the 5 U insulin doses delivered from the 4 quarters of the cartridges for either pen (P = .22 for JuniorSTAR; P = .8 for VetPen 0.5-8 U; Table 4).

4 | DISCUSSION

This study investigated the accuracy and precision of the human and veterinary pen-injectors and syringes commonly used for pets. The results showed that pen-injectors underdosed the amount of insulin at all the doses tested, with a mean percentage error which decreased as the dose increased. The differences between the intended and the delivered doses were not significant only using JuniorSTAR and VetPen 0.5-8 U at insulin doses of 0.5, 1, 2, and 4 U; however, the mean percentage error was ≤−6.86% for all pen-injectors tested, result that is consistent with what has been reported in human literature.[12-15] Similarly to the mean percentage error, also the CV (which did not exceed the value of 7.67%) decreased with an increasing dose.

In this study, it was investigated whether the insulin cartridges, and not the devices, were the most important source of error. For this purpose, the 2 pen-injectors with the lowest CVs were selected, but no differences were found between the 5 U doses delivered from the different quarters of the cartridges, suggesting that the glass cylinder was not a significant source of error.

Using a 30 U/0.3 mL insulin syringe, the dose delivered was not statistically different from the intended dose when dispensing 4 U; conversely, the dose delivered was statistically higher for doses <4 U and statistically lower for doses >4 U. The 40 U/mL insulin syringe was the only 1 of the 8 devices tested to dispense doses of 8 and 16 U not statistically different from the intended dose; however, similarly to the 30 U/0.3 mL insulin syringes, it significantly overestimated at doses of 0.5, 1, and 2 U. For the syringes, as for the pen-injectors, the CV also decreased with an increasing dose, and precision was similar to that of the pen-injectors, except when attempting to dispense 0.5 U (CV =12.08% for 30 U/0.3 mL insulin syringe; CV =9.39% for 40 U/mL insulin syringe).

At low insulin dosages, the fact that pen-injectors tended to underdose and syringes to overdose has already been shown in some studies.[12-15,18] This concept should be considered when a patient is shifted from a syringe to a pen-injector or vice versa as this change could involve a variation of up to 35% of the dose administered. The smaller magnitude of the underestimation of pen-injectors as compared to the more severe magnitude of the overestimation of syringes

results in a preference for pen-injectors when doses of 0.5 and 1 U are to be administered. However, not all the pen-injectors were equally accurate, and the results in the present study demonstrated that JuniorSTAR and VetPen 0.5-8 U were the most reliable tools for diabetic patients receiving insulin doses ≤2 U.

At doses ≥8 U, the fact that accuracy was high only when using 40 U/mL insulin syringe could have 2 possible explanations. First, it should be considered that human insulins (glargine, detemir, and lispro) and veterinary insulin (porcine insulin zinc) have a concentration of 100 and 40 U/mL, respectively. This implies that the volume corresponding to a given insulin dose is 2.5 times greater in the case of porcine insulin zinc. It is reasonable to assume that the volume to be delivered influences the accuracy of the device used to dispense it. Consequently, it is possible that the better performance of the devices suitable for use with porcine insulin zinc might be justified by the different concentration of this type of insulin, and it is conceivable that better accuracy is more evident with increasing doses of insulin. The introduction of more diluted insulin solutions could ensure greater accuracy in dosing; however, if different concentrations of the same insulin preparation were available, this could contribute to increasing confounding factors for both owners and veterinarians, especially regarding the type of syringe to be used for administration. In some countries, a 20 U/0.5 mL syringe is available for porcine insulin zinc; it has the advantage of 0.5-unit increment markings and for this reason it could be preferred by many clinicians and owners. Unfortunately, this type of syringe is not available in our country and it was not possible to include it in this study. Second, it must be considered that the veterinarians were aware that they were participating in an accuracy and precision study. The awareness of being tested and having taken multiple consecutive insulin measurements in a single session might have increased their effort in dosing insulin with syringes as compared to what happens in daily practice. The interoperator variability investigated in this study showed that in 15/120 comparisons (1/60 using the 30 U/0.3 mL insulin syringes and 14/60 using the 40 U/mL insulin syringes) the doses dispensed by the operators were significantly different. For this reason, it is recommended that the same operator always handle and administer insulin to a diabetic pet.

In clinical practice, changes in insulin therapy are based on clinical response, blood glucose curves or, more recently and effectively, on interstitial glucose trends, assessed using continuous glucose monitoring systems.[19] For this reason, the ability of a device to deliver the same insulin dose (precision) should be preferred over its ability to deliver the intended dose (accuracy), as precision ensures that equal insulin doses are delivered every time (regardless that are accurate with respect to the prescribed dose), thus limiting fluctuations in blood glucose concentrations and ensuring greater homogeneity of treatment. In this context, the better repeatability of pen-injectors as compared to insulin syringes could ensure better glycemic control in diabetic dogs and cats. However, their misuse could introduce numerous opportunities for error, for example when owners do not remove the needle from the pen between injections, do not perform an air shot when using a new cartridge or do not wait 5-10 seconds after pushing the plunger down.

A limitation of this study is that the correction coefficient (which converts weight to units) of insulin glargine was used for all human insulins tested; this might have influenced the accuracy (but not the precision) results obtained for the other insulin preparations. Another important limitation is that a sample size calculation based on ample data from previously published human studies with an identical design was not performed.

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CONFLICT OF INTEREST DECLARATION

Authors declare no conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

Authors declare no IACUC or other approval was needed.

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

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