

# Comparison of drug delivery with autoinjector versus manual prefilled syringe and between three different autoinjector devices administered in pig thigh

Robert L Hill<sup>1,\*</sup>John G Wilmot<sup>1,\*</sup>Beth A Belluscio<sup>1</sup>Kevin Cleary<sup>2</sup>David Lindisch<sup>3</sup>Robin Tucker<sup>4</sup>Emmanuel Wilson<sup>2</sup>Rajesh B Shukla<sup>1</sup>

<sup>1</sup>Meridian Medical Technologies Inc., Columbia, MD, <sup>2</sup>Children's National Medical Center, <sup>3</sup>Washington DC VA Medical Center, <sup>4</sup>Georgetown University Medical Center, Washington, DC, USA

\*These authors have contributed equally to this work

**Abstract:** Parenteral routes of drug administration are often selected to optimize actual dose of drug delivered, assure high bioavailability, bypass first-pass metabolism or harsh gastrointestinal environments, as well as maximize the speed of onset. Intramuscular (IM) delivery can be preferred to intravenous delivery when initiating intravenous access is difficult or impossible. Drugs can be injected intramuscularly using a syringe or an automated delivery device (autoinjector). Investigation into the IM delivery dynamics of these methods may guide further improvements in the performance of injection technologies. Two porcine model studies were conducted to compare differences in dispersion of injectate volume for different methods of IM drug administration. The first study compared the differences in the degree of dispersion and uptake of injectate following the use of a manual syringe and an autoinjector. The second study compared the spatial spread of the injected formulation, or dispersion volume, and uptake of injectate following the use of five different autoinjectors (EpiPen® [0.3 mL], EpiPen® Jr [0.3 mL], Twinject® [0.15 mL, 0.3 mL], and Anapen® 300 [0.3 mL]) with varying needle length, needle gauge, and force applied to the plunger. In the first study, the autoinjector provided higher peak volumes of injectate, indicating a greater degree of dispersion, compared with manual syringe delivery. In the second study, EpiPen autoinjectors resulted in larger dispersion volumes and higher initial dispersion ratios, which decreased rapidly over time, suggesting a greater rate of uptake of injectate than the other autoinjectors. The differences in dispersion and uptake of injectate are likely the result of different functional characteristics of the delivery systems. Both studies demonstrate that the functional characteristics of the method for delivering IM injections impact the dispersion and uptake of the material injected, which could significantly affect the pharmacokinetics and, ultimately, the effectiveness of the drug.

**Keywords:** anaphylaxis, autoinjector device, injector pen, intramuscular drug administration, dispersion volume

## Introduction

The key to treating medical emergencies such as anaphylaxis and prolonged seizures is rapid administration of the appropriate medications.<sup>1,2</sup> Delayed treatment is associated with poorer outcomes.<sup>3-5</sup> One important variable affecting time to treatment is the route of drug administration. The onset of action with oral administration is inherently slow and therefore not suitable for patients experiencing a medical emergency. Other routes of administration (ie, rectal, intranasal, transdermal, and sublingual) may be inconvenient, difficult for administration, or physiologically and/or pharmacologically impractical.<sup>6-8</sup>

Correspondence: Robert L Hill  
Meridian Medical Technologies Inc.,  
6350 Stevens Forest Road, Columbia,  
MD 21046, USA  
Tel +1 443 259 7888  
Fax +1 845 474 4206  
Email bob.hill@meridianmt.com



Parenteral drug therapy usually provides a more rapid uptake of drug and is therefore preferred over oral therapy, when available. Among the possible parenteral routes, the subcutaneous route generally has the longest time to effect and is the simplest to administer. The intravenous (IV) route has the most rapid onset of action but IV access can be difficult, time-consuming, and sometimes impossible to achieve. The intramuscular (IM) route provides a compromise, since it often results in an intermediate time to onset of action and can often be accomplished without difficulty. IM administration of benzodiazepines via an autoinjector has been shown to be at least as safe and effective as the IV route for treating prolonged convulsive seizures in the prehospital setting.<sup>9</sup> An additional advantage of IM drug administration is that it may provide greater consistency in absorption than subcutaneous administration.<sup>10–12</sup>

There are several methods for delivering drugs by the IM route, and recent advances in IM drug transport dynamics<sup>13</sup> may guide further improvements to the performance of current and alternative injection technologies. To best evaluate the growing variety of methodologies and their unique design characteristics, it is important to develop experimental models that provide a means to evaluate various devices with respect to discrete properties of the IM injection. Our studies build on the work of Wu et al<sup>13</sup> which documented the mechanical influences of active tissue on drug permeability and transport by using isolated muscle model systems. In this study, we developed an animal model that has the advantages of muscle mass parameters close to human skeletal muscle and nonischemic, living tissue. A computed tomography (CT) imaging technique was used to measure the dispersion and uptake of the injectate. CT image analysis provided a means to evaluate the influence of device parameters, such as needle length, needle gauge, injection volume, and plunger force (ie, speed and pressure of delivery provided either manually or by a spring), on specific aspects of IM injection that ultimately affect drug pharmacokinetics and effectiveness.

A manual syringe requires that the user applies a force sufficient to deliver the drug. The extent of this force is dependent on a number of parameters including user dexterity, fluid viscosity, needle length and gauge, friction between the syringe plunger and syringe barrel, cross-sectional area of the syringe plunger, and plunger displacement.<sup>14</sup> An autoinjector provides a consistent spring force profile to push the drug out of the syringe. The internal spring is compressed prior to activation and is released either by a button press or by applying pressure to the needle end of the autoinjector, depending on the design. The spring force is designed to be

sufficient to deliver the drug, which is affected by the same parameters as for the manual syringe.

Two studies using our animal model and imaging technique were conducted separately to compare different devices used to deliver an IM drug administration. The first study compared the use of a manual syringe and an autoinjector, and, for each method, assessed whether needle length and gauge were related to injectate dispersion volume (spatial spread of injectate) and uptake (reduction in injectate volume in tissue). The second study compared the impact of five different autoinjectors with varying needle length, needle gauge, and spring force on the dispersion volume and uptake of injectate.

## Materials and methods

### Study I: autoinjector versus manual syringe

The dispersion volumes of the injectate from an autoinjector (Diazepam Auto-Injector; Pfizer Inc., New York, NY, USA)<sup>10,15</sup> were compared with that of a manual syringe (Monoject™ 3 mL syringe; Covidien, Mansfield, MA, USA) using CT imaging in a pig animal model. The study was conducted according to US Food and Drug Administration Good Laboratory Practice for Nonclinical Studies<sup>16</sup> in the Department of Radiology at Georgetown University between March 18, 2006, and April 29, 2006, under an Institutional Animal Care and Use Committee-approved animal care and use protocol (#05-021).

### Pigs

Nine female Yorkshire pigs were purchased from Thomas D Morris, Inc. (Reisterstown, MD, USA). Animals were identified by the vendor using permanent ear tags. Animals were acclimated 3–4 days prior to each investigation. All animals were examined upon arrival, housed in a controlled environment, and fed Purina™ Lab Diet 5084 (Purina Lab Diet, St Louis, MO, USA, noncertified) with tap water provided by an automatic water system, available ad libitum from the day of arrival to the end of study. A total of eight animals (one animal died due to anesthetic complications prior to injection) were randomized by random card draw and were studied in two groups of four animals each (groups P1 and P2, Table 1).

### Injection devices and injectate

The investigation was conducted using eight autoinjectors and eight manual syringes. The Diazepam Auto-Injector (Pfizer Inc.) was a cylindrically shaped, pressure-activated,

**Table 1** Study details

Study group (n=4/group)	Needle gauge (Ga) × length (in)	Administration	Evaluation
<b>Study 1: Diazepam Auto-Injector versus Monoject™ manual syringe</b>			
P1	22×0.6 autoinjector versus 22×0.6 syringe	Autoinjector in left thigh, manual syringe in right thigh	Dispersion and uptake of injectate
P2	20×0.8 autoinjector versus 20×0.8 syringe		
Study group (n=4/group)	Autoinjector comparison	Administration	Evaluation
<b>Study 2: Anapen® and Twinject® autoinjectors versus EpiPen® autoinjector</b>			
P1	Anapen 0.3 mL versus EpiPen 0.3 mL	Each animal was injected with EpiPen in the left thigh and test injector in the right thigh	Dispersion and uptake of injectate
P2	Twinject 0.15 mL versus EpiPen® Jr 0.3 mL		
P3	Twinject 0.3 mL versus EpiPen 0.3 mL		

prefilled 3 mL automatic syringe delivery device. One version contained a 22 gauge ×0.6 inch (22 Ga ×0.6 in [length of needle extended from the device]) needle and the other contained a 20 Ga ×0.8 in needle. Two versions of the manual (Monoject™, Covidien) 3 mL syringes were also used in the study: one with a 22 Ga ×1.5 in needle and one with a 20 Ga ×1.5 in needle. A needle depth marker (Cook Inc., Bloomington, IN, USA) was manually placed and secured onto each Monoject™ needle (Covidien) so that the maximum IM penetration of the 22 Ga needle was 0.6 in and the maximum penetration of the 20 Ga needle was 0.8 in to ensure direct comparability to the autoinjectors. The measurement from the tip of the needle to the proximal edge of the needle depth marker was assessed with digital calipers (VWR, Clarksburg, MD, USA).

The injectate used in both the autoinjector and the standard syringe was a solution containing 0.25 mL per mL Omnipaque 300™ (Amersham Health Inc., Princeton, NJ, USA) combined with 0.75 mL per mL of a solution made using the following formula (per mL solution): 447.50 mg propylene glycol USP, 94.50 mg ethanol (95%) USP, 17 mg benzyl alcohol NF, 45.50 mg sodium benzoate NF, 3.75 mg benzoic acid USP, and a sufficient quantity of purified water to bring solution to 1 mL. Both autoinjectors and syringes were pre-filled with 2 mL of injectate.

### Study 1 procedure

Animals were weighed and anesthetized in the Division of Comparative Medicine (Georgetown University) on the day of testing. Anesthesia was induced by the administration of IM ketamine/xylazine given in the lateral neck muscles or rear leg and IV atropine and thiopental given via an ear vein catheter. The animals were intubated, ventilated, and placed on isoflurane gas (1%–3%) to maintain anesthesia. During transport and throughout the study, the pigs were placed on their backs on a V-trough and oriented on the CT table with the head toward the front of the gantry. Anesthetized pigs received two simultaneous IM injections of 2 mL injectate.

Two technicians performed the injections: one administered the injectate with the manual syringe (right thigh) and the other used the autoinjector (left thigh). To identify equivalent injection sites on each thigh, each target was found by palpating the patella and then measuring 3 cm medially or laterally from the patella into the muscle mass and marked with indelible ink prior to the injection.

Tissue at each of the marked sites was pinched and rotated to allow better access to the designated muscle belly, and either the autoinjector or syringe was applied and deployed. Autoinjectors and syringes were held in place for 5 seconds after completing the injection. Following the injection, the length of the manual syringe needle was remeasured using the digital calipers to evaluate whether or not the needle depth marker had shifted.

The first group (P1) was injected with the 22 Ga needles of the manual syringe and autoinjector; the second group (P2) was injected with the 20 Ga needles of the manual syringe and autoinjector.

### CT imaging analysis

CT imaging (Somatom Volume Zoom CT Scanner with fluoroscopy capability; Siemens, Forchheim, Germany) was used to measure the dispersion parameters of the injectate. An initial CT fluoroscopy image was obtained during the injection, and then a series of CT volumes was obtained following completion of injection. The first of these CT volumes was obtained approximately 10 seconds from the time of injection to the first scan. Subsequent CT volumes were then obtained at 1, 5, 10, 15, 20, 30, 45, and 60 minutes after injection. The CT images were acquired using 165 mAs at 120 kV with a rotation time of 0.5 seconds. Narrow collimation (1.0 mm) was used with a 3.0 mm slice width and a rotation/table feed of 5.0 mm.<sup>14</sup> A medium smooth reconstruction kernel (B30f) and a reconstruction increment of 1.0 mm were used.

CT image analysis was performed using the Analyze® software (Mayo Clinic, Rochester, MN, USA). Analyze 5.0

was used. Total volume measure (in mm<sup>3</sup>) based on voxel signal intensity was derived for each time point using a manual threshold technique.<sup>17</sup> An intensity threshold that adequately visualized injectate and bone was manually identified in the first CT scan. Scans collected at subsequent time intervals use this same threshold to segment the CT dataset. The injectate volume is identified through a region growing method, seeded with manually selected points identifying injectate site. For each segmented injectate volume, the mean and standard deviation of voxel intensities were computed. For each trial, a reduction in the injectate volume over time was interpreted as representing dispersion of injectate from tissue. The average rate of uptake of injectate was calculated as  $\Delta V/\Delta t = [(V_p - V_{60})/(t_{60} - t_p)]$  where  $V_p$  = peak volume,  $V_{60}$  = volume at 60 minutes,  $t_p$  = time point of peak volume, and  $t_{60}$  = 60-minute time point.

Animals were euthanized at the end of the study, following completion of CT scans (on March 18 and March 26), using a commercially available euthanasia solution (Euthasol™; Virbac AH, Inc., Fort Worth, TX, USA).

A statistical analysis of the results was not performed since the number of animals included in this study did not support a statistical approach.

## Study 2: autoinjectors with different mechanical properties

The parameters relating to dispersion volume and uptake were measured following injections with five autoinjectors (EpiPen 0.3 mL and EpiPen Jr 0.3 mL [Mylan Specialty LP, Basking Ridge, NJ, USA], Twinject 0.15 mL and Twinject 0.3 mL [Shionogi Pharma, Inc., Atlanta, GA, USA], and Anapen 300 0.3 mL [Lincoln Medical, Wiltshire, UK] autoinjectors) using CT imaging in a pig animal model. The study was performed in the Division of Comparative Medicine at Georgetown University on March 1, 2010 and July 24, 2010 under an Institutional Animal Care and Use Committee-approved animal care and use protocol (#10-005).

## Pigs

Thirteen female Yorkshire pigs were purchased from Thomas D Morris, Inc. Animals were identified by the vendor using permanent ear tags. One animal in Study 2 was used for a prestudy procedural assessment and was euthanized on the day after arrival and not entered into the study. This animal was used to determine the attachment method for a denim patch (to be injected through) and the specific location for the injection sites to optimize the injection procedure. As in the previous study, the remaining animals were examined upon arrival, housed in a controlled environment, and provided with food and water as described above. A total of 12 animals were placed into three groups of four animals each (groups P1, P2, and P3, Table 1).

## Injection devices and injectate

Each study group was used to test two autoinjector devices as follows: P1) Anapen 300, a round, prefilled, pressure-activated, automatic syringe (27 Ga ×0.3 in [length of needle extended from the device]) intended to deliver 0.3 mL, and EpiPen, an oval, prefilled, pressure-activated, automatic syringe (22 Ga ×0.6 in) intended to deliver 0.3 mL; P2) Twinject, a round, prefilled, automatic syringe (25 Ga ×0.5 in needle) intended to deliver 0.15 mL and EpiPen Jr, an oval, pressure-activated, prefilled automatic syringe (22 Ga ×0.5 in) intended to deliver 0.3 mL; and P3) Twinject (25 Ga ×0.5 in), as described, intended to deliver 0.3 mL, and EpiPen Jr (22 Ga ×0.5 in) as described, intended to deliver 0.3 mL (Table 1). The functional characteristics of each autoinjector type that could influence dispersion of the injectate within muscle are listed in Table 2.

## Study 2 procedure

Anesthesia was induced by the administration of Telazol (Zoetis, Fort Dodge Animal Health, New York, NY, USA) (6 mg/kg, IM), and atropine (0.5 mg/kg, IM) given in the lateral neck muscles or rear leg. The animals had an ear

**Table 2** Typical functional characteristics of autoinjectors used in Study 1 and Study 2

	Spring force <sup>a</sup> (lbs)	Needle extended length (in) <sup>b</sup>	Needle gauge (Ga)	Dispense time (s)	Activation force <sup>c</sup> (lbs)
Diazepam 2 mL	23 <sup>d</sup>	0.51 <sup>e</sup>	22	1.6 <sup>e</sup>	3.6 <sup>e</sup>
Diazepam 2 mL	23 <sup>d</sup>	0.75 <sup>f</sup>	20	1.0 <sup>f</sup>	4.3 <sup>f</sup>
Anapen® 0.3 mL	2.1 <sup>g</sup>	0.29 <sup>g</sup>	27 <sup>g</sup>	0.78 <sup>g</sup>	2.1 <sup>g</sup>
Twinject® 0.15 mL	6.5 <sup>g</sup>	0.48 <sup>g</sup>	25 <sup>g</sup>	0.28 <sup>g</sup>	5.6 <sup>g</sup>
Twinject 0.3 mL	6.5 <sup>g</sup>	0.51 <sup>g</sup>	25 <sup>g</sup>	0.63 <sup>g</sup>	5.9 <sup>g</sup>
EpiPen® 0.3 mL	22.7 <sup>g</sup>	0.59 <sup>g</sup>	22 <sup>g</sup>	0.29 <sup>g</sup>	6.6 <sup>g</sup>
EpiPen® Jr 0.3 mL	23.6 <sup>g</sup>	0.52 <sup>g</sup>	22 <sup>g</sup>	0.30 <sup>g</sup>	5.7 <sup>g</sup>

**Notes:** <sup>a</sup>Spring force: the force applied to plunger the moment the drug is dispensed; <sup>b</sup>needle extended length: the length of the needle that is available to enter the subject's thigh; <sup>c</sup>activation force: the force required to trigger the automated injection; <sup>d</sup>diazepam Auto-Injectors use the same spring as the EpiPen, implicating that the spring force will be typically similar; <sup>e</sup>certificate of Conformance for Lot RP 452-2, data from Meridian Medical Technologies; <sup>f</sup>certificate of Conformance for Lot RP-476-B, data from Meridian Medical Technologies; <sup>g</sup>R01-651 Functionality Report, data from Meridian Medical Technologies.



vein catheter placed, were intubated, ventilated, and given isoflurane (1%–3%) gas as maintenance anesthesia. The anesthetized pigs were placed on the CT table in a V-trough on their backs. The injection sites (one per thigh) were then identified using digital calipers to measure 3 cm laterally from the top of the patella. The injection site was marked with indelible ink directly on the skin prior to injection. Both the right and left thighs were injected simultaneously, with different technicians performing each injection. Each autoinjector was positioned  $\sim 90^\circ$  to the injection surface. Following activation, the autoinjectors were held in place for 5 seconds to ensure complete delivery of the injectate.<sup>18</sup>

### CT imaging analysis

CT imaging (Somatom Emotion 16 CT Scanner; Siemens) was used to determine the injectate dispersion into the muscle and subsequent uptake of the injectate over time. Serial CT images were acquired as previously described for Study 1. However, the interval between images was shorter than was used for Study 1, as was the total time period over which the series was collected. This change was made in order to get a better definition of the time resolution for injectate uptake during the earlier time points when the greatest change was observed in Study 1. An initial scan was obtained as soon as the technicians performing the injection left the room (designated time zero) and then at times 1, 2, 3, 4, 5, 7, 9, 11, 13, and 15 minutes postinjection. CT images were acquired at 110 kV with a rotation time of 0.1 seconds. Narrow collimation (1.0 mm) was used as before, with a 1.0 mm slice width and a medium smooth reconstruction kernel (B30f), with a reconstruction increment of 1.0 mm.

Analysis of CT images was performed as described previously. A statistical analysis of the results was not performed since the number of animals included in this study did not support a statistical approach.

After removal of the autoinjectors from the injection site, the postinjection exposed needle lengths were determined using CT imaging. The postinjection needle scans were loaded into Analyze (Analyze 7.0 Software Suites, AnalyzeDirect, Inc., Overland Park, KS, USA), and the threshold was adjusted so that only the needle and plastic housing were visible. For each article, the tip of the needle was chosen as the start point and the base of the needle proximal to the plastic housing was chosen as the end point when measuring.

Animals were euthanized as described previously. The pig carcasses were returned to the necropsy room and the skin directly over the injection site was incised with a scalpel, and the depth of the combined skin/fat layer was measured using

digital calipers. The skin/fat layer was quantified to determine that the depth of tissue was consistent and to ensure that the extended needles of the autoinjectors were long enough to reach the muscle tissue underlying the fat layer.

## Results

### Study 1: autoinjector versus syringe

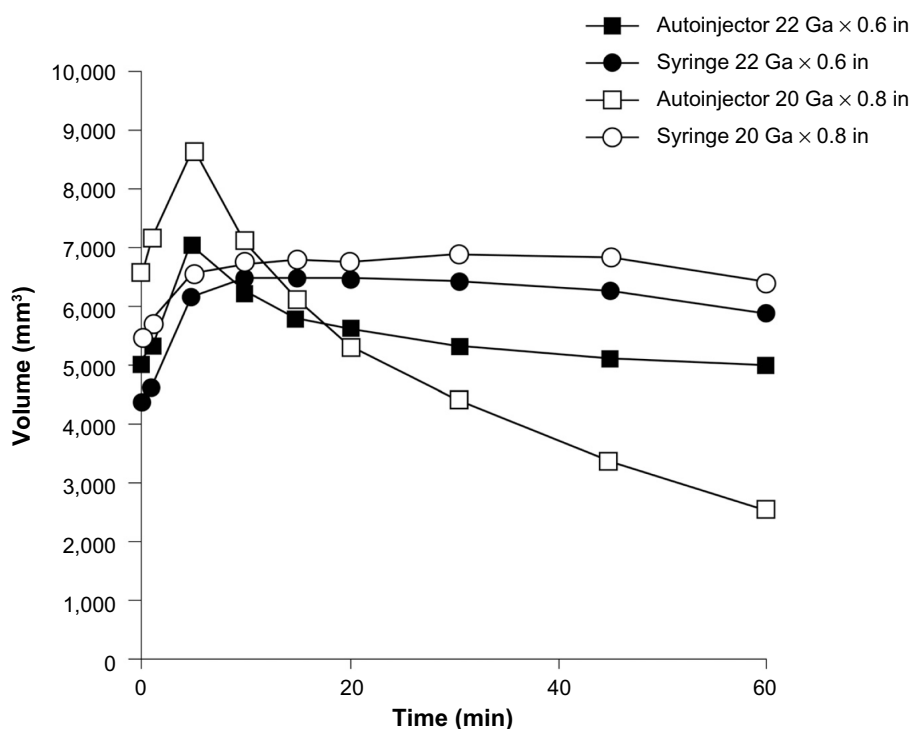
Injection using both autoinjectors (20 Ga  $\times$  0.8 in and 22 Ga  $\times$  0.6 in) resulted in larger peak dispersion volumes (8,677 and 7,049 mm<sup>3</sup>, respectively) than injections using the manual syringes (6,917 mm<sup>3</sup> for the 0.8 in syringe and 6,521 mm<sup>3</sup> for the 0.6 in syringe), as shown in Figure 1. In addition, use of devices (autoinjector or syringe) with 20 Ga  $\times$  0.8 in needles (P2) resulted in larger dispersion volumes than use of devices with 22 Ga  $\times$  0.6 in needles (P1) (Figure 1), suggesting that needle gauge and/or length affected injectate delivery. Autoinjection with the 20 Ga  $\times$  0.8 in needle gave both the highest peak dispersion volume (8,677 mm<sup>3</sup>; Figure 1) and greatest uptake (29% peak volume remaining in the tissue at 60 minutes; Figure 2) of the four injection groups studied.

Additionally, both autoinjectors showed more rapid and complete uptake of the injectate within the 60-minute period studied compared to the syringes, as evidenced by the percentage of peak volume remaining in the muscle tissue at 60 minutes (Figure 2: 30% for the 20 Ga  $\times$  0.8 in autoinjector versus 87% for the 20 Ga  $\times$  0.8 in syringe and 71% for the 22 Ga  $\times$  0.6 in autoinjector versus 83% for the 22 Ga  $\times$  0.6 in syringe). The average rate of uptake at the 60-minute time point for the 20 Ga  $\times$  0.8 in autoinjector and the 22 Ga  $\times$  0.6 in autoinjector was 111.5 and 38.1 mm<sup>3</sup>/min, respectively, as compared to 15.8 and 14.0 mm<sup>3</sup>/min for the 20 Ga  $\times$  0.8 in syringe and 22 Ga  $\times$  0.6 in syringe, respectively.

Across the four injection devices (autoinjector and syringe, each with two needle types), there was a positive relationship between peak dispersion volume and percentage uptake, as indicated by the percentage reduction in dispersion volume from peak to 60 minutes (Figure 3).

### Study 2: autoinjectors with different mechanical properties

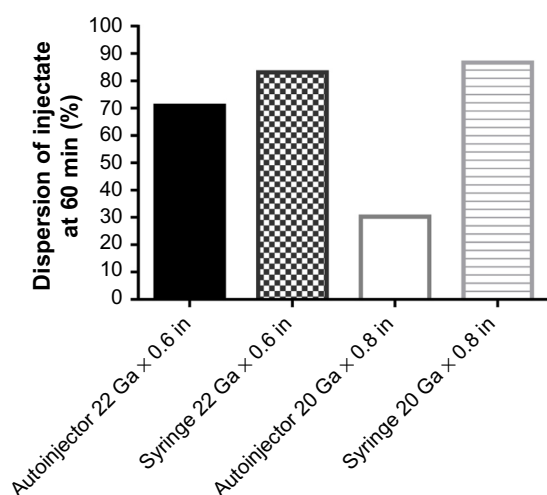
The postinjection exposed needle lengths were determined by CT analysis for all autoinjectors in this study. EpiPen exposed needle lengths ranged from 0.59 to 0.62 in (15.0–15.7 mm). Twinject 0.30 mL exposed needle lengths ranged from 0.48 to 0.50 in (12.2–12.7 mm). EpiPen Jr exposed needle lengths ranged from 0.56 to 0.58 in (14.2–14.7 mm). Twinject 0.15 mL exposed needle lengths ranged from 0.47



**Figure 1** Injectate dispersion volume of diazepam autoinjectors and syringes (Study 1).

to 0.52 in (11.9–13.2 mm). Anapen exposed needle lengths ranged from 0.29 to 0.33 in (7.4–8.4 mm).

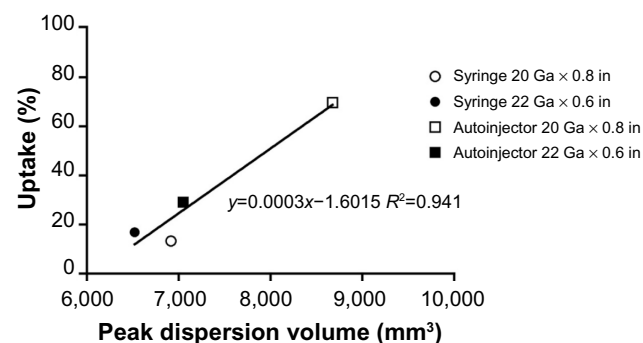
The postmortem measurement of the combined depth of the skin/fat layer directly under the autoinjection site demonstrated a similar measured depth of skin/fat layer in the left thigh and right thigh across all animals in all groups (P1, P2, and P3) of  $2.18 \pm 0.51$  mm (mean  $\pm$  standard deviation) ( $0.086 \pm 0.02$  in) and  $2.31 \pm 0.36$  mm ( $0.09 \pm 0.01$  in), respectively (Table 3). The average depth of the skin/fat layer was  $2.24 \pm 0.44$  mm ( $0.09 \pm 0.02$  in).



**Figure 2** Percentage dispersion of injectate at 60 minutes (Study 1).

There were differences in tissue dispersion volume among the autoinjectors tested. Study group P1 compared Anapen and EpiPen, both delivering 0.3 mL injectate. The initial dispersion volume was greater for EpiPen ( $949.76 \text{ mm}^3$ ) than for Anapen ( $576.70 \text{ mm}^3$ ), and the injectate reached its peak dispersion volume in a shorter time for EpiPen (1 minute) than for Anapen (9 minutes). In addition, there was greater uptake of the injectate from the site of injection 15 minutes postinjection for EpiPen (80%) than for Anapen (<5%).

Study group P3 compared Twinject 0.3 mL and EpiPen, both delivering 0.3 mL injectate. The EpiPen had a greater initial injectate dispersion volume ( $791.94 \text{ mm}^3$ ) than did Twinject 0.3 mL ( $721.18 \text{ mm}^3$ ). There was greater uptake



**Figure 3** Percentage uptake versus peak dispersion volume (Study 1).

**Table 3** Study 2: injection site skin fat layer measurements

Study comparison and animal	Autoinjector applied to left thigh (Ga × in)	Autoinjector applied to right thigh (Ga × in)	Measured skin/fat depth (mm [in])	
			Left thigh (EpiPen®)	Right thigh (test injector)
Study group P1				
Animal 1	Anapen® 27×0.3	EpiPen 22×0.6	1.86 (0.07)	2.41 (0.10)
Animal 2	Anapen 27×0.3	EpiPen 22×0.6	1.65 (0.07)	2.04 (0.08)
Animal 3	Anapen 27×0.3	EpiPen 22×0.6	1.80 (0.07)	1.91 (0.08)
Animal 4	Anapen 27×0.3	EpiPen 22×0.6	2.64 (0.10)	2.38 (0.09)
Mean ± SD			1.99±0.44 (0.08±0.02)	2.19±0.25 (0.09±0.01)
Study group P2				
Animal 1	Twinject® 25×0.5	EpiPen® Jr 22×0.5	2.01 (0.08)	1.93 (0.08)
Animal 2	Twinject 25×0.5	EpiPen Jr 22×0.5	2.18 (0.09)	2.51 (0.10)
Animal 3	Twinject 25×0.5	EpiPen Jr 22×0.5	2.24 (0.09)	2.22 (0.09)
Animal 4	Twinject 25×0.5	EpiPen Jr 22×0.5	3.57 (0.14)	2.37 (0.09)
Mean ± SD			2.50±0.72	2.26±0.25
Study group P3				
Animal 1	Twinject 25×0.5	EpiPen 22×0.6	1.91 (0.08)	3.27 (0.13)
Animal 2	Twinject 25×0.5	EpiPen 22×0.6	2.09 (0.08)	2.00 (0.08)
Animal 3	Twinject 25×0.5	EpiPen 22×0.6	1.93 (0.08)	2.28 (0.09)
Animal 4	Twinject 25×0.5	EpiPen 22×0.6	2.26 (0.09)	2.35 (0.09)
Mean ± SD			2.05±0.16	2.48±0.55

**Abbreviation:** SD, standard deviation.

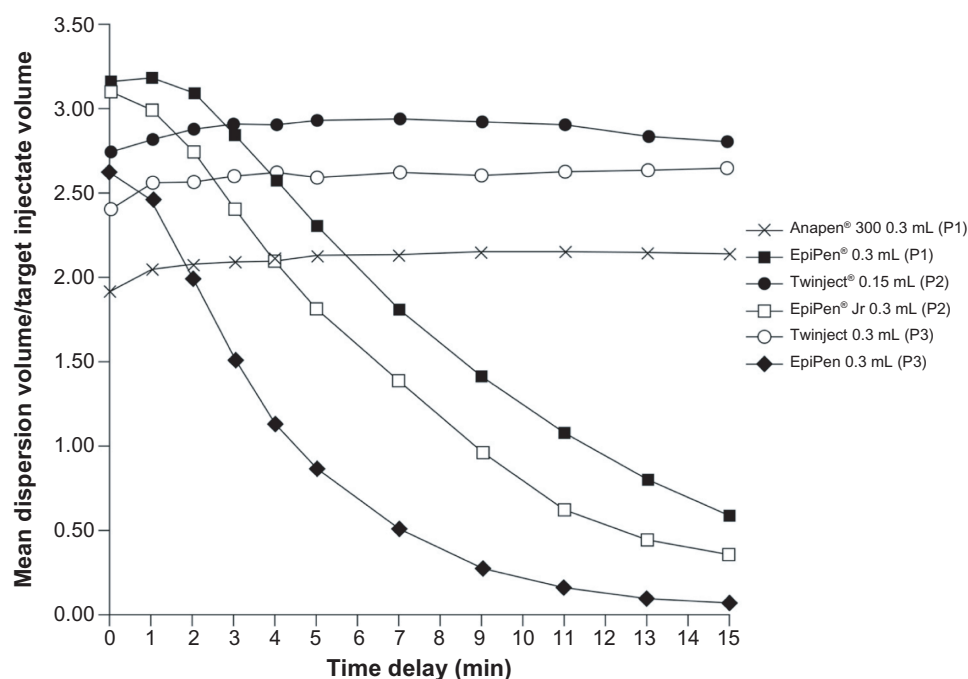
of the injectate 15 minutes postinjection for EpiPen (97%) than for Twinject 0.3 mL (<5%).

Study group P2 compared Twinject delivering 0.15 mL and EpiPen Jr delivering 0.3 mL. EpiPen Jr had a greater peak injectate dispersion volume (934.77 mm<sup>3</sup>) than Twinject 0.15 mL (412.04 mm<sup>3</sup>). It was noted that the EpiPen Jr 0.3 mL injects twice the volume of injectate than the Twinject 0.15 mL. To obtain a more effective interpretation of the difference in dispersion between the two devices, the data was normalized by dividing the dispersion volume by the injectate volume (Figure 4), resulting in a dispersion ratio (average measured dispersion volume/target injectate volume). Of the three test devices evaluated in this study (Anapen, EpiPen, and Twinject) the Anapen had the lowest initial dispersion ratio of 1.9. Twinject 0.15 mL had a higher initial dispersion ratio than Twinject 0.3 mL (2.7 versus 2.4), both of which were higher than Anapen. The EpiPen autoinjectors achieved higher initial dispersion ratios (range: 2.6–3.2) than Anapen and higher than or similar dispersion ratios to Twinject.

A notable difference between EpiPen and the other two autoinjectors was the decrease in dispersion volume over the 15-minute testing period. For EpiPen autoinjectors, the dispersion ratio was <30% of the initial value by 15 minutes, suggesting substantial uptake of injectate, whereas the dispersion ratio for Anapen and Twinject remained relatively constant, at >95% of the initial value by 15 minutes, suggesting negligible uptake (Figure 4).

## Discussion

Our investigations demonstrated that the functional characteristics of IM delivery systems influence dispersion and uptake of the injected material. In the first study, there was a clear difference between the autoinjector and the manual syringe with regard to characteristics of the injectate within the tissue. The greater dispersion volume of injectate for the autoinjectors, representing a wider tissue contact, is likely due to the greater force of injection provided by the spring within the autoinjector compared to that anticipated for



**Figure 4** Dispersion volume/target injectate volume ratio over time for autoinjectors (Study 2).

manual injection with a syringe. The autoinjector used in the first study has a spring force of ~23 lbs (Table 2), whereas a comparable design parameter for manual strength when using a syringe to give an injection, sustained thumb–finger grip strength, is 6.4–8 lbs for the 5th percentile of males.<sup>19</sup> The results also provide evidence that needle gauge and/or length affect injectate dispersion, since for both the manual syringe and the autoinjector, the 20 Ga  $\times$ 0.8 in needle produced a greater dispersion volume of injectate than for devices with the 22 Ga  $\times$ 0.6 in needle. This relationship could be a result of greater speed of delivery through the larger diameter (lower gauge) or the deeper injection depth of the 0.8 in needle.

The results of Study 1 also suggest that the greater dispersion provided by the autoinjector delivery systems correlates with greater uptake of the injected material. The positive relationship shown between peak dispersion volume and percentage uptake across the four injection devices (autoinjector and syringe, each with two needle types) could be because with a larger dispersion volume, the injectate comes into greater contact with the vascular bed, leading to more rapid absorption of material.

The results of Study 2 confirmed and extended those of Study 1. In particular, there were substantial differences in the dispersion and uptake of injectate among autoinjectors that differed with regard to spring force (ie, speed and pressure of delivery), needle gauge, needle length, injection

volume, and resulting dispense time. The most noteworthy difference in injectate parameters was between the EpiPen autoinjectors and the two other brands, Anapen and Twinject. The EpiPen resulted in greater dispersion volume, and substantially greater uptake at the 15-minute postinjection time point than either Anapen or Twinject. Since the most substantial functional difference between EpiPen and the other autoinjectors is the spring force which drives the injection<sup>18</sup> (23 lbs for EpiPen compared to 6 lbs for Twinject and 2.1 lbs for Anapen; Table 2), this factor is most likely responsible for the difference in dispersion and uptake of injectate. The lower gauge (larger needle diameter) of the EpiPen needle may also have contributed to the differences among autoinjectors, since this parameter affects injectate dispersion volume, as observed in Study 1.

One characteristic of the autoinjectors which could have contributed to a difference in dispersion volume is extended needle length. If any of the autoinjectors had an extended needle length that was not sufficient to reach the muscle layer, this could have produced a significant decrease in the average dispersion volume for that type of autoinjector. However, the results demonstrate that this was not a factor in this study, since the shortest postinjection needle length was 7.4 mm and the thickest skin/fat layer was 2.68 mm. Thus, all of the needles penetrated well beyond the skin and fat, and the autoinjections were given into muscle in all animals.



It is worth emphasizing that the greatest difference between EpiPen and the other autoinjectors was the percentage uptake of injectate. This is the measure most likely to correlate to drug serum concentration, which is a key contributor to the effectiveness of the treatment.

Adrenaline administration by autoinjector is viewed as the most effective first-line treatment for the management of anaphylaxis in the community. Autoinjectors provide fixed dosing, consistent needle penetration and depth, and can be administered quickly with a consistent dispersion pattern, which are important attributes in an anaphylaxis emergency. It is more difficult for patients and caregivers to achieve accurate and timely IM self-administration of adrenaline using an ampoule, needle, and syringe. The use of autoinjectors is associated with a higher cost in a health-care setting, whereas a manual syringe and needle may offer a more cost-effective treatment. However, the force of injection and needle depth associated with syringe and needle use may be more variable.

The limitations of this study include the small number of animals tested in each device group. Furthermore, injections into subcutaneous tissue were not part of this study, so the dispersion characteristics described apply only to injections into muscle tissue. Given the robust nature of the results, however, it is likely that the conclusions accurately reflect the relationship between functional aspects of drug delivery devices and the dispersion volume and uptake of injectate. Also, because individual functional aspects of the devices were not tested in isolation, any one aspect (eg, spring force) cannot definitely be attributed to a difference in dispersion volume or uptake. Although an understanding of the relationship between functional aspects of the devices and the force and speed of injectate delivery provides a reasonable basis for interpreting what led to differences among devices, additional studies are required to confirm the conclusions presented here. At the time of this study, the Anapen was not available in the US, but has been available in Europe since 2003. The Twinject autoinjector used in Study 2 has been withdrawn from the market since the completion of this study, and replaced with a similar device called Adrenaclick. There have been no functional changes affecting the design of EpiPen since this study was conducted that would affect the results seen in this study. The EpiPen design used in this study is the one that is currently commercially available.

## Conclusion

This study demonstrated the effective use of an animal model and an imaging methodology to assess the impact of specific functional properties of injection devices on discrete

parameters of an IM injection. Uptake of injected material, which is likely to contribute significantly to serum levels and effectiveness of a drug, was greatest under circumstances in which the force of injection was highest. This was true among different autoinjector types and when comparing autoinjector delivery to injection by a manual syringe. Needle size including gauge and length contributed to a lesser extent, with lower gauge (larger diameter needle) resulting in greater dispersion and uptake. These results may be used to guide further improvements to the performance of injection technologies.

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## Disclosure

Authors Robert L Hill, John G Wilmot, and Rajesh B Shukla were employees of Meridian Medical Technologies, Inc. during the conduct of this study and preparation of the manuscript. The authors report no other conflicts of interest in this work.

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