Project Number: 1509

Generic Epinephrine Auto-Injector Handling Study

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1. EXECUTIVE SUMMARY

1.1 WHAT DID WE DO?

Interface Analysis Associates ("IAA") conducted a simulated-use handling study of a proposed epinephrine auto-injector that would serve as a generic alternative for the EpiPen® auto-injector. This device would be intended to deliver epinephrine for the emergency treatment of allergic reactions, including anaphylaxis. This proposed epinephrine auto-injector uses the Vibex™ injector platform, and is understood to be very similar to the Vibex™ platform auto-injector used with the drug Otrexup™ (methotrexate). Therefore, this study was conducted using a prototype device based on a photograph of the proposed generic epinephrine auto-injector released by Antares, the manufacturer of the device, and examination of the Otrexup™ product.

The main objectives of this handling study were to:

- Assess how real EpiPen auto-injector users would react to the proposed generic device in terms of how they would manipulate and handle the device when attempting to inject with it (simulated) for the very first time.

- Assess whether or not EpiPen auto-injector users expect operation of the proposed generic device to mimic the procedure required to use the EpiPen auto-injector.

This study was conducted with a total of 30 participants; 15 of whom were EpiPen auto-injector patient caregivers with knowledge of how to use the EpiPen auto-injector (e.g., parents, siblings, relatives), and 15 of whom were EpiPen auto-injector patients. Of the patients, 9 were adults (age 18 and above) and 6 were juveniles (ages 10-17). All participants demonstrated their knowledge of how to correctly use an EpiPen auto-injector in the course of their screening, although there was variance in their level of training and use experience.

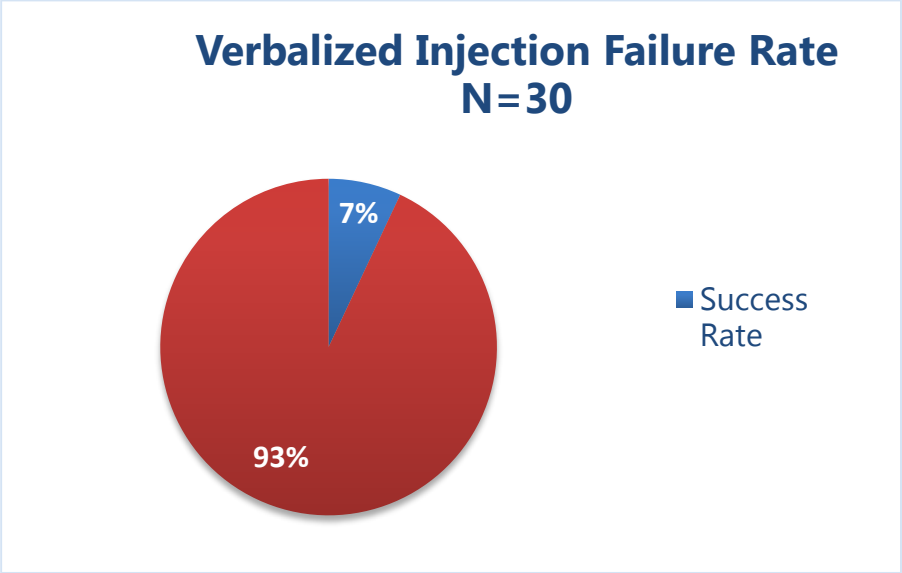
None of the participants were provided training on the proposed generic epinephrine auto-injector prior to their exposure to the device. This is consistent with the

expectation that a generic product would be substituted at the pharmacy, and that no training would be given, nor would the patient/caregiver be prompted or instructed to review the product labeling. Each participant took part in one study session that lasted for approximately 10 minutes. Participants were informed that the device was not an EpiPen auto-injector, but was a generic substitute, and were presented with a scenario in which they were to attempt to use the proposed generic epinephrine auto-injector to rescue another person (caregivers) or themselves (patients) from a severe allergic reaction. Participants were asked to perform a "think-aloud" mock injection, in which they verbalized and gestured their interaction with the device without actually physically manipulating it or performing the injection. This allowed us to study the initial reaction to, and use of, the proposed generic epinephrine auto-injector during a realistic rescue scenario.

1.2 What Did We Find?

Did participants describe the correct procedure with the proposed generic epinephrine auto-injector?

No. All but two participants (28/30) described their intended manipulation of the device in a manner that would have resulted in a failed injection attempt. Thus, the failure rate was 93%. Two participants, both juvenile patients, correctly verbalized their intended manipulation of the generic device to deliver an injection. That is, they stated they would remove both the safety clip and the yellow needle cap prior to injecting. Of the 28 who failed, 27 mimicked the **exact** EpiPen auto-injector procedure, stating they would remove the blue safety clip and nothing else prior to injecting, while one participant suggested removing the yellow needle cap but not the blue safety clip prior to injecting. The overall failure and success rates across the 30 participants are shown below.



Did participants demonstrate any negative transfer from the EpiPen auto-injector to the proposed generic epinephrine auto-injector?

Yes. All but three participants (27/30, 90%) did not verbalize the need to remove the needle cap on the proposed generic. These 27 participants described their interaction with the proposed generic device in the identical manner in which they described their interaction with the EpiPen auto-injector. Simply stated, they verbalized and motioned a procedure which included removal of the blue safety clip followed immediately by the injection into the outer thigh. This is consistent with the EpiPen auto-injector instructions for use, but with the proposed generic device this would lead to a failed injection attempt. This is because the Vibex™ device requires an additional step – to remove a yellow cap that is over the needle end of the device.

Observations

Most participants first noticed the familiar blue safety clip and attempted to remove that almost immediately. Although some of the participants (n=6) noticed the yellow needle cap and a few (n=3) explicitly contemplated its purpose, all but three participants ultimately concluded that the needle would extend through the opening in the cap, as occurs with the EpiPen auto-injector. The photos below show a comparison of the EpiPen auto-injector and generic device needle end.

Yellow Needle Cap on Generic with Hole

EpiPen Auto-Injector Needle End with Hole Through Which Needle Protrudes

Before entering the rescue scenario room, participants were told that the proposed generic device was not stored in any case. Nonetheless, three (3) participants thought that the device was inside of a clear container, which is how the EpiPen auto-injector is packaged. This design element created additional confusion that resulted in a delay to

the process, as the user tried to figure out how the device would be removed from the outer container. The photo below shows a side-by-side image of an EpiPen auto-injector in its carrier case next to the clear bodied proposed generic device.

EpiPen auto-injector in Case (above) and Generic Device Itself (below)

1.3 What Do We Conclude?

The results of the study confirmed our prior prospective analysis of the implications of the design similarities and differences between the two devices. Because the proposed generic device has design features similar to those of the EpiPen auto-injector, such as a nearly identical looking and familiar safety clip, the participants assumed the device operation to be the same as that of the EpiPen auto-injector.

Accordingly, they removed the blue safety clip and nothing else before demonstrating how they would jab the device into the outer thigh to initiate the injection. Of the small number of participants who noticed the yellow needle cap, half dismissed it, most likely because of the open hole at the distal end of the cap, which appears to allow the needle to pass through, as occurs with the EpiPen auto-injector. Further, consistent with the labeled warning and their training, EpiPen auto-injector users habitually did not put their hands near the distal end of the device (let alone remove anything from that end of the device). This is part of the explanation for why all but three of the participants did not even attempt to remove the needle cap. Additionally, although all participants were told that the proposed generic device was not stored in any case, some participants experienced delay and confusion because the proposed generic device appeared as if it must be removed from a clear container prior to use, as is necessary with the EpiPen auto-injector.

Simply stated, the proposed generic device has design features that trigger the learned behaviors associated with the EpiPen auto-injector, and there is no strong design cue to suggest otherwise. The result is an injection attempt that mimics that of the EpiPen auto-injector, but because of important differences in operating principles, results in a failure to deliver therapy.

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2. STUDY BACKGROUND AND OBJECTIVES

2.1 BACKGROUND

Interface Analysis Associates ("IAA") conducted a simulated-use handling study of a proposed epinephrine auto-injector that would serve as a generic alternative for the EpiPen auto-injector. This device would be intended to deliver epinephrine for the emergency treatment of allergic reactions, including anaphylaxis. This proposed epinephrine auto-injector uses the Vibex™ injector platform, and is understood to be very similar to the Vibex™ platform auto-injector used with the drug Otrexup™ (methotrexate). Therefore, this study was conducted using a prototype device based on a photograph of the proposed generic epinephrine auto-injector released by Antares, the manufacturer of the device, and examination of the Otrexup™ product.

Compared to the EpiPen auto-injector, the proposed generic device introduces both design and procedural similarities and differences. The similarities that are familiar to EpiPen auto-injector users could lead to negative transfer effects and result in potential misuse and delayed or failed therapy. In that regard, the differences between the two devices introduce design deviations and additional procedural requirements that, if unnoticed by the user, can lead to delayed or failed therapy. Accordingly, it is possible that EpiPen auto-injector users could attempt to use the proposed generic device, which differs in design and operation from the EpiPen auto-injector, based off their expectations and experience with the EpiPen auto-injector, with a resultant delay or failure in delivering epinephrine. Importantly, this is a product intended for use by patients and caregivers, not medical professionals, in an emergency situation in which the user would be highly agitated and may be experiencing the initial effects of what could be a life-threatening situation. For this reason, the potential for use that is unsafe or ineffective is heightened, as are the potential negative consequences.

Therefore, the purpose of this study was to investigate how patients and caregivers who are trained on, and are familiar with, the EpiPen auto-injector may use the proposed generic epinephrine auto-injector in an emergency.

Vibex Platform Epinephrine Auto-Injector
(http://www.antarespharma.com/files/5813/4693/7448/Investor_Presentation_-_September_2012.pdf)

EpiPen Auto-Injector

2.2 OBJECTIVES

The main objectives of this handling study were to:

- Assess how real EpiPen auto-injector users would react to the proposed generic device in terms of how they would manipulate and handle the device when attempting to inject with it (simulated) for the very first time.
- Assess whether or not EpiPen auto-injector users expect operation of the proposed generic device to mimic the procedures required to use the EpiPen auto-injector.

2.3 STUDY DESIGN OVERVIEW

This study was conducted with a total of 30 participants; 15 of whom were EpiPen auto-injector patient caregivers with knowledge of how to use the EpiPen auto-injector (e.g., parents, siblings, relatives), and 15 of whom were EpiPen auto-injector patients. Of the patients, 9 were adults (age 18 and above), and 6 of whom were juvenile (ages 10-17) EpiPen auto-injector patients. All participants demonstrated their correct knowledge of how to use an EpiPen auto-injector in the course of their screening, although there was variance in their level of training and use experience.

None of the participants were provided training on the proposed generic epinephrine auto-injector prior to their exposure to the device. This is consistent with the expectation that generic product would be substituted at the pharmacy, and no training would be given, nor would the patient/caregiver be prompted or instructed to review the product labeling. Each participant took part in one study session that lasted for approximately 10 minutes. Participants were informed that the device was not an EpiPen auto-injector, but was a generic substitute, and were presented with a scenario in which they were to attempt to use the proposed generic epinephrine auto-injector to rescue another person (caregivers) or themselves (patients) from a severe allergic reaction. Participants were asked to perform a "think-aloud" mock injection, in which they verbalized and gestured their interaction with the device without actually physically manipulating it or performing the injection. This allowed us to study the initial reaction

to, and use of, the proposed generic epinephrine auto-injector during a realistic rescue scenario.

Refer to the Study Methods section and the Test Procedure section for a full description of the study design.

3. DEVICE USER INTERFACE DESCRIPTION

3.1 PROPOSED GENERIC EPINEPHRINE AUTO-INJECTOR

The proposed generic epinephrine auto-injector is a disposable, single-use device intended to allow users to administer a dose of epinephrine into the thigh during an emergency to treat anaphylaxis. It uses the Vibex™ platform, and in that regard is understood to be very similar to the auto-injector used in the drug product, Otrexup™ (methotrexate). Accordingly, because the proposed generic epinephrine auto-injector is not available, this study was conducted using a non-functioning mock-up of the proposed generic that is based on a photograph of a prototype of the epinephrine auto-injector released by Antares, the manufacturer of the auto-injector (see images below), and examination of the Otrexup™ product.

Otrexup™ Injector, to which Proposed Generic Epinephrine Auto-Injector is Very Similar

Prototype of the Vibex™ Platform Epinephrine Auto-Injector

The following is a high level summary of the injection procedure based on the Otrexup™ device. We expect that users will be directed to perform the steps in the following order.

Remove Needle Cap

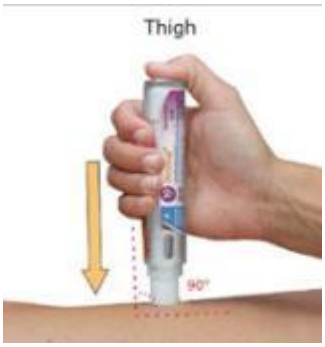
Users are instructed to remove the needle cap by twisting the cap from its body, exposing the needle end.

Remove Safety Clip

Users are then instructed to "flip" the safety clip to remove to ready the device for injection.

Administer the Injection

To administer the injection, the user should place the auto-injector against the thigh at a 90 degree angle and firmly push until a click sounds. Uses are instructed to hold for 10 seconds and remove from the site.



3.2 EPIPEN AUTO-INJECTOR

The EpiPen auto-injector is a disposable, single-dose device (0.3 mg or 0.15 mg) that allows users (primarily patients and caregivers) to administer a dose of epinephrine into muscular tissue in the thigh. As with all epinephrine auto-injectors, the EpiPen auto-injector is intended to allow patients to inject themselves (or caregivers to inject patients for whom they are responsible) to treat anaphylaxis, a potentially life-threatening reaction to a number of triggers, including food, insect stings, and medicines.

EpiPen® Auto-Injector

Remove Safety Release

Users are instructed to grasp the auto-injector with the orange tip pointing downward and to remove the blue safety release by pulling straight up without bending or twisting. Moreover, users are warned NOT to touch the needle end of the auto-injector.

Administer the Injection

To administer, users are instructed to hold the auto-injector with the orange tip near the outer thigh. To deliver a dose, a user should swing and firmly push the orange tip against the outer thigh so it "clicks" AND HOLD on thigh for approximately 10 seconds to deliver the drug.

4. STUDY METHODS

4.1 STUDY METHODS

4.1a User Groups

This study had three (3) main user groups with a total of thirty (30) participants. All participants were well-versed and experienced using the EpiPen auto-injector.

- **Adult Patients (N=9).** This groups contained users age 18 and older who have been diagnosed as at risk of anaphylaxis, and who currently have a prescription for and carry an EpiPen auto-injector.
- **Juvenile Patients (N=6).** This groups contained users aged 10-17 who have been diagnosed as at risk of anaphylaxis, and who currently have a prescription for and carry an EpiPen auto-injector.
- **Caregivers (N=15).** This group consisted of caregivers (e.g., parents, siblings, relatives) of juvenile or adult patients with a prescription for an EpiPen auto-injector.

Table 1: User Group Summary

EpiPen auto-injector Adolescent Patients	EpiPen auto-injector Adult Patients	EpiPen auto-injector Caregivers
N=6	N=9	N= 15

4.1b Training

In order to investigate transfer effects and expectations in circumstances that reflect a likely real-world scenario, none of the participants were provided any training on the proposed generic epinephrine auto-injector prior to their exposure to the device. This is consistent with the expectation that a generic product would be substituted at the pharmacy, and no training would be given, nor would the patient/caregiver be prompted or instructed to review the product labeling. Moreover, participants were not

given any instructional guides for the device. Participants were informed that the device was not an EpiPen® Auto-Injector, but was a generic substitute. This simulates a real-world scenario, where a patient or caregiver prescribed an EpiPen auto-injector might find him/herself in a potentially life-threatening emergency, and will need to use an unfamiliar device on which he/she has received no training. Users would be expected to respond instinctively, relying on their EpiPen auto-injector training and the expectation, reinforced by the design features of the proposed generic device, that the device operates by the same procedures as the EpiPen auto-injector.

4.1c Limitations

The study was conducted with a mock-up of an auto-injector that was the result of best efforts to represent the proposed generic device, based on a picture of the prototype made public by the manufacturer and examination of the Otrexup™ product. The device had no label or labeling, except for a "Needle End" sticker on the body of the device and a faint "2" on the blue safety clip. (See image below for 360° view.) In addition, this study was conducted with participants who were naïve to, and untrained in using, the proposed generic device.

User training on the use of the proposed generic device, user review and comprehension of the full instructions, or user interaction with a device that has labeling on the device body may affect these findings. The implications of the obtained study results would nonetheless remain valid and meaningful. The study provided evidence about the natural design language of the proposed generic device and the expected behavior of current EpiPen auto-injector users, under a real-world substitution scenario – where users will have received training with the EpiPen auto-injector and would respond to an emergency by instinctively implementing their learned behavior (Step 1: Remove blue safety cap; Step 2: Inject drug); they likely will receive no training on the generic product; they are unlikely to read the product labeling or review the label, particularly when responding to an emergency; and they quite likely will assume that the generic device operates identically to the EpiPen auto-injector.

Prototype of the Proposed Generic Auto-Injector Used in This Study

4.2 PARTICIPANT RECRUITMENT & DEMOGRAPHICS

Caregivers and patients, both adults and juveniles, who were proficient in using the EpiPen auto-injector were recruited for this study. Potential participants were asked to verbally describe the EpiPen auto-injector procedure in order to be qualified for the study.

4.2a Exclusionary Criteria

All participants were screened by trained IAA personnel for the following to determine eligibility for the study.

Study Specific Exclusionary Criteria

Potential participants were excluded from the study if:

- Their description of how to use an EpiPen auto-injector was not consistent with the FDA-approved directions for use.
- They self-described their EpiPen auto-injector experience/knowledge level as "Novice" or "Basic."
- They indicated that they were not prescribed and did not carry with them an EpiPen auto-injector (patients).

General Exclusionary Criteria

Potential participants were excluded from the study if they:

- Did not demonstrate the ability to speak, read and understand the English language.
- Were under the age of 10.
- Had any physical or psychological condition that may affect their ability to use the device.

- Showed signs of characteristics that might prevent them from using the device in a safe manner, for example high levels of frustration, or using the device in a non-compliant manner.

Demographic Summary

A total of thirty (30) people, fifteen (15) individuals with a prescribed EpiPen auto-injector and fifteen (15) caregivers to someone with a prescribed EpiPen auto-injector, participated in the study. Our recruitment efforts included phone calls, emails to support groups, posts to online forums, and online advertisements.

The table below outlines the screening parameters, additional criteria applied for inclusion or exclusion in the study, as well as the demographic summary of the study participants. Our screening criteria are broken down into three main categories:

- **Pure Exclusion (E)** – A question asked to all potential participants where a given answer would exclude one from being included in the study.
- **Response Variance (RV)** – A factor that required a mix of specific responses in order to manipulate variance along this factor in the study.
- **FYI** – A question asked to all potential participants where no specific response was required or variance manipulated.

Table 2: Participant Demographic Summary

Factor	Criteria Applied	Participant Demographic Summary
Factors Applicable To Caregivers (N=15)		
Caregiver (E)	All caregivers were screened for whether or not they care for someone with a current prescription for an epinephrine auto-injector. *Excluded if does not care for someone with a current prescription for an epinephrine auto-injector.*	Yes: 15/15 (100%) No: 0/15 (0%)
Device (E)	All caregivers were screened for the type of epinephrine auto-injector the person for whom they care uses. *Excluded if the person for whom they care does not use an epinephrine auto-injector.* *Excluded if they reported the person for whom they care used anything other than an EpiPen auto-injector.*	EpiPen auto-injector: 9/15 (60%) EpiPen Jr. auto-injector: 6/15 (40%)
Gender (RV)	All caregivers were screened for their gender. *A mix of genders was desired.*	Female: 11/15 (73%) Male: 4/15 (27%)
Age (RV)	All caregivers were screened for their age. *A mix of ages was desired.*	Ranged from: 31-72 years Mean Age: 43 years Median Age: 40 years Standard Deviation: 11.66 years
Ethnicity (FYI)	All caregivers were screened for their ethnicity.	African American: 1/15 (7%) Asian: 4/15 (27%) Caucasian: 7/15 (47%) Hispanic: 2/15 (13%) Pacific Islander: 1/15 (7%)
Education (FYI)	All caregivers were screened for their highest level of completed education.	High School: 5/15 (33%) Associate Degree: 3/15 (20%) Bachelor's Degree: 5/15 (33%) Master's Degree: 1/15 (7%) PhD: 1/15 (7%)

Factor	Criteria Applied	Participant Demographic Summary
Factors Applicable To Caregivers (N=15)		
Occupation (FYI)	All caregivers were screened for their occupation.	Administrative Assistant: x1 Bartender: x1 Civil Engineer: x1 Clinical Research Coordinator: x1 • (Pediatric Oncology Patients) Graphic Designer: x1 Homemaker: x3 Human Resources: x1 Neuropsychology: x1 Recreation Leader: x1 Retired: x2 • (Fire Captain) • (Office Manager) Student: x1 Substitute Aide: x1
Training (E)	All caregivers were screened for whether or not they have been trained on how to use the device. *Excluded if they reported having no training with the device.*	No: 0/15 (0%) Yes: 15/15 (100%)
Past Training (FYI)	All caregivers were screened for when they were last trained on their epinephrine device.	Ranged from: 0-22 years ago Mean: 5.13 years ago Median: 1 year ago Standard Deviation: 6.08 years
Trainer (FYI)	All caregivers were screened for who trained them on how to use the device.	Cousin: 2/15 (13%) Daughter: 2/15 (13%) Doctor: 5/15 (33%) Mother of Child: 1/15 (7%) Nurse Practitioner: 2/15 (13%) Pharmacist: 3/15 (20%)
Instructions (FYI)	All caregivers were screened for whether or not they have read the full instructions that come with the device.	No: 7/15 (47%) Yes: 8/15 (53%)
Label on Device Body (FYI)	All caregivers were screened for whether or not they have read the instructions printed on labels affixed to the device body.	No: 3/15 (20%) Yes: 12/15 (80%)

Factor	Criteria Applied	Participant Demographic Summary
Factors Applicable To Caregivers (N=15)		
Observed Injections (FYI)	All caregivers were screened for whether or not they have ever watched someone else perform an injection with the device.	No: 9/15 (60%) Yes: 6/15 (40%)
Device Use (FYI)	All caregivers were screened for whether or not they have ever performed a rescue injection with the device.	No: 13/15 (87%) Yes: 2/15 (13%)
Frequency of Use (FYI)	All caregivers who have performed a rescue injection were screened for how many times they have done so.	2 caregivers reported having used the device: • 2x • 5x Ranged from: 2-5 times Mean: 3.50 times Median: 3.5 times Standard Deviation: 2.12 times
Recent Use of Device (FYI)	All caregivers who have performed a rescue injection were screened for when they last did so.	2013: 1/15 (7%) 2014: 1/15 (7%)
Practice With the Device (FYI)	All caregivers were screened for whether they practice with the device.	No: 3/15 (20%) Yes: 12/15 (80%)
Last Time Practiced Device (FYI)	Those caregivers who reported they practice were screened for when they last practiced using the device.	2013: 2/12 (17%) 2014: 8/12 (67%) 2015: 2/12 (17%)
Practice Frequency (FYI)	Those caregivers who reported they practice were screened for how often they train with the device.	1-2x/year: 6/12 (50%) 3-4x/year: 1/12 (8%) Not Regularly: 5/12 (42%)
Confidence in Using the Device (E)	All caregivers were screened for how confident they are about being able to properly use the device.	Confident: 15/15 (100%)
Rating of Proficiency (E)	All caregivers were asked to rate their experience level on how proficient they consider themselves with the device.	Novice: 0/15 (0%) Basic Knowledge: 0/15 (0%) Intermediate: 0/15 (0%) Expert, I Could Teach Others: 15/15 (100%)

Factor	Criteria Applied	Participant Demographic Summary
Factors Applicable To Patients (N=15)		
Prescription for Epinephrine Auto-Injector (E)	All patients were screened for whether or not they have a current prescription for an epinephrine auto-injector. *Excluded if does not have a current prescription for an epinephrine auto-injector.*	No: 0/15 (0%) Yes: 15/15 (100%)
Device (E)	All patients were screened for the type of epinephrine auto-injector they use. *Excluded if do not use an epinephrine auto-injector injector.* *Excluded if they reported they carried anything other than an EpiPen auto-injector.*	EpiPen auto-injector: 14/15 (93%) EpiPen Jr. auto-injector: 1/15 (7%)
Gender (RV)	All patients were screened for their gender. *A mix of genders was desired.*	Female: 10/15 (67%) Male: 5/15 (33%)
Age (E & RV)	All patients were screened for their age. *A mix of ages was desired.* *Excluded if under 10 years of age.*	Ranged from: 10-56 years old Mean Age: 29.67 years old Median Age: 26 years old Standard Deviation: 17.56 years old
Ethnicity (FYI)	All patients were screened for their ethnicity.	African-American: 1/15 (7%) Asian: 1/15 (7%) Caucasian: 11/15 (73%) Hispanic: 2/15 (13%)
Education (FYI)	All patients were screened for their highest level of completed education.	3rd Grade: x1 4th Grade: x1 5th Grade: x1 6th Grade: x2 9th Grade: x1 High School Diploma: x3 Associate Degree: x2 Bachelor's Degree: x3 Master's Degree: x1

Factor	Criteria Applied	Participant Demographic Summary
Factors Applicable To Patients (N=15)		
Occupation (FYI)	All patients were screened for their occupation.	Caregiver: x2 Cashier: x1 Disability: x2 • Architect • International Business Homemaker: x1 Human Resources: x1 Student: x7 Yard Duty Attendant: x1
Date of Prescription (FYI)	All patients were screened for when they were first prescribed their device.	Ranged from: 0-27 years ago Mean: 8.27 years ago Median: 6 years ago Standard Deviation: 8.37 years ago
Training (E)	All patients were screened for whether or not they have been trained on how to use their device.	No: 0/15 (0%) Yes: 15/15 (100%)
Past Training (FYI)	All patients were screened for when they were last trained on their epinephrine device.	Ranged from: 0-25 years ago Mean: 5.93 years ago Median: 3 years ago Standard Deviation: 6.95 years
Trainer (FYI)	All patients were screened for who trained them on how to use their device.	Doctor: 6/15 (40%) Nurse: 2/15 (13%) Pharmacist: 6/15 (40%) Red Cross: 1/15 (7%)
Instructions (FYI)	All patients were screened for whether or not they have read the full instructions that come with their device.	No: 6/15 (40%) Yes: 9/15 (60%)
Label on Device Body (FYI)	All patients were screened for whether or not they have read the instructions printed on labels affixed to the device body.	No: 0/15 (0%) Yes: 15/15 (100%)
Observed Injections (FYI)	All patients were screened for whether or not they have ever watched someone else perform an injection with the device.	No: 7/15 (47%) Yes: 8/15 (53%)
Epinephrine Usage (FYI)	All patients were screened for whether they ever used their device.	No: 12/15 (80%) Yes: 3/15 (20%)

Factor	Criteria Applied	Participant Demographic Summary
Factors Applicable To Patients (N=15)		
Use Epinephrine Injector (FYI)	Those who reported they have used their device were screened for who performed the injection.	• Mom: x1 • Self-Injected: x2
Frequency of Use (FYI)	Those who reported they have used their device were screened for how many times they have used it.	3 patients reported having used the device: • 1x (Mom) • 2x (self) • 5x (self)
Recent Use of Device (FYI)	All patients who have used the device were screened for when they last used the device.	2014: 1/15 (7%) 2015: 2/15 (13%)
Practice With the Device (FYI)	All patients were screened whether they practice with their device.	No: 3/15 (20%) Yes: 12/15 (80%)
Last Time Practiced Device (FYI)	Those patients who reported they practice were screened for when they last practiced using the device.	2012: 1/12 (8%) 2013: 1/12 (8%) 2014: 9/12 (75%) 2015: 1/12 (8%)
Practice Frequency (FYI)	Those patients who reported they practice were screened for how often they train with their device.	1-2x/year: 11/12 (92%) 3-4x/year: 1/12 (8%)
Confidence in Using the Device (E)	All patients were screened for how confident they are about being able to properly use their device.	Confident: 15/15 (100%)
Rating of Proficiency (E)	All patients were asked to rate their experience level on how proficient they consider themselves with the device.	Novice: 0/15 (0%) Basic Knowledge: 0/15 (0%) Intermediate: 0/15 (0%) Expert, I Could Teach Others: 15/15 (100%)

4.3 TEST ARTICLES

The following materials were used for this study:

Proposed Generic Epinephrine Auto-Injector

Bag (Containing the device)

Mannequin

4.4 Facility, Personnel and Test Environment

4.4a Test Facility and Personnel

All sessions for the study were conducted in the usability testing laboratory owned and operated by Interface Analysis Associates in San Jose, CA. The lab consists of 3 main rooms/areas: 1) Participant Greeting/Reception Room, 2) Test Room, and 3) AV Control Room.

The Participant Greeting Room/Reception is located in the reception area. Here, participants were greeted by the receptionist and asked to read and sign a consent form, and to read a session introduction/overview. Participants were then introduced to the moderator. The moderator gave an introduction, presented the scenario, and then led the participant to the Test Room where the participant was to perform the rescue mock injection presented in the protocol.

The Test Room included four cameras, with two cameras located in line with the participant and recorded to DVD throughout the study.

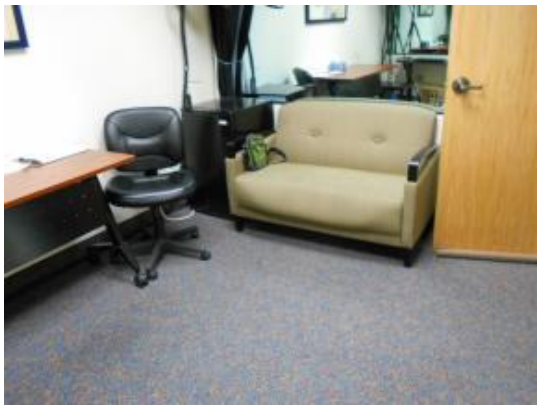
The AV Control Room housed the AV controller and data logger. Between the test room and AV control room is a one-way mirror that allows the test personnel to directly observe the participant. The video and audio channels were fed into the AV control room where the AV controller mixed, and recorded onto 2 digital hard drive recorders (DVR). In addition, this room housed a computer workstation where the data logger recorded real-time observational and performance data.

4.4b Test Room Environment

Before the participant arrived, the test room was set up to simulate a real life home-type atmosphere and to create conditions a patient or caregiver may experience when using the device being tested.

The room was set up with a table, chairs, and a couch. For caregivers, a mannequin was placed on the floor to represent a person suffering from an allergic reaction. For

patients, a couch was set up for them to sit if they were suffering from an allergic reaction to administer a dose. The epinephrine auto-injector was either on the couch or on the floor next to the mannequin, in a nylon carrying bag.



Example of Test Room Setup for Patient

Example of Test Room Setup for Caregiver

4.5 MEASURES

Our measurement plan included the Human Factors triad of measurements - performance, behavior, and subjective experience.

During each session, IAA personnel observed the performance and behaviors of each participant. Participants' subjective narrative and unprompted opinions of the device were transcribed.

4.5a Performance Measures

A successful mock injection was defined as any injection where the participant verbalized and motioned the correct procedure with the proposed generic epinephrine auto-injector.

Overall performance success was achieved when the user verbally prepared and administered the dose. Our measurement plan included observing participants verbalizing the necessary steps to successfully administer an injection using the proposed generic epinephrine auto-injector.

Table 3 below provides an overview of the general steps involved in delivering a dose of epinephrine with the proposed generic epinephrine auto-injector, and the measures related to each step.

Table 3: Measures Observed

Steps	Measures
Remove Needle Cap	Participants were observed verbalizing the need to remove the needle cap.
Remove Safety Clip	Participants were observed verbalizing the need to remove the safety clip.
Orientation of Auto-Injector	Participants were observed which way they oriented the device.
Injection Site	Participants were observed regarding the proper placement of the device (thigh).
Hold Device in Place until Injection is Complete	Participants were observed verbalizing the wait time for injection to be complete.

4.5b Behavioral Measures

Behavioral measures included indices of excessive effort or frustration, verbal comments made by the participant during the study (when applicable) and expressed reactions to the device.

4.5c Unsolicited Comments

Subjective measures included any comments made about the device and its procedure during or after the think-aloud mock injection.

4.6 TEST PROCEDURE

The following is an overview of the study procedure that occurred for all 30 participants.

Before the participant arrived for the session, the test team verified that the Test Room was set up and all supplies were in the room.

Test Room Setup

When the participant arrived, an IAA employee greeted him/her in the Greeting/Reception Room and let the moderator know that the participant had arrived. While waiting, the participant was asked to sign a consent form that gave consent for IAA and the client to record audio and video of the session, and required the participant to not disclose anything about what he/she would learn or use during the session. The participant also read an initial session introduction/overview.

Participant Reception Room

4.6a Procedure

- Before the participant was taken to the Test Room, the study moderator presented an overview that included the nature, context, and focus of the study. The participant was presented with a scenario in which he/she must rescue him/herself (patient) or another person (caregiver) from an allergic reaction using an epinephrine auto-injector that was dispensed as a generic replacement for the EpiPen auto-injector. The participant was asked to perform a "think-aloud mock injection," requiring him/her to verbalize and gesture the rescue without actually physically manipulating or deploying the device.
- Because the participant was tasked with "a think-aloud mock injection" during the study, the moderator simulated how to accomplish this by verbalizing the process of shredding paper as an example. The moderator verbally explained and motioned how he would shred paper using a paper shredder, including how he would power it on, orient the paper, and feed the paper into the machine without actually performing it. This demonstrated how participants should verbalize the rescue injection using the generic epinephrine auto-injector.
- Following, the moderator explained to the participant that upon entering the Test Room, he/she must act fast as though he/she is in a rescue situation, either for him/herself (patient) or another person (caregiver). The participant was again instructed to demonstrate how he/she would perform a rescue injection using the generic epinephrine auto-injector by ***verbalizing*** and ***gesturing*** the procedure, but **not to actually manipulate the device** or perform the injection.
- The participant was then escorted to the Test Room. The participant was observed verbalizing the procedure with attention to whether he/she: removed the needle cap, removed the safety clip, oriented the device

correctly, placed the device in the correct position on the thigh, and held the device down for an adequate amount of time (approximately 10 seconds).

- After completing his/her simulated think-aloud mock injection, the participant was thanked for his/her participation and escorted to the receptionist, who compensated the participant for his/her time ($50) and asked the participant to sign a log confirming receipt of payment.

During all think-aloud mock injections note the following:

- The study moderator was in the room with the participant.

During all study sessions note the following:

- During each session, IAA employees recorded participant interaction, performance, behaviors, and subjective responses in real time.

4.7 Data Storage & Security

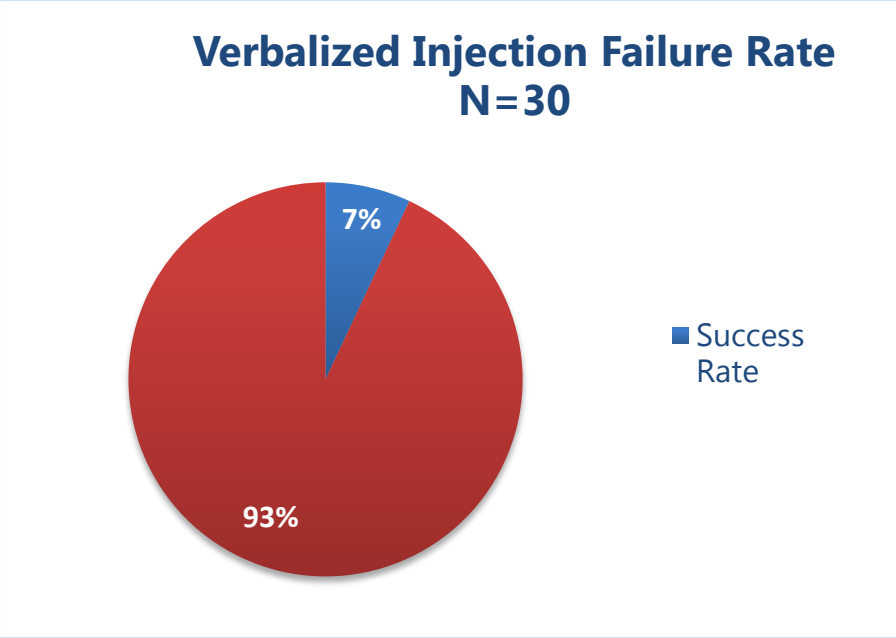
During the study, the data (test prototypes, video files, computer files, written logs, etc.) were stored in IAA's secured, locked test facility.

5. STUDY OBSERVATIONS AND FINDINGS

5.1 SUMMARY OF FINDINGS

Did participants describe the correct procedure with the proposed generic epinephrine auto-injector?

No. All but two participants (28/30) described their intended manipulation of the device in a manner that would have resulted in a failed injection attempt. Thus, the failure rate was 93%. Two participants, both juvenile patients, correctly verbalized their intended manipulation of the generic device to deliver an injection. That is, they stated they would remove both the safety clip and the yellow needle cap prior to injecting. Of the 28 who failed, 27 mimicked the **exact** EpiPen auto-injector procedure, stating they would remove the blue safety clip and nothing else prior to injecting, while one participant suggested removing the yellow needle cap but not the blue safety clip prior to injecting. The overall failure and success rates across the 30 participants are shown below.



Did participants demonstrate any negative transfer from the EpiPen auto-injector to the proposed generic epinephrine auto-injector?

Yes. All but three participants (27/30, 90%) did not verbalize the need to remove the needle cap on the proposed generic. These 27 participants described their interaction with the proposed generic device in the identical manner in which they described their interaction with the EpiPen auto-injector. Simply stated, they verbalized and motioned a procedure which included removal of the blue safety clip followed immediately by the injection into the outer thigh. This is consistent with the EpiPen auto-injector instructions for use, but with the proposed generic device this would lead to a failed injection attempt. This is because the Vibex™ device requires an additional step – to remove a yellow cap that is over the needle end of the device.

5.2 VERBALIZED INJECTION FINDINGS

A total of thirty participants (N=30) were asked to verbalize and simulate an injection using the proposed generic epinephrine auto-injector. Below is a summary of participants' performance on the rescue simulated injection.

Verbalized Injection Procedure Performance

All but two participants (28/30) described their intended manipulation of the device in a manner that would have resulted in a failed injection attempt. Thus, the failure rate was 93%. The following summarizes the results for each performance metric.

- Two participants (2/30) correctly articulated the injection procedure, producing a 7% success rate.
- Three participants (3/30, 10%) correctly verbalized the need to remove the yellow needle cap on the device.
- Ninety-six percent of participants (29/30) correctly verbalized the need to remove the blue safety clip on the device.

- All participants (30/30, 100%) correctly verbalized/held the auto-injector in the correct orientation.
- All participants (30/30, 100%) correctly verbalized and placed the auto-injector on the thigh.
- Additionally, all participants (30/30, 100%) correctly verbalized an adequate hold time amount (10 seconds) before removing the auto-injector from the site.

Observations

Most participants first noticed the familiar blue safety clip and attempted to remove that almost immediately. Although some of the participants (n=6) noticed the yellow needle cap and a few (n=3) explicitly contemplated its purpose, all but three participants ultimately concluded that the needle would extend through the opening in the cap, as occurs with the EpiPen auto-injector. The photos below show a comparison of the EpiPen auto-injector and generic device needle end.

Yellow Needle Cap on Generic with Hole

EpiPen Auto-Injector Needle End with Hole Through Which Needle Protrudes

Before entering the rescue scenario room, participants were told that the proposed generic device was not stored in any case. Nonetheless, three (3) participants thought that the device was inside of a clear container, which is how the EpiPen auto-injector is packaged. This design element created additional confusion that resulted in a delay to the process, as the user tried to figure out how the device would be removed from the

outer container. The photo below shows a side-by-side image of an EpiPen auto-injector in its carrier case next to the clear bodied proposed generic device.

EpiPen auto-injector in Case (above) and Generic Device Itself (below)

IAA Analysis

The results of the study confirmed our prior prospective analysis of the implications of the design similarities and differences between the two devices. Because the proposed generic device has design features similar to those of the EpiPen® Auto-Injector, such as a nearly identical looking and familiar safety clip, the participants assumed the device operation to be the same as that of the EpiPen auto-injector.

Accordingly, they removed the blue safety clip and nothing else before demonstrating how they would jab the device into the outer thigh to initiate the injection. Of the small number of participants who noticed the yellow needle cap, half dismissed it, most likely because of the open hole at the distal end of the cap, which appears to allow the needle to pass through, as occurs with the EpiPen auto-injector. Further, consistent with the labeled warning and their training, EpiPen auto-injector users habitually did not put their hands near the distal end of the device (let alone remove anything from that end of the device). This is part of the explanation for why all but three of the participants did not even attempt to remove the needle cap. Additionally, although all participants were told that the proposed generic device was not stored in any case, some participants experienced delay and confusion because the proposed

generic device appeared as if it must be removed from a clear container prior to use, as is necessary with the EpiPen auto-injector.

Simply stated, the proposed generic device has design features that trigger the learned behaviors associated with the EpiPen auto-injector, and there is no strong design cue to suggest otherwise. The result is an injection attempt that mimics that of the EpiPen auto-injector, but because of important differences in operating principles, results in a failure to deliver therapy.

Generic Device Example of Yellow Needle Cap with Hole

For all performance measures and user comments made during the session refer to section 5.2a and section 5.2b below.

5.2a Verbalized Injection Findings - Performance Measures

The following table reports the performance measures observed regarding the proposed generic device procedure.

	EpiPen auto-injector Patients (N=15)		EpiPen auto-injector Caregivers N=15	Overall (N=30)
	Juvenile (N=6)	Adult (N=9)		
Correct procedure verbalized	2/6 (33%)	0/9 (0%)	0/15 (0%)	**2/30 (7%)**
Incorrect Procedure verbalized	4/6 (67%)	9/9 (100%)	15/15 (100%)	**28/30 (93%)**
• Failure to verbalize remove needle cap	4/6 (67%)	9/9 (100%)	14/15 (93%)	**27/30 (90%)**
• Failure to verbalize remove safety clip	0/6 (0%)	0/9 (0%)	1/15 (7%)	**1/30 (3%)**
• Failure to verbalize/hold correct orientation	0/6 (0%)	0/9 (0%)	0/15 (0%)	**0/30 (0%)**
• Failure to verbalize/show correct injection site	0/6 (0%)	0/9 (0%)	0/15 (0%)	**0/30 (0%)**
• Failure to verbalize adequate hold time (10 seconds)	0/6 (0%)	0/9 (0%)	0/15 (0%)	**0/30 (0%)**

5.2b Verbalized Injection Findings - Subjective Comments

The following are unsolicited comments made by participants regarding the proposed generic device during their verbalized mock injection.

- *P3 (Caregiver) – It looks like this is probably the casing, I would just pop it out and get the device out.*
- *P7 (Caregiver) - It almost looks like you have to take this yellow piece off but I'm going to go off what I know and base it off my normal one (EpiPen).*
- *P9 (Caregiver) - Kind of weird looking. I wasn't sure if there were any buttons or anything.*
- *P18 (Adult Patient) - It looks like a regular one (EpiPen).*

6. IAA OVERALL CONCLUSIONS

6.1 IAA CONCLUSIONS

The purpose of this study was to assess how real EpiPen auto-injector users would react to the proposed generic device in terms of how they would manipulate and handle the device when attempting to inject with it (simulated) for the very first time. Additionally, we assessed whether participants expected the proposed generic device to mimic the procedure required of the EpiPen auto-injector by observing 30 participants attempt to rescue another person or themselves from a severe allergic reaction, using the proposed generic epinephrine auto-injector. The study results confirmed that EpiPen auto-injector users given the generic device are likely to fail to inject on their first injection attempt using the proposed generic device. The vast majority (90%) of participants mimicked the exact EpiPen auto-injector procedure, stating they would remove the blue safety clip and nothing else prior to injecting.

Our analysis concluded that the similar design elements (blue safety clip) associated with the EpiPen auto-injector may have influenced expectations with the generic device. Additionally, the design and procedure deviations (yellow needle cap removal) introduced an additional step and was overlooked 90% of the time, likely due to the open hole at the distal end of the cap, a design feature similar to the EpiPen auto-injector. Further, despite being told that the proposed generic device was not stored in any case, some participants experienced delay and confusion because the proposed generic device appears as if it must be removed from a clear container prior to use, as is necessary with the EpiPen auto-injector.

Simply stated, the proposed generic device has design features that trigger the learned behaviors associated with the EpiPen auto-injector, and there is no strong design cue to suggest otherwise. Indeed, because the proposed generic device likely will be substituted at the pharmacy without training, and because users are unlikely to review the labeling or label (especially in an emergency), and can be expected to assume the substituted generic works the same as the EpiPen auto-injector, it is unlikely that

labeling would overcome the design cues that trigger the learned EpiPen auto-injector behaviors. The result is an injection attempt that mimics that of the EpiPen auto-injector, but because of important differences in operating principles, results in a failure to deliver therapy.

Although user training on the use of the proposed generic device, user review and comprehension of the full instructions, or user interaction with a device that has labeling on the device body may affect these findings, it would be in terms of the number of failures, but not whether failures occur. The implications of the obtained study results would nonetheless remain valid and meaningful with regard to the suitability of the proposed device as a generic alternative to the EpiPen auto-injector. That is, the study provided evidence regarding the natural design language of the proposed generic device and the expected behavior of current EpiPen auto-injector users under a real-world substitution scenario – where users will have received training with the EpiPen auto-injector and would respond to an emergency by instinctively implementing their learned behavior (Step 1: Remove blue safety cap; Step 2: Inject drug); they likely will receive no training on the generic product; they are unlikely to read the product labeling or review the label, particularly when responding to an emergency; and they quite likely will assume that the generic device operates identically to the EpiPen auto-injector. Indeed, the results of this study confirm that users would assume that the proposed generic device operates the same as the EpiPen auto-injector.[1]

This is not to suggest that every patient or caregiver prescribed an EpiPen auto-injector, if dispensed the proposed generic epinephrine auto-injector, would experience a meaningful delay or complete failure in delivering an injection. We are concluding, however, that the proposed generic device will produce a predictable number of

[1] Interestingly, the specific scenario tested in this study was anecdotally confirmed as a valid context of use when one of the participants (patient) recognized that she had recently been dispensed a different epinephrine auto-injector (a generic to Adrenaclick, not EpiPen auto-injector) when she submitted her prescription renewal for an EpiPen auto-injector. She said she had not received any introduction to, let alone training on, the substituted device, and had not even looked at the device, or even read the instructions, because she had assumed it worked like her EpiPen auto-injector. With her consent, we opened the carrier tube for her device, and asked how she would use it. She first said she would follow the EpiPen auto-injector procedure, but the moderator then pointed out that her device did NOT operate like her EpiPen auto-injector and required her to remove two caps, one on each end of the device. The participant was surprised at the additional steps and felt that she would need to "retrain herself mentally."

injection failures (or delays in therapy) attributed directly to the product's specific design similarities and deviations relative to the EpiPen auto-injector.

7. IAA CONTACT INFORMATION

Interface Analysis Associates (IAA) is a human factors, ergonomics, and usability consulting firm. IAA specializes in the research, design, testing, and analysis of software and hardware user interfaces, computer and other high technology consumer products, medical devices, office environments, and aerospace systems.

IAA believes that interface design, ergonomics, and usability dramatically impact the utility of a product or work environment, as measured by the productivity, satisfaction, and safety of those who interact with it. To each project IAA brings the highest level of knowledge in interface design, human factors, ergonomics, and usability testing, along with the practical skills necessary to pragmatically apply theory and principle to product and workplace research, design, testing, and analysis.

IAA's goal is to make the interaction between people, products, and the environment safe, productive, and satisfying.