Human factors study of a newly approved prefilled syringe of epinephrine for the treatment of anaphylaxis

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ABSTRACT

Background: *Epinephrine remains the treatment of choice for acute anaphylaxis. However, currently available autoinjectors are costly, and studies have demonstrated human factor issues that result in incorrect use as well as device failures.*

Objective: *A recent U.S. Food and Drug Administration approved prefilled syringe of epinephrine for the treatment of anaphylaxis was examined in a prospective human factors validation study to determine the likelihood that the product would be used effectively by intended users.*

Methods: *A total of 82 participants were enrolled in this prospective study, including adults with and without epinephrine injector experience, adolescents with and without epinephrine injector experience, and lay caregivers with and without epinephrine injector experience. Half of the participants in each user group were trained to use the newly approved prefilled epinephrine syringe before its first use in the study. Critical tasks that could cause harm and compromise the successful use of epinephrine were assessed and included five categories: (1) open the case, (2) retrieve prefilled syringe, (3) remove needle cap, (4) insert needle in the thigh by using a needle pad, and (5) press plunger until it stops. The participants were scored by an independent observer on the correct use of the device.*

Results: *Of the participants, 100% (82/82) completed category 1, 100% of the participants (82/82) completed category 2, 100% (82/82) completed category 3, 93% (71/76) completed category 4 (six participants were observed to have a device with a bent needle and were taken out of the analysis), and 99% (81/82) completed category 5.*

Conclusion: *In this prospective study of human factors that effect correct epinephrine injection, a high rate of participants successfully completed the tasks when using the prefilled syringe, a newly approved epinephrine syringe for the treatment of anaphylaxis. These results indicated that the newly approved prefilled syringe of epinephrine should provide a user-friendly treatment for acute anaphylaxis.*

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INTRODUCTION

Self or caregiver administration of epinephrine is considered the treatment of choice for acute anaphylaxis.[1] The correct use of a device that contains epinephrine is critical in achieving the appropriate treatment during an acute allergic reaction. In June 2017, the U.S. Food and Drug Administration (FDA) approved SYMJEPI (Adamis Pharmaceuticals, San Diego, CA), a prefilled syringe used for the administration of epinephrine (Fig. 1).[2]

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Objective

In this study, SYMJEPI was examined in a prospective human factors validation study to determine the likelihood that the product would be used safely and effectively by the intended users.

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METHODS

This study was conducted in accordance with the FDA Guidance[3] and independently performed by Core Human Factors, Inc. (Bala Cynwyd, PA). Adamis employees, who developed SYMJEPI, were not involved in the conduct of the study. All the participants were observed using the product in a one-on-one moderated simulated-use session. Approximately half of the participants underwent an additional training session at least 24 hours before their testing session. During the testing session, all the participants were presented with a scenario that simulated an allergic emergency and were exposed to a reasonably stressful environment with distractions. Testing sessions lasted up to 30 minutes, and the participants were asked to use the product as they would in real life. All the participants simulated a single dose: adults and adolescents simulated a self-injection into an injection pad, and caregivers injected into a manikin that represented an ill person.

The test simulated a home environment and a stressful situation, including a soundtrack of distracting sounds (random beeping, street ambience, television playing, dogs barking, and random knocking). Approximately half of the participants had a brightly lit study room, and approximately half had a dimly lit

COLOR

Figure 1. *Symjepi™, a prefilled syringe used for the administration of epinephrine.*

Table 1 **User group sample size breakdown**

User Group	Trained	Untrained
Experienced adult patients	9	9
Inexperienced adult patients	8	8
Experienced adolescent patients	7	8
Inexperienced adolescent patients	7	8
Mixed lay caregivers (experienced and inexperienced)	9	9
Total	40	42

room (counterbalanced between user groups). Supplies in the room included home-like furnishings, such as comfortable seating and table surfaces. An injection pad was used to simulate the injection site. The participants (except for the caretaker subgroup) were asked to strap the injection pad onto themselves wherever they would choose to give the injection in real life. Caregiver participants were asked to indicate on a manikin where they would inject in real life, and the moderator helped attach the injection pad to the manikin.

A total of 82 participants enrolled and participated in this study. The sample size was estimated based on the FDA Guidance.[3] This study included adult patients, adolescent patients, and lay caregivers. The participants represented five user groups (Table 1), which are defined as the following: T1

- Adult Experienced. Adult patient participants who had been prescribed an epinephrine injection device and were experienced with using the device were thus categorized as "adult experienced." The study sample size was 18 participants.
- Adult Inexperienced. Adult patient participants who were inexperienced with using an epinephrine injection device were categorized as "adult inexperienced." The study sample size was 16 participants.
- Caregiver.

Lay caregivers included a mix of experienced and inexperienced epinephrine injection device users. The study sample size was 18 caregivers.

- Adolescent Experienced. Adolescent patient participants who had been prescribed an epinephrine injection device and either had experience with using the device or had been trained on how to use the device were categorized as "adolescent experienced." The study sample size was 15 participants.
- Adolescent Inexperienced. Adolescent patient participants who did not have a prescription for an epinephrine device, had not been trained on how to use an epinephrine injection device, and did not have experience with using an epinephrine injection device were categorized as "adolescent inexperienced." The study sample size was 18 participants.

The age and gender of the participants in this study are found in Tables 2 and 3. Approximately half of the participants underwent a training session at least 24 hours before their testing session because it was expected that some users would be trained by health care providers on how to use the product and some would not be trained. Training sessions lasted up to 20 minutes. These were one-on-one sessions with a trainer, in which the trainer verbally walked the participant through the instructions for use and the device labeling but did not actually use the drug. The participants were given an opportunity to handle, but not use, the product and ask any questions. The trainer only answered questions with information in the instructions for use, the device labels, or the patient information leaflet. T3

During the testing session, all the participants were presented with a scenario that simulated an allergic emergency and were exposed to a reasonably stressful environment with distractions. The participants were asked to use the product as they would in real life. All the participants simulated a single dose: adults and adolescents simulated a self-injection into an injection pad and caregivers injected into a manikin that represented an ill person. Each task was evaluated by hav-

Table 2 **Age ranges of all the participants**

	Age			
	12–14 y	**15–17 y**	**18–30 y**	**≥31 y**
Experienced adult (n = 18)	—	—	4	14
Inexperienced adult (n = 16)	—	—	5	11
Caregivers (n =18)	—	—	4	14
Experienced adolescents (n = 15)	9	6	—	—
Inexperienced adolescents (n = 15)	7	8	—	—
Total (N = 82)	16	14	13	39

Table 3 **Gender of the participants**

	Gender	
	Female	**Male**
Experienced adult (n = 18)	11	7
Inexperienced adult (n = 16)	10	6
Caregivers (n = 18)	12	6
Experienced adolescents (n = 15)	7	8
Inexperienced adolescents (n = 15)	4	11
Total (N = 82)	44	38

ing the participants use the product independently and in as realistic a manner as possible, without guidance, coaching, praise, or critique from the moderator. Tasks were assessed by observation of performance. All the participants were assessed on the tasks shown in Table 4. Moderators scored the tasks as follows: (1) successful, defined as performance without the participant describing struggle or difficulty; (2) resolved, defined as resolved performance that included struggling, describing difficulty, or taking some action to avoid harm that would have otherwise resulted in incomplete or incorrect use; and (3) incomplete/incorrect, defined as the participant did not complete the task as intended.

T4

RESULTS

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As shown in Table 5, all the participants completed tasks 1, 2, and 3. For task 4, five participants incorrectly injected into the forearm, deltoid, biceps, or triceps muscles instead of the thigh. All of these participants were untrained. These use errors were all in adolescents (four inexperienced and one experienced). Six participants were excluded from this analysis because of an artifact (the needle bent due to the impact of the protective backing on the injection pad used). For task 5, one participant failed to push the plunger and complete an injection with the device. Overall, 81 of 82 participants gave an injection with the device.

CONCLUSION

Human factor studies are important to support the safe and effective use of epinephrine devices used in the treatment of anaphylaxis. In this study, the correct use of SYMJEPI, a newly approved epinephrine device for the treatment of acute anaphylaxis was examined in a human factors study in a broad population of experienced and inexperienced adults, adolescents, and caregivers. Critical tasks were taught *a priori* of the proper administration of epinephrine during a simulated anaphylaxis episode. All the participants were able to correctly perform the tasks of opening the case, retrieving the device, and removing the needle cap. However, five participants incorrectly injected the device into muscle groups other than the thigh (arm muscle or hip). Interestingly, all five participates who incorrectly injected into the wrong muscle were in the adolescent subgroup (four inexperienced and one experienced). All of these subjects were untrained, which supported the importance of proper training for epinephrine devices. Although the injection of epinephrine into muscles other than the thigh may lead to less favorable kinetics,[4] it is not considered a safety risk. Overall, all the participants in this study, except one, were able to correctly press the plunger on the device that simulated an injection and would have received a dose of epinephrine. It should be noted that six participants were excluded from this analysis because of artifact (needle bent due to impact of the protective backing on the injection pad used). These subjects were excluded because it could not be determined if the bent needle could impact on the ability to receive or not receive epinephrine.

The requirements for the application of human factor studies during drug-device development began in 1996 when the FDA updated the Current Good Manufacturing Practice guidelines to include the design controls process for medical devices.[5] Human factors studies can only simulate the appropriate use of epinephrine during an anaphylactic episode, and thus this study had those limitations. The study was designed to validate the usability of

Table 4 **Assessed tasks table**

Task No.	Critical Tasks	Task Assessment	Success Criteria
1	Open case	Observation of performance	Participant opens the case
2	Retrieve Pre-filled Syringe	Observation of performance	Participant retrieves the product from the case
3	Remove needle cap	Observation of performance	Participant removes needle cap without prematurely deploying the needle guard
4	Insert needle into the thigh by using a needle pad	Observation of performance and knowledge task	Participant inserts needle into the thigh and demonstrates knowledge of the intended injection location
5	Press plunger until it stops	Observation of performance	Participant presses the plunger after the needle has been inserted into the thigh and completely presses the plunger until hearing and/or feeling a click, or the plunger stops

Table 5 **Critical Task Analysis**

Tasks	No. Successful/Total*	Percentage	Use Events Analysis
Open case	82/82	100	
Retrieve Pre-filled Syringe	82/82	100	
Remove needle cap	82/82	100	
Insert needle into the thigh	71/76	93	Injection into forearm, deltoid, biceps, or triceps (4), or hip (1)
Press plunger until it stops	81/82	99	Failed dose attempt

**Includes successful and resolved tasks that were not considered incorrect use.*

the device by different user groups. Because injection in this study used an injection pad, it could only approximate actual human use because of the fear of needle injections that many subjects have. However, human factor studies are very useful to test devices to approximate their correct or incorrect use in real-life situations and in different populations.

The incorporation of the guidelines on the use of human factors studies of the risk-management process into the FDA approval process for medical devices was uncommon until 2008, and thus comparison of these results to human factors studies for autoinjectors is limited. Of note, one study examined autoinjector use by physicians on five critical steps for the correct use of the device.[6] Before education, only 23% correctly administered the autoinjector but improved to 75% after education.[6] As noted in this study, adolescents were more likely to inject into other muscle groups besides the thigh. However, in another study, SYMJEPI was compared with the EpiPen (Mylan N.V., Canonsburg, PA) in 34 untrained adolescents in a prospective human factors study.[7] The results revealed no use errors in the adolescents when using SYMJEPI and four errors when using the EpiPen trainer (Epipen device without a needle used for training purposes).[7] Of note, adolescents and young adults make up the largest population of fatalities caused by anaphylaxis due to food.[8] All of these subjects were untrained,[8] which suggests the importance of proper training. In small children, the positioning of the child may be important in preventing needle injury. A recent article indicated that the proper compassionate restraint of small children may help prevent needle injury due epinephrine administration.[9] This prospective human factors study for a newly approved epinephrine device supported the ease and correct use of SYMJEPI for the acute treatment of anaphylaxis. SYMJEPI is a newly approved epinephrine syringe for the treatment of anaphylaxis and should provide a user-friendly treatment for acute anaphylaxis.

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