MULTIDISCIPLINARY REVIEW

Application Type	NDA
Application Number(s)	201739, S-008 201739, S-009
Priority or Standard S-008 S-009	 Priority (6 months) Standard (6 months)
Submit Date(s) S-008 S-009	 May 19, 2017 May 19, 2017
Received Date(s) S-008 S-009	 May 19, 2017 May 19, 2017
PDUFA Goal Date(s) S-008 S-009	 November 17, 2017 November 17, 2017
Review Discipline/Division/Office Clinical Clinical Pharmacology	 DPARP/OND OTS/OCP/DCPII
Reviewer Name(s) Clinical Clinical Pharmacology	 Peter Starke, MD Yunzhao Ren, MD, PhD
Review Completion Date	September 26, 2017
Established Name	Epinephrine injection, USP, 0.1 mg
Trade Name	Auvi-Q
Therapeutic Class	Catecholamine: alpha and beta adrenergic agonist
Applicant	Kaléo
Formulation(s)	Auto-Injector with solution for injection
Dosing Regimen	0.1 mg IM or SC
Proposed Indication(s)	Emergency [self or caregiver] treatment of severe allergic reactions (Type I) including anaphylaxis
Intended Population(s)	Weight range: ≥7.5 to 15 kg, corresponding to ~1 to ~3 years of age
Recommended Regulatory Action S-008 S-009	 Approval Approval

SUBMISSIONS REVIEWED IN THIS DOCUMENT			
Document Date	**CDER Stamp Date**	**Submission**	**Comments**
May 19, 2017	May 19, 2017	SD-652	Supplement S-008, for 0.1 mg dosage strength
May 19, 2017	May 19, 2017	SD-653	Supplement S-009, for changes to voice prompts and shortening hold time to 2 seconds
June 6, 2017	June 6, 2017	SD-656	Response to Agency's IND advice fax of May 10, 2017
July 18, 2017	July 18, 2017	SD-669	Response to IR of July 7, 2017; Upgrade S-008 from CMC to Efficacy supplement
July 19, 2017	July 19, 2017	SD-670	Update to S-008, deleting labeling to be submitted to S-009
July 19, 2017	July 19, 2017	SD-671	Update to S-009, adding labeling previously submitted to S-008
July 19, 2017	July 19, 2017	SD-672	ISS and ISE
July 21, 2017			*Clinical IR*
July 28, 2017	July 28, 2017	SD-676	Response to Clinical IR

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1 Recommendations

1.1 Recommendation(s) on Regulatory Action

Clinical

The Clinical Reviewer recommends Approval of supplements S-008 and S-009.

Clinical Pharmacology

The Office of Clinical Pharmacology (OCP) reviewer recommends approval of the proposed fixed-dose of 0.1 mg epinephrine for use in children with a body weight of 7.5 kg to <15 kg.

1.2 PREA and Pediatric Recommendations

Auvi-Q® (epinephrine injection, USP) is an epinephrine auto-injector (EAI) that is approved for the emergency treatment of severe allergic reactions including anaphylaxis. Two dosage strengths of Auvi-Q are approved: a 0.3 mg dosage strength for patients who weigh 30 kg (66 lbs) or more, and 0.15 mg dosage strength for patients who weigh ≥15 to 30 kg (≥33 to 66 lbs). Approval of these dosage strengths (0.3 and 0.15 mg) did not trigger PREA because they did not represent new active ingredient, indication, dosage form, dosing regimen, or route of administration.

The Agency has long recognized that there is a public health need for a lower dosage strength of an EAI for use in patients who weigh less than 15 kg, because this corresponds to an age range in which anaphylaxis occurs and there are currently no prepackaged (i.e., prefilled syringe) epinephrine products available that are designed for convenient and immediate parent or caregiver use in the outpatient setting while seeking further medical care. The only alternative for emergent treatment of these patients is for parents or caretakers to administer epinephrine that has been drawn up from a vial with a needle and syringe, a treatment modality that is well-recognized as associated with frequent medication and dosing errors as well as stability issues if the epinephrine has been drawn up in advance. Alternatively, dosage strengths intended for patients who weigh between 15-30 kg are often recommended and/or used in these patients, but use of these products places patients at risk of the needle hitting bone as well as safety issues from using a dose that is higher than intended. As a result, the Agency performed pharmacokinetic / pharmacodynamic (PK/PD) modeling with the aim of determining the most appropriate dosage and weight range for a fixed-dose EAI product that would be intended for use in patients who weigh less than 15 kg. In addition, the Agency held discussions with the manufacturers of the US-approved EAI products, requesting them to consider development of a fixed 0.1 mg dosage strength of their product that could be marketed for the treatment of anaphylaxis in patients who weigh less than 15 kg.

The Division believes that the new Auvi-Q 0.1 mg dosage strength that is part of supplement S-008 triggers PREA because the new dosage strength represents a new

dosing regimen that will be used in patients who weigh between 7.5 and 15 kg, corresponding to children who are approximately 1 to 3 years of age. An agreed iPSP, which was previously reviewed by the Pediatric Review Committee (PeRC), was submitted with the supplement. No clinical studies are/were needed. The iPSP included: 1) literature to support PK/PD modeling, which supports the use of a fixed-dose of 0.1 mg for patients who weigh 7.5 to <15 kg, and 2) an sonographic study that supports the safety of the exposed needle length proposed for the new dosage strength, such that when the new dosage strength is administered as directed in the mid antero-lateral thigh it will not hit bone (major safety risk). This information was submitted with the supplement, and the Division believes that this fulfills the PREA requirement for patients who weigh 7.5 kg and above, because the 0.1 mg dosage strength (along with the approved 0.15 mg and 0.3 mg dosage strengths) cover all of the pediatric weight / age range above 7.5 kg or 1 year of age.

Since a standardized (fixed) dose is not appropriate for patients who weigh less than 7.5 kg, and since vial formulations of epinephrine that allow for appropriate weight-based dosing are available, the Division recommends granting a waiver under PREA for patients who weigh less than 7.5 kg, corresponding to children who are less than approximately 1 year of age.

The Division discussed the two supplements with PeRC on September 6, 2017. PeRC agreed with the Division's recommendations.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None

1.4 Recommendations for Postmarket Requirements and Commitments

None. Kaléo already has two PMCs to develop appropriate device reliability requirements for Auvi-Q, which were agreed to with approval of the CMC supplement in early 2017, just prior to reintroduction of the device after the 2015 voluntary recall.

2 Introduction and Regulatory Background

2.1 Introduction and Background

This is a multidisciplinary review of two supplements that were simultaneously submitted by Kaléo on May 19, 2017, for Auvi-Q® (epinephrine injection, USP), NDA 201739, S-008 and S-009. Supplement S-008 is for a new 0.1 mg dosage strength of Auvi-Q® that is intended for use in patients who weigh ≥7.5 to 15 kg (≥16.5 to 33 lbs), corresponding to patients who are approximately 1 to 3 years of age, and Supplement S-009 deals with modifications to the instructions for use for Auvi-Q, changing the voice prompts embedded in the computer chip and shortening the hold time instruction from 5 to 2 seconds.

Auvi-Q is a single-dose epinephrine auto-injector (EAI) that is approved and marketed in the United States (NDA 201739, approved August 10, 2012) and Canada (where it is marketed under the name Allerject) for the emergency treatment of severe allergic reactions including anaphylaxis. Two dosage strengths are approved: a 0.3 mg dosage strength for patients who weigh 30 kg (66 lbs) or more, and 0.15 mg dosage strength for patients who weigh ≥15 to 30 kg (≥33 to 66 lbs). Note that ownership of the NDA for Auvi-Q was transferred from Sanofi to Kaléo in March 2016.

S-008

Supplement S-008 is a prior approval supplement for a new 0.1 mg dosage strength of Auvi-Q® that is intended for use in patients who weigh ≥7.5 to 15 kg (≥16.5 to 33 lbs), corresponding to patients who are approximately 1 to 3 years of age. The supplement was submitted as a CMC supplement but was modified to be a 505(b)(2) efficacy supplement because, from a regulatory perspective, the supplement requires evaluation by the Agency of the efficacy and safety, as well as labeling, of the proposed new dosage strength for this new population, i.e., the supplement relies on the published literature to support that the proposed fixed 0.1 mg dosage strength is appropriate for the proposed range of weights between 7.5 to 15 kg (see further details below). It also requires review of a sonographic study to support the proposed exposed needle length.

The Agency has long recognized that there is a public health need for a lower dosage strength of an EAI for use in patients who weigh less than 15 kg, because this corresponds to an age range in which anaphylaxis occurs (Lane and Bolte 2007) and there are currently no prepackaged (i.e., prefilled syringe) epinephrine products available that are designed for convenient and immediate parent or caregiver use in the outpatient setting while seeking further medical care (Cheng 2011) (Sicherer, Simons et al. 2007) (Simons 2004) (Simons 2005) (Simons 2007). The only alternative for emergent treatment of these patients is for parents or caretakers to administer epinephrine that has been drawn up from a vial with a needle and syringe, a treatment modality that is well-recognized as associated with frequent medication and dosing errors (Chime, Riese et al. 2017) (Simons, Chan et al. 2001) as well as stability issues if the epinephrine has been drawn up in advance (Rawas-Qalaji, Simons et al. 2009). Alternatively, dosage strengths intended for patients who weigh between 15-30 kg are

often recommended and/or used in these patients (Halbrich, Mack et al. 2015), but use of these products places patients at risk of the needle hitting bone (Leyland and Severance 1991) (Kim, Nevis et al. 2014) (Kim, Dinakar et al. 2016) as well as safety issues from using a dose that is higher than intended (Simons 2006) (Lane and Bolte 2007).

As a result, the Agency performed pharmacokinetic / pharmacodynamic (PK/PD) modeling with the aim of determining the most appropriate dosage and weight range for a fixed-dose EAI product that would be intended for use in patients who weigh less than 15 kg. The modeling was based on data from studies published in the literature (see Section 4.2) [*Editorial note*: Thank you, Estelle Simons]. The literature upon which the Agency performed the modeling, and upon which this supplement also relies, is the same literature that supported approval of Adrenalin vials (NDA 204200 and NDA 204640, Par Sterile Products) in 2012, the only difference being that the same literature-based PK/PD modeling performed by the Agency that supported approval of weight-based dosing of 0.01 mg/kg for treatment of anaphylaxis when epinephrine is drawn up from a vial, also supports that a unit-dose of 0.1 mg would be safe and effective when used in patients within the weight range of 7.5 and 15 kg. It was because the Agency had [previously] performed this analysis that the Division could both approve the Adrenalin application and advise companies, including Kaléo, that a 0.1 mg dosage strength would in fact be appropriate for patients who weigh 7.5 to 15 kg.

A few years ago, the Agency held discussions with the manufacturers of the US-approved EAI products, requesting them to consider development of a fixed 0.1 mg dosage strength of their product that could be marketed for the treatment of anaphylaxis in patients who weigh less than 15 kg. The Agency explained that companies would need to develop a product that would reliably deliver the new dose (presumably, the new dosage strength would be an extension of their current product line), propose a lower weight bound for the 0.1 mg fixed dose based on the literature, and provide [sonographic or other] data to support the safety of the proposed exposed needle length (i.e., that the proposed needle length would allow safe delivery to either the subcutaneous (SC) and/or intramuscular (IM) compartment without hitting bone when injected into the mid anterior thigh). As part of this process, the Division explored the possibility of issuing a Written Request under the Best Pharmaceuticals for Children Act (BPCA) to perform the required sonographic study and develop the new product. However, the Agency determined that, because no clinical studies would be required (a sonographic study does not qualify as a clinical study because it would not use actual drug product and no medication would be administered to patients), the Agency could neither offer companies the chance for obtaining Pediatric Exclusivity under BPCA, nor could the companies claim exclusivity based on submission of the sonographic study.

In response, Kaléo notified the Agency of its intention to develop a new Auvi-Q 0.1 mg presentation. During several rounds of interactions with the Agency, they proposed a lower weight bound of 7.5 mg (to which the Agency agreed), and (based on the Agency's feedback regarding study design) performed the requested ultrasound study prior to proposing the exposed needle length for the new dosage strength. As requested, they also submitted an iPSP in advance of submission of the supplement (see Section 2.2 for further details).

With the submission, Kaléo has requested a priority review of this supplement. Given the recognized public health need for this new dosage strength, a priority review is considered appropriate and was agreed to by the Agency in the 74-day letter.

The submission is all electronic in eCTD format, and was received on May 19, 2017. The PDUFA date is November 17, 2017.

S-009

Supplement S-009 is a prior approval labeling supplement to change the Prescribing Information (PI), Patient Information Leaflet (PIL), Instructions for Use (IFU), and the programming of the voice prompts embedded in the Auvi-Q computer chip. As part of this supplement, Kaléo has taken the opportunity to update the language in the IFU, and include [among other changes] shortening of the hold time for all the dosage strengths from 5 seconds to 2 seconds. The proposed changes to the voice prompts correspond with those proposed for the written Instructions for Use. Supplement S-009 coordinates with S-008 such that the changes to the instructions for use are being implemented for the Auvi-Q 0.3 and 0.15 mg dosage strengths at the same time as introduction of the new 0.1 mg dosage strength [which also has those changes].

The submission is all electronic in eCTD format, and was received on May 19, 2017. The PDUFA date is the same as for S-008, November 17, 2017.

2.2 Summary of Presubmission Regulatory Activity

S-008

At a teleconference held with Sanofi on June 4, 2013, the Agency expressed that we had made the determination that there is a public health need for a lower dosage strength of epinephrine auto-injectors for use in the pediatric population of patients less than 15 kg in weight who may experience anaphylaxis. The Agency outlined a regulatory path forward that would not require clinical studies, and noted that we would be happy to provide further interactions regarding development of the new dosage strength if so desired. It should be noted that the Agency made it clear to the manufacturers of each of the approved EAI products that this path was available to them should they choose to pursue drug development.

Following that, Sanofi notified the Agency that they were interested in pursuing development of a new lower dosage strength of Auvi-Q, opened an IND (IND 119,686) in October 2013, and had multiple interactions with the Agency regarding the development program over the next 3½ years. With opening of the pre-IND, they submitted a meeting request to discuss development of the new dosage strength, to which the Agency responded with written responses in November 2013. Sanofi proposed to develop the 0.1 mg dosage strength for patients (b) (4) kg by (b) (4) Sanofi asked whether a Written Request could be issued as part of development of the product.

The Agency responded that a Written Request could not be issued because it had been determined that a clinical investigation in the proposed age (weight) group would not be required to support the application. The Agency agreed that, given the published pharmacokinetic data that shows that epinephrine PK is linear across a wide range of ages and weights (Clutter, Bier et al. 1980), as well as published PK data in children (Simons, Gu et al. 2002) as well as PD data that show similar effects on various measurable parameters (Simons, Gu et al. 2002), PK/PD modeling supports that a 0.1 mg dosage strength would be appropriate for patients who weigh approximately (b) (4) kg. However, the Agency outlined that support would be needed for an exposed needle length for this dosage strength to assure that the proposed exposed needle length would not hit bone, and that the support would need to come from an ultrasound study that mimics the way the proposed product would be used in the proposed weight range (i.e., after compression of the skin of the upper thigh in a manner similar to what would occur when the device is triggered).

A second written interaction occurred in October of 2014, at which time the Agency responded to questions related to the lower weight bound for a 0.1 mg dosage strength. Sanofi proposed a lower weight bound of (b) (4) kg, to which the Agency responded that PK/PD relationships in children weighing less than 15 kg suggest that a dose of 0.1 mg can be safely and effectively administered to children in the weight range of 7.5 to 15 kg, but that children weighing under 7.5 kg should be administered a lower dose. As such, the Agency recommended that the lower weight limit for a 0.1 mg dosage strength be fixed at 7.5 kg. The Agency also reaffirmed the need for a sonography study to determine the appropriate exposed needle length rather than using the same exposed length as the current 0.15 mg dosage strength product along with (b) (4) .

In February of 2015, the Agency responded to additional questions related to the proposed sonography study, at which time Sanofi was informed that the new dosage strength would likely trigger PREA, and recommended submission of a Pediatric Study Plan (PSP), “so that we can come to agreement on your pediatric plan prior to the submission of the supplement.” Sanofi subsequently submitted a PSP, which was agreed to on February 1, 2016.

Sponsorship of the IND changed from Sanofi to Kaléo effective as of March 23, 2016, at the same time that ownership of the NDA for Auvi-Q was transferred from Sanofi to Kaléo.

Additional questions were answered in written responses to Kaléo in June 2016, at which time the Agency responded to questions about a Priority review and PDUFA fees. While the Agency agreed that anaphylaxis is a serious condition and that there is a public health need for the lower dose epinephrine product, the Agency stated that a Priority review determination could only be made after submission of the supplement (note that a Priority review was granted after the application was submitted). Sanofi was referred to the User Fee office to discuss the user fee requirements. Through each of these interactions, the written responses included that the regulatory pathway would be via a 505(b)(2) application.

S-009

This supplement includes changes to the PI, PIL, IFU, and programming the embedded computer chip voice prompts, including [among other changes] to shorten the hold time for all the dosage strengths from 5 seconds to 2 seconds.

The supplement was submitted in partial response to a safety issue first identified in 2015, and published in 2016, regarding lacerations and embedded needles caused by epinephrine auto-injector use in young children who are uncooperative and kick or move during an injection (Brown, Tuuri et al. 2016) (Brown and Tuuri 2016). In response, the Agency opened a tracked safety issue (TSI 1541), notified all of the manufacturers of epinephrine auto-injectors, requested data regarding events that had been reported as well as suggestions for possible solutions, and eventually requested FDAAA safety labeling changes (SLC) for all of the products. The Agency also requested information related to the hold time instruction in the IFU, including the specification for and data related to the injection dispensing time. Safety labeling changes were made for each of the products on May 16, 2016, including shortening of the hold time instruction whenever possible.

The safety labeling changes for Auvi-Q were made as part of supplement S-004. While no cases of lacerations were reported with Auvi-Q, one case of a bent needle was reported. Sanofi noted that the Auvi-Q instructional system includes a printed label with instructions on the side of the device, along with electronic voice instructions and an accompanying LED, all of which provide audiovisual feedback to guide the user through correct administration. Sanofi pointed out that Auvi-Q has a retractable needle that fully retracts into the housing once the injection is complete, minimizing the likelihood of lacerations due to a caregiver trying to hold in the product place on the leg for an extended period of time or re-insert an exposed needle into the skin of a child who is struggling against an injection. They noted that the hold time instruction of 5 seconds is built into the Auvi-Q computer chip, whereas the actual injection dispensing time is much shorter and the specifications call for an injection dispensing time of no more than (NMT) $^{(b)}_{(4)}$ seconds. As a result, changes to the instructions for use would take time to accomplish. Sanofi committed to reprogramming the computer chip to shorten the hold time for all the dosage strengths at the same time as they introduce the 0.1 mg dosage strength.

In October 2016, Kaleo submitted a request to the IND for Auvi-Q 0.1 mg dosage strength, requesting that the Agency provide feedback on proposed changes to the instructions for use, voice prompts, and carton container labels. A brief description of a proposed Human Factors validation study for the voice prompts was provided. In response, a brief clarification teleconference was held in December 2016. Kaléo submitted an additional request for feedback on the proposed graphics for the carton and container labeling in March 2017. CDRH reviewed the initial submission, the Division of Medication Error Prevention and Analysis (DMEPA) reviewed the second submission, and a unified response was sent by the Agency on May 9, 2017.

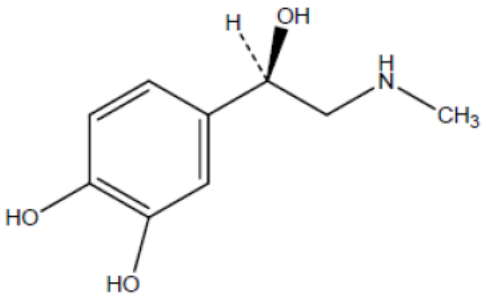
3 Summary of Information from Other Review Disciplines

3.1 Chemistry Manufacturing and Controls / Device

3.1.1 Drug substance

The drug substance [API] used in Auvi-Q is manufactured by (b) (4) (DMF# (b) (4) .

The active ingredient in Auvi-Q is epinephrine [API is epinephrine free base], a phenylethylamine in the class of naturally occurring endogenous hormones and neurotransmitters called catecholamines, which include epinephrine, norepinephrine, and dopamine. Epinephrine is produced by the adrenal medulla. Epinephrine is a non-selective (both alpha and beta) adrenergic receptor agonist that results in the physiologic effects of vasoconstriction, increased peripheral vascular resistance, increased cardiac contractility and heart rate, decreased mediator release, and bronchodilation. The chemical formula of epinephrine is $C_9H_{13}NO_3$, and its chemical structure is shown below. The chemical structure consists of benzene ring and an ethylamine side chain.



(b) (4)

In the United States, the term epinephrine is the preferred name for this chemical, and the United States Approved Name (USAN) and International Nonproprietary Name (INN) is epinephrine. However, the British Approved Name (BAN) and European Pharmacopoeia (EP) term is adrenaline [with an e]. Pharmaceuticals that mimic the effects of epinephrine are termed 'adrenergics', and their receptors are called 'adrenergic receptors'. As a result, both epinephrine and adrenaline are terms used in the literature, whereas Adrenalin® [without an e] is the registered trade name for an approved epinephrine drug product in the United States.

3.1.2 Drug Product

Auvi-Q is a gas-powered auto-injector that contains a single dose of sterile epinephrine injection, USP at a concentration of 0.1 mg/mL. Auvi-Q also contains a computer chip, speaker, and LED that provide auditory and visual feedback during use. The proposed 0.1 mg dosage strength uses the same formulation as the approved Auvi-Q 0.3 mg and 0.15 mg dosage strengths. The formulation includes epinephrine, sodium chloride, sodium bisulfite, HCl qs to pH 2.2-5.0, and water for injection. Changes to the device are contained within device masterfile (MAF-1570), which is now contained within the NDA.

The 0.1 mg dosage strength uses a slightly modified Auvi-Q device. As with the other Auvi-Q dosage strengths, the product contains 0.76 mL of sterile epinephrine injection solution that has been aseptically filled into a (b) (4) glass cartridge and enclosed by an (b) (4) (primary container closure) (Figure 1). The needle remains 23 gauge. The main difference between this and the other dosage strengths is the (b) (4) and thereby limits the dose to 0.1 mL (0.1 mg) and provides a shorter exposed needle length. Other device attributes remain the same.

Based on the sonographic study, Kaléo is proposing an exposed needle length of 0.29 inches (~7.27 mm) for this dosage strength, as compared with exposed lengths of 0.63 inches and 0.50 inches for the 0.3 mg and 0.15 mg dosage strengths, respectively. Note: The specifications for the new dosage strength call for an exposed needle length within the range of (b) (4) to (b) (4) inches [3.2.P.5.1, Specifications.pdf, p3], as measured and verified by a high-speed video camera with a verified frame rate [maf-1570-15-3.pdf, p2], and verification testing shows that the product has an average exposed needle length of (b) (4) inches [maf1570-section 15.pdf, T15.1-6, p21].

Of note, although the specifications call for completion of both dispensing and needle retraction within (b) (4) seconds [dispensing time NMT (b) (4) ms], because there is less volume to dispense in the 0.1 mg dosage strength product, the actual (i.e., measured) dispensing and needle retraction times for this dosage strength are slightly shorter than those for the 0.3 and 0.15 mg dosage strengths, and all strengths are well below the actual specification limit [maf1570-section 15-2.pdf, p10-11]. Both the specification and the actual times support an injection countdown time (i.e., instruction to hold the product in place) of 2 seconds after activation, although the current hold instruction is for a countdown time of 5 seconds.

Figure 1. Diagram of the key components of Auvi-Q
Source: maf1570-section12.pdf, F12.1.1, p1

Kaleo had requested 18-months expiration dating for the drug product ((b) (4) months for the drug constituent) when stored at the recommended label storage conditions of 20° to 25° C (68° to 77° F). This is the same as currently approved for the 0.3 and 0.15 mg dosage strengths. To support the proposed expiry dating, Kaléo submitted stability data from 21 months of storage under longer term (25° C / 60% RH). Given that the drug constituent component has not changed with this new dosage strength, the proposed expiry dating period seems reasonable, although as of completion of this review a decision regarding the expiry dating has not been made.

3.1.3 Voice Prompt Changes

As noted above, Kaléo submitted changes to the written Instructions for Use (IFU) along with corresponding changes to the voice prompts embedded in the computer chip for all of the Auvi-Q devices. The proposed changes to the IFU and the voice prompts were reviewed by the Division and by CDRH, and were found to be acceptable.

A small Human Factors validation study was performed to support the changes. The study included 47 participants, 17 pharmacists/pharmacy technicians, 15 parents of children under 5 years old with severe allergies, and 15 pediatric participants (7 to 10 years) with severe allergies. The EAI devices used in the study did not contain a needle or gas cylinder to power an injection, but otherwise were the same as the actual Auvi-Q devices. In the first phase, pharmacist/pharmacy technician and parent participants were asked to select the EAI 0.1 mg carton, and parent participants were asked to select the EAI 0.1 mg device from among all three EAI doses (i.e., 0.3 mg, 0.15 mg, 0.1 mg). In the second phase, a nurse trainer provided up to 30 minutes EAI training to parent participants (EAI 0.1 mg) and pediatric participants (EAI 0.15 mg). Simulated

use scenarios were performed approximately 24 hours later, during which parent participants were asked show how they would use the EAI 0.1 mg by on mannequin of an infant experiencing a severe allergic reaction and were asked to answer task questions about injection location and hold time for self-administration of EAI 0.3 mg, and pediatric participants were asked to simulate self-administration of EAI 0.15 mg. The results are stated to have demonstrated that the updated instructions for use do not introduce any new usability issues. The Division accepted the results at face value and did not refer the HF study to the Division of Medication Errors and Prevention Analysis (DMEPA) for review because the changes are considered minor and the original HF study that supported approval of Auvi-Q was considered sufficient.

3.2 Clinical Microbiology

There were no microbiological issues noted in this application, and the recommendation from Clinical Microbiology is approval. Since there are no changes to the formulation or container/closure system, no new data were required.

3.3 Preclinical Pharmacology/Toxicology

No new nonclinical pharmacology and toxicology data were submitted. Since there are no changes to the formulation or container/closure system, no new data were required.

3.4 Clinical Pharmacology

This section summarizes the findings of the Office of Clinical Pharmacology (OCP) review of this supplement. OCP recommends approval of the proposed fixed-dose of 0.1 mg epinephrine for use in children with a body weight of 7.5 kg to <15 kg.

No new clinical pharmacology studies were submitted for this supplement. Currently there are no fixed-dose EAI products approved in children with body weight less than 15 kg. Literature-based evidence suggests that a 0.01 mg/kg epinephrine dose via intramuscular and subcutaneous injection is effective and safe in children with body weight less than 30 kg for emergency treatment of allergic reactions (Type 1), including anaphylaxis, and therefore, the body weight-based dose has been recommended by World Allergy Organization (Kemp, Lockey et al. 2008). In fact, 0.01 mg/kg via intramuscular and subcutaneous injection is the approved recommended dose of epinephrine for children weighing 30 kg or less (Adrenalin®, NDA 204200 and NDA 204640; Epinephrine injection, USP, NDA 205029).

This section provides clinical pharmacology support for use of the proposed 0.1 mg fixed dose in children with body weight of 7.5 kg to <15 kg through literature-based evidence. Two major clinical pharmacology findings are listed as below. The detailed discussion of these two findings follows.

PK/PD

Following absorption into the systemic circulation, epinephrine exhibits linear PK in both adults and children. The vital signs, such as systolic blood pressure and heart rate, increase proportionally with increase in epinephrine plasma concentration.

The threshold concentration for vital sign changes ranges from 50-200 pg/mL (Clutter, Bier et al. 1980), whereas the mean C_{max} following the approved dose (fixed dose or 0.01 mg/kg body weight-based dose down to 15 kg) in children with history of anaphylaxis is approximately 2000 ng/mL (Simons, Roberts et al. 1998). In these children, the mean systolic blood pressure and heart rate increased maximally by approximately 70 mmHg and 30 bpm from the baseline within 10 minutes post-dose, respectively.

Body-Weight Based Dosing

Compared to the approved 0.01 mg/kg dosing scheme in children weighing 30 kg or less (NDA 204200 and NDA 204640), the proposed fixed dose of 0.1 mg EAI product may result in at most 33% lower systemic exposure at the high body weight end (close to 15 kg) and at most 33% higher systemic exposure at the low body weight end (at 7.5 kg). Considering the relatively high PK variability (CV ~50%) of epinephrine observed in adults, the 33% exposure difference between the two dosing schemes in children weighing 7.5 kg to <15 kg is acceptable.

Based on these findings, the Office of Clinical Pharmacology recommends approval of the proposed fixed-dose of 0.1 mg epinephrine for children with a body weight of 7.5 kg to <15 kg.

The following discussion will demonstrate that the systemic exposure of epinephrine following 0.1 mg fixed dosing scheme in children weighing 7.5 kg to <15 kg does not deviate remarkably from the 0.01 mg/kg body weigh-based dosing scheme. Since the patient population and indication remains the same, a similar systemic exposure is expected to result in similar PD, efficacy and safety profiles.

3.4.1 Linear PK/PD of epinephrine following intravenous infusion

Epinephrine PK generally follows linear trend once the plasma concentration reaches above 90 pg/mL following continuous intravenous (IV) infusion in healthy adult subjects (Clutter, Bier et al. 1980). This indicates that the systemic exposure of epinephrine (AUC) increases proportionally with increase in dose. A similar dose-proportional trend for epinephrine was also observed in children aged 7 months to 16 years upon continuous epinephrine IV infusion (Fisher, Schwartz et al. 1993). In this study, each child received at least two different infusion rates. The IV infusion rate ranged from 0.03 to 0.23 μg/min/kg and the steady state plasma concentration of epinephrine ranged from 600 to 9430 pg/mL.

The adrenergic effects of epinephrine on vital signs are dependent on its plasma concentration. In the same study in healthy adult subjects (Clutter, Bier et al. 1980), the threshold steady state concentration of plasma epinephrine required for increment of heart rate, increment of systolic blood pressure and decrement of diastolic blood pressure ranged from 50-200 pg/mL (Figure 2). The vital sign changes were proportional to epinephrine's systemic concentration up to approximately 1000 pg/mL (Figure 2).

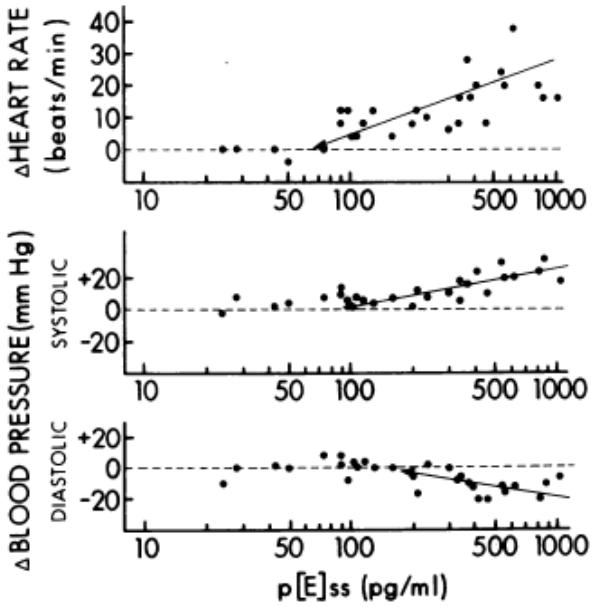


Figure 2. The relationship of vital sign changes and epinephrine steady state plasma concentration following IV infusion. The epinephrine plasma concentration ranged from 24 to 1020 pg/ml.
Source: (Clutter, Bier et al.1980), page 98, Figure 5

3.4.2 PK/PD of epinephrine following intramuscular injection

The PD effect of epinephrine following intramuscular injection is expected to be the same as IV infusion as long as certain threshold level of plasma epinephrine concentration is reached. In a study performed in children aged 7 to 11 years with history of anaphylaxis, the epinephrine mean C_{max} of 2136 ± 351 pg/mL was reached at 8 min (T_{max}) following 0.01 mg/kg intramuscular injection (n=8, body weight = 18.3 to 39.3 kg) (Simons, Roberts et al. 1998). The maximal effect on vital signs was observed within 10 minutes post-intramuscular injection with increase in mean systolic blood pressure and mean heart rate of approximately maximally 70 mmHg and 30 bpm from the baseline, respectively. Following a fixed dose intramuscular injection of 0.15 and 0.3 mg epinephrine in children aged 5 to 8 years, the mean C_{max} was 2037 ± 541 pg/mL (n=5, body weight = 16 to 20.4 kg) and 2289 ± 405 pg/mL (n=5, body weight - 21.5 to 30 kg), respectively (Simons, Gu et al. 2002). Therefore, the C_{max} of epinephrine following administration of a fixed dose (0.15 mg and 0.3 mg) was comparable to that of body weight-based dose (0.01 mg/kg) in children weighing >15 kg.

3.4.3 Body weight-based dosing of epinephrine in children

The mean epinephrine systemic clearance was 29.3 ± 16.1 mL/min/kg following IV infusion (Fisher, Schwartz et al. 1993). A trend of increment in epinephrine clearance with body weight was observed. This indicates that upon administration of a fixed dose, the systemic exposure decreases with increase in body weight. The estimated allometric scaling factor for epinephrine clearance was 0.80 (95% CI=0.51, 1.08) [$CL \sim (BW)^{0.80}$] (Figure 3). Since the 95% confidence interval of this scaling factor

included 1, the body weight-based dosing scheme (0.01 mg/kg) of epinephrine in children is considered reasonable.

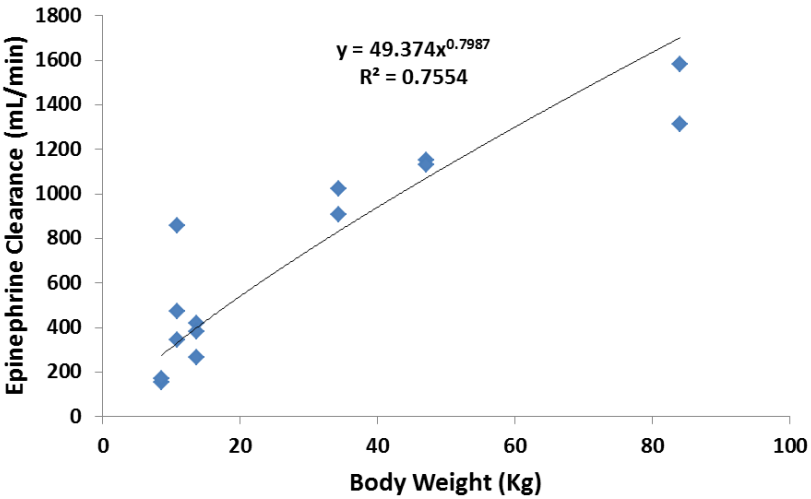


Figure 3. The effect of body weight on epinephrine clearance in children. Blue dots represent observed data whereas the curve stands for estimated trend ($CL=49.4 \times BW^{0.80}$, $p<0.001$).
Source: Reviewer's analysis of published results (Fisher, Schwartz et al. 1993)

In order to match the systemic exposure of epinephrine between subjects in different body weight categories, the theoretical dosing scheme could follow an allometric scaling with a factor of 0.80. Starting with 0.15 mg as the approved dose in children weighing 15 kg, the theoretical dosing scheme and the approved 0.01 mg/kg dosing scheme for epinephrine in children weighing 15 kg or less are listed below in Table 1. Table 1 also compares the epinephrine dose difference between the fixed dose (0.1 mg, proposed) and the body weight-based dosing scheme.

Compared to the approved 0.01 mg/kg dosing scheme, the proposed fixed dose of 0.1 mg EAI product is 33% less at the high body weight end (close to 15 kg) and 33% more at the low body weight end (at 7.5 kg). Compared to the theoretical allometric dosing scheme, the proposed fixed dose of 0.1 mg EAI product is 33% less at the high body weight end (close to 15 kg) and only 16% more at the low body weight end (at 7.5 kg). Since epinephrine's PK is linear within the therapeutic dose range, the exposure differences following different dosing schemes is expected to be same as the dose difference. By considering the relatively high PK variability (CV ~ 50% for both C_{max} and $AUC_{0\text{-}inf}$) of epinephrine observed in adults following intramuscular injection (refer to Clinical Pharmacology Review of NDA 201739 by Dr. Zhao in Drug Approval Package dated 08/10/2012), the at most 33% difference in systemic exposure between the proposed fixed dose (0.1 mg) compared to the approved dose (0.01 mg/kg) or the theoretical dose (based on allometric scaling) in children weighing 7.5 kg to <15 kg is acceptable.

Table 1 Summary and Relative Differences between Three Dosing Schemes

Body Weight (kg)	Theoretical Dose (mg) (95% CI)*	0.01 mg/kg Dose (mg)	Fixed Dose (proposed)		
			Dose (mg)	% of Theoretical Dose	% of 0.01 mg/kg Dose
7.5	0.086 (0.071, 0.105)	0.075	0.10	116%	133%
8	0.091 (0.076, 0.109)	0.08	0.10	110%	125%
9	0.100 (0.086, 0.115)	0.09	0.10	100%	111%
10	0.108 (0.097, 0.122)	0.10	0.10	92%	100%
11	0.117 (0.107, 0.128)	0.11	0.10	85%	91%
12	0.125 (0.118, 0.134)	0.12	0.10	80%	83%
13	0.134 (0.128, 0.139)	0.13	0.10	75%	77%
14	0.142 (0.139, 0.145)	0.14	0.10	70%	71%
15	0.15	0.15	0.15	100%	100%

*based on allometric scaling model: Dose = $0.15 \times (\text{body weight}/15)^{0.80}$

Source: Reviewer's analysis

The currently approved label of Auvi-Q states that "*With severe persistent anaphylaxis, repeat injections with an additional Auvi-Q may be necessary*" in adults and children weighing at least 15 kg. Since this product is indicated for a life-threatening condition, similar recommendations of repeat dosing are reasonable for the intended patient population, i.e., children with body weight 7.5 kg to <15 kg. Please refer to section 4.2 of the review for detailed dosing recommendations for the proposed product.

4 Risk/Benefit Analysis

4.1 Risk/Benefit Summary

The risk/benefit assessment supports approval of this 0.1 mg Auvi-Q dosage strength presentation for use in patients who weigh between 7.5 and 15 kg, corresponding to children who are approximately 1 to 3 years of age.

No clinical trials were conducted (or needed) to support the application. In conformance with the iPSP agreed to by the Agency on April 18, 2016, in which the Agency agreed that submission of relevant literature to support the proposed dosage strength and an ultrasound study to support safety of the proposed 0.1 mg dosage strength, would be acceptable, this information was submitted as part of the supplement: the iPSP was submitted in Module 1, relevant literature references were submitted in Module 5, overview documents were submitted in Module 2, and the sonographic study was submitted in Module 5.

4.2 Efficacy

4.2.1 Summary of Efficacy

Anaphylaxis is “a severe, potentially fatal, systemic allergic reaction that occurs suddenly after contact with an allergy-causing substance.” (Sampson, Muñoz-Furlong et al. 2006) Although no clinical trials were performed to support the new dosage strength, the applicant conducted a review of the literature that supports the efficacy and safety of epinephrine use for the treatment of anaphylaxis. Use of epinephrine for this indication is supported by a vast medical literature published over a span of over 115 years of clinical use. Such use is supported by the pharmacology of the drug and is accepted by all medical authorities, including the FDA.

The [historically clinically accepted and] approved dosage of epinephrine for treatment of anaphylaxis is 0.01 mg/kg, up to 0.3 mg for patients who weigh up to 30 kg (66 pounds), and 0.3 to 0.5 mg for patients who weigh 30 kg or more, administered either by IM or SC injection. (Kemp, Lockey et al. 2008) This is the dosage that is approved for use by healthcare providers in the supervised medical setting, where the dose may be drawn up based on the patient’s weight and repeated every 5-15 minutes as needed while the patient is being actively monitored.

It should be noted that the FDA-approved dosing recommendations for epinephrine products intended for treatment of anaphylaxis in the supervised medical setting intentionally differ from those for the fixed-dose epinephrine products that are intended for use in the unsupervised medical setting, in that the former are vial-based products that are drawn up with a needle and syringe and include weight-based dosing up to 30 kg (0.3 mg), whereas the latter include products with fixed-doses for given weight ranges. The standardized epinephrine doses for a given weight range currently include 0.3 mg for patients who weigh ≥30 kg (≥66 pounds), and 0.15 mg for patients who weigh ≥15 up to 30 kg (≥33 to 66 pounds). As a practical matter, standardized doses of epinephrine allow for the use of epinephrine auto-injectors by patients and caregivers for the immediate treatment of anaphylaxis in the unsupervised medical setting while seeking emergency medical assistance (calling 911 in locations where available or going directly to an emergency department), avoiding the need to draw up epinephrine from a vial with a needle and syringe during a potentially life-threatening emergency. In the unsupervised setting, the dosage is also limited to a maximum of 0.3 mg, which may be repeated once, if needed, whereas in the supervised setting dosages up to 0.5 mg may be used and repeated as needed.

The proposed 0.1 mg dosage strength for Auvi-Q would extend the range of available fixed-dose epinephrine auto-injector products that are intended for immediate treatment of anaphylaxis by patients and caregivers in the unsupervised medical setting. It will also be noted that range of weight-based dosing for the products intended for use in the supervised medical setting encompasses the proposed 0.1 mg dosage strength for this product, since the approved weight-based dosing includes all weights and doses below 30 kg (0.3 mg). As such, this dosage strength relies on the same well-documented, published medical literature with regard to the efficacy, safety, linear pharmacokinetics, and pharmacodynamic properties of epinephrine that support the already approved use of epinephrine for treatment of anaphylaxis in the supervised medical setting. As such,

the Agency has determined that a fixed-dose 0.1 mg dosage strength would be appropriate for patients who weigh ≥7.5 mg up to 15 kg, which corresponds to approximately patients aged 1 to 3 years.

4.2.2 Background on Anaphylaxis and Use of Epinephrine

Anaphylaxis is "a severe, potentially fatal, systemic allergic reaction that occurs suddenly after contact with an allergy-causing substance." (Sampson, Muñoz-Furlong et al. 2006) Although there is no universal agreement on the definition or the criteria for diagnosis, significant strides have been made in the last decade in this respect, with multiple publications from panels of scientific experts that help to standardize the criteria for diagnosis as well as treatment. (Sampson, Muñoz-Furlong et al. 2006) (Lieberman, Nicklas et al. 2010) (Simons, Ardusso et al. 2011) Anaphylaxis has thereby been defined via one of three clinical scenarios, [often referred to as the Sampson criteria] as shown in Table 4.

Previously, the term "anaphylactoid reaction" was used for episodes that were clinically similar to anaphylaxis, but were not IgE-mediated. However, the World Allergy Organization (WAO) has suggested that this term be eliminated, and that all episodes clinically similar to IgE-mediated reactions be called anaphylaxis. Anaphylaxis may then be divided into immunologic and non-immunologic reactions. Likewise, immunologic reactions may be divided into those mediated by IgE mast cell/basophil mediator release and those occurring through other immunologic mechanisms (e.g., certain transfusion reactions). (Johansson, Bieber et al. 2004) This is a reasonable approach from a clinical perspective, since the available evidence suggests that treatment is the same regardless of etiology.

During an anaphylactic reaction, vasoactive mediators are released from tissue mast cells and circulating basophils, including histamine, eosinophilic chemotactic factor of anaphylaxis (ECF-A), slow-reacting substance of anaphylaxis (SRS-A), platelet activating factor (PAF), kinins, and prostaglandins. Mediator release is independent of the trigger, i.e., it is not dependent upon whether the trigger is IgE mediated (so-called 'anaphylactic reaction') or directly mediated (so-called 'anaphylactoid reaction'); therefore anaphylaxis includes both types of reactions. Histamine, one of the mediators of the initial or acute manifestations, causes decreased systemic vascular resistance through effects on vascular smooth muscle, increased vascular permeability, and coronary vasoconstriction. These effects are mediated by both H_1 and H_2 receptors, although evidence suggests that H_1 and H_2 antihistamines are not effective in treating anaphylaxis once these mediators have been released.

Table 2 Clinical Criteria for Diagnosing Anaphylaxis

Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled: 1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula) AND AT LEAST ONE OF THE FOLLOWING a. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia) b. Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], s ncope, incontinence) 2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours): a. Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula) b. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia) c. Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence) d. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting) 3. Reduced BP after exposure to known allergen for that patient (minutes to several hours): a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in s stolic BP* b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline
PEF, Peak expiratory flow; BP, blood pressure. *Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg 1 [2 3 age]) from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years.

Source: Sampson 2006, Table 1.

From a regulatory viewpoint, supports for accepting the use of epinephrine for the indication of anaphylaxis comes from the Agency's previous findings of efficacy and safety of various epinephrine products for the same indication, from the literature, and from PK/PD modeling that the Agency has performed based on the literature.

The Agency has made a number of prior regulatory decisions with regard to efficacy and safety of epinephrine for this indication, including 1) auto-injectable forms of epinephrine (EpiPen, Twinject/Adrenaclick, and Auvi-Q) and 2) a prefilled epinephrine syringe (Symjepi), which are all approved for emergency [self- or caretaker-administration for the initial] treatment of anaphylaxis [while seeking further medical care], and 3) epinephrine vials (Adrenalin [Par], Epinephrine Injection [Belcher]), which are approved for treatment of anaphylaxis [by caregivers in the medical setting]. EpiPen was the first product approved, but it should be noted that the approval of EpiPen in December 1987, was itself based entirely on literature support and no clinical trials, and the same is true for all subsequent NDA applications for epinephrine products that have been approved for treatment of anaphylaxis.

The basis for approval of EpiPen was briefly summarized by Richard Nicklas, MD[1], the Medical Officer who reviewed the original EpiPen application, after which he cited all of the references that served to support the indication [Medical Officer Review of NDA 19-430, dated February 18, 1985]:

> "The onset of anaphylaxis is usually sudden and unexpected. Reactions are characterized by rapid progression with involvement of the cutaneous, respiratory, and/or circulatory systems. The most common manifestations of anaphylaxis are urticaria, flushing, or angioedema. Major life-threatening manifestations are those involving the circulatory and respiratory systems. Reactions occurring immediately tend to be more severe. Control of mild symptoms can prevent more severe reactions (Patterson and Valentine, 1982). The clinical course is extremely variable and can be fatal.
>
> Epinephrine is the drug of choice in the initial treatment of anaphylaxis. The pharmacologic actions of epinephrine inhibit further release of mediators and reverse end-organ responses. Its use is indicated in all major or severe reactions and acutely in apparent minor reactions to abort a potential severe reaction (Fath and Cerra, 1984).
>
> Due to the rapid clinical course and potentially life-threatening nature of anaphylaxis, prompt therapy is essential. Because prevention by avoidance is not always possible, emergency self-treatment is widely advocated. In fact, increasing the availability of emergency treatment for insect sting allergy was the subject of a NIH Consensus Development Conference in 1978.
>
> The EpiPen Auto-Injector is designed for easy use by the lay person. It is a reliable means for injecting epinephrine in a predetermined therapeutic dose, quickly, safely, and conveniently. The EpiPen Auto-Injector is especially useful in emergency circumstances where rapid administration is critical. The simplicity of use of the auto-injector allows wider availability of earlier treatment, an important therapeutic objective in that the incidence of severe and fatal reactions may be reduced."

Use of epinephrine for the treatment of anaphylaxis makes sense from a pharmacological and physiological perspective. Historically, the use of epinephrine for anaphylaxis is supported by pharmacologic and physiologic experiments in multiple animal models dating to the early to mid-20th century, thereby providing a substantial and reasoned body of evidence to support the pharmacologic basis for carrying this treatment into humans. Additional knowledge of specific α and β receptor subtypes and functions, which were not fully worked out until into the 1970s and 1980s, further supports this use. The efficacy of epinephrine for anaphylaxis is based on its mixed α and β adrenergic receptor effects, including α_1, α_2, β_1, and β_2 effects. Alpha$_1$-receptor activation reduces mucosal edema and membrane leakage and increases vasoconstriction and vascular resistance, resulting in increased blood pressure to treat hypotension. Beta$_1$-receptor activation stimulates the myocardium to increase

1 Note: Dr. Nicklas is currently a Clinical Professor of Medicine at The George Washington University School of Medicine. He has served on multiple expert panels, including those for anaphylaxis. As such, he is listed a co-author of some of the expert opinion presented in the applicant's references.

contraction force and heart rate, resulting in increased cardiac output. $Beta_2$-receptor activation produces bronchodilation, decreases mediator release, and relaxes coronary blood vessels. And mixed α and β effects stimulate glycogenolysis and redirect blood flow to vital end-organs. This combination is ideal from a pharmacologic and physiologic perspective, as it prevents and treats all of the signs and symptoms of anaphylaxis, including upper airway edema, urticaria, bronchospasm, hypotension, and shock. (Simons and Simons 2010) (Simons, Ardusso et al. 2011) (Westfall and Westfall 2011)

Since the original isolation of epinephrine in later part of 1900, and its introduction into the market by Parke, Davis & Co. the following year, there has been extensive anecdotal clinical experience with the use of epinephrine at the dosages proposed and used for treatment of anaphylaxis. This experience comes from use to treat anaphylaxis, asthma, and shock, the doses being similar for all three indications except that the doses used during cardio-respiratory arrest (codes) can extend to much higher levels. Although no prospective, controlled clinical trials have been performed to substantiate the use of epinephrine for treatment of anaphylaxis (Sheikh, Shehata et al. 2008), one prospective, uncontrolled trial (Brown, Blackman et al. 2004) provides significant support, as discussed below. The lack of prospective, controlled clinical trials for the treatment of anaphylaxis in humans is not surprising, and has its basis in the fact that anaphylaxis is a true life-threatening medical emergency and there is no other first-line therapy. Therefore, withholding of available treatment, even for short periods of time, would not allow for equipoise in a clinical trial. On the basis of this vast clinical experience, and as noted in Dr. Nicklas' review, epinephrine has been adopted as the standard-of-care, first-line treatment of anaphylaxis. This treatment is accepted by all medical authorities and all allergy and anaphylaxis experts in the United States and abroad. (Lieberman, Nicklas et al. 2010) (Sampson, Muñoz-Furlong et al. 2006) (Simons, Ardusso et al. 2011) (Soar, Pumphrey et al. 2008)

All other treatments of anaphylaxis are often critical, but they are either supportive or second-line, and therefore adjunctive in nature. They include: discontinuation of any suspected allergen, recumbent positioning; establishment of an adequate airway and administration of oxygen; rapid administration of IV fluids to expand blood volume (crystalloids) for patients in shock; H_1 antihistamines such as diphenhydramine or chlorpheniramine; H_2 antagonists such as cimetidine or ranitidine; inhaled beta-agonists such as albuterol, glucocorticoids; and sedatives and vasodepressor agents. Additional treatment may include blood pressure support with intravenous norepinephrine or other pressors until adequate volume expansion has been achieved and glucagon for patients taking beta-blockers who have refractory hypotension. (Lieberman, Nicklas et al. 2010) (Simons, Ardusso et al. 2011)

As noted above, one prospective, uncontrolled trial supports the use of epinephrine for the treatment of anaphylaxis. (Brown, Blackman et al. 2004) This study prospectively evaluated a protocol for the treatment of sting anaphylaxis using an infusion of IV epinephrine 0.01 mg/mL (previously referred to by the ratio 1:100,000), oxygen, and volume resuscitation (if needed) in adults who had systemic allergic reactions to a diagnostic sting challenge following either venom or placebo immunotherapy. All 19 patients who experienced a reaction to insect venom received epinephrine treatment

and recovered fully. Additionally, 5 patients required volume resuscitation and 2 patients also required atropine to treat bradycardia. Importantly, physical signs of anaphylaxis recurred in 9 of the cases after epinephrine was initially stopped, but resolved after restarting the infusion, suggesting that these patients fulfill Koch's postulates. The conclusion from this study was that carefully titrated intravenous epinephrine combined with volume resuscitation is an effective strategy for treating anaphylaxis due to stings.

Use of epinephrine is also indirectly supported by outcome studies that have looked, for example, at deaths due to anaphylaxis. These studies note the appalling lack of use, or late use, of epinephrine in these patients. However, many of these patients did not have immediate access to epinephrine, as would be expected in the case of first-time anaphylaxis episodes, in large part explaining why the numbers are not better. Additionally, in those unfortunate fatal cases in which the patient had been identified as needing a kit and had one available, only a few used it or used it correctly, suggesting that had it been available and used in a timely fashion many of these lives could have been saved. It is clear from these publications that much work remains in identifying patients at risk, and ensuring that they are adequately trained and prepared to deal with an allergic emergency and carry their medication with them at all times. (Pumphrey 2000) (Pumphrey and Gowland 2007) (Sampson, Mendelson et al. 1992)

Repeated dosing is based on the clinical response, i.e., the presence of continued or recurrent [as in the case of biphasic reactions] signs and symptoms. In the literature, the number of patients reported to require more than one dose of epinephrine for treatment of anaphylaxis is generally quoted as between12% and 36%. (Jarvinen, Sicherer et al. 2008) (Kelso 2006) (Kemp, Lockey et al. 2008) (Korenblat, Lundie et al. 1999) (Manivannan, Campbell et al. 2009) (Rudders, Banerji et al. 2010) (Rudders, Banerji et al. 2010) (Simons and Simons 2010) As a result, epinephrine auto-injectors are generally packaged in two-packs (although the Division believes that single packs should also be available for refills or should the prescriber feel that a single pack is appropriate), and the Dosage and Administration and Instructions for Use instruct patients and caregivers to both seek emergency medical help right away and to use a second dose should it be needed, as shown below:

> "With severe persistent anaphylaxis, repeat injections with an additional AUVI-Q may be necessary. More than two sequential doses of epinephrine should only be administered under direct medical supervision [*see WARNINGS AND PRECAUTIONS (5.1)*]."

This dosing schema appears to be effective for the majority of patients. Although some patients do not respond, for many the failure to respond may be due to a variety of other issues, such as a delay in recognition of the diagnosis, delay before administration or not administering the dose for any of a number of other reasons (including failure to recognize the severity of a reaction, and failure to have a dose immediately available). (Sampson, Mendelson et al. 1992) (Pumphrey 2000) (Bock, Munoz-Furlong et al. 2001) (Bock, Munoz-Furlong et al. 2007) (Garvey, Belhage et al. 2011) (Pumphrey and Gowland 2007) (Simons, Ardusso et al. 2011)

Dosing recommendations allow either intramuscular (IM) or subcutaneous (SC), administration, and there are reasons to that both routes are acceptable depending upon the clinical setting. The proposed IM/SC dosing regimen is supported by pharmacodynamic data in animals, PK data in adult and children, and a vast amount of clinical experience in all age groups. It is in keeping with the literature and is consistent the latest anaphylaxis dosing and treatment recommendations from the Joint Task Force on Practice Parameters (representing the American Academy of Allergy, Asthma and Immunology; the American College of Allergy, Asthma and Immunology; and the Joint Council of Allergy, Asthma and Immunology). (Lieberman, Nicklas et al. 2010) The IM route, which is associated with shorter time to maximum concentration, is definitely the preferred route in the medically supervised setting because it reaches the central circulation promptly, whereas the SC route leads to vasoconstriction and slower absorption. (Sampson, Muñoz-Furlong et al. 2006) (Lieberman, Nicklas et al. 2010) (Simons and Simons 2010) This recommendation is sensible in the medically supervised setting, where speed of onset is the overriding concern, repeated doses are available, and monitoring is also available. However, in the self-administered, medically unsupervised setting the dosing recommendation and rationale may reasonably differ. In this setting, either route is acceptable, and an argument may be made that the slightly slower absorption associated with SC injection may aid in prolonging the effects of initial self-therapy while awaiting additional emergency medical care, especially in situations where additional doses may not be available. (Pijak and Gazdik 2006) Further, the needle length of the approved self-administered auto-injectors cannot guarantee IM administration into the vastus lateralis muscle because of variability in the overlying fat layer of the thigh, and this is also acceptable for self-administered use. (Simons, Gu et al. 2001) (Chowdhury and Meyer 2002) (Simons and Simons 2010) The same applies to the proposed needle length for this product, which is 0.29 inches.

It is also of note that the anterolateral thigh (vastus lateralis muscle) is the appropriate [and recommended] location/muscle for SC/IM administration because of its location, size, and available blood flow. Injection into (or near) smaller muscles, such as in the deltoid, is not recommended because of differences in PK associated with this use. (Simons, Gu et al. 2001) Injection into the buttock is not recommended because there have been reports of gas gangrene infections after dosing into this area. (Harvey and Purnell 1968)

In sum, the efficacy [and safety] of epinephrine for the treatment of anaphylaxis by this vast array of data and is unquestionable.

4.2.3 Support for the 0.1 mg Dosage Strength: Historical Basis

As noted in the previous section, epinephrine has historically been used for the treatment of anaphylaxis. At the time that the first EAI product (EpiPen) was approved in 1987, epinephrine was widely available and routinely used for the treatment of anaphylaxis. Several marketed and unapproved formulations/products were available in the United States, including epinephrine in vials to be drawn up and administered with a needle and syringe (e.g., Adrenalin and others), prefilled syringes (e.g., Epinephrine in a Tubex® closed injection system, Wyeth-Ayerst Laboratories), and a kit (Ana-Kit, Miles Inc./Wyeth-Ayerst Laboratories) that contained a prefilled syringe with two variable

doses of up to 0.3 mg of epinephrine 1 mg/mL, four 2 mg chlorpheniramine maleate tablets, two isopropyl alcohol pads, and a tourniquet. For the vial formulations, the accepted dosage was 0.01 mg/kg up to 0.3 mg for patients who weigh up to 30 kg (66 pounds), and 0.3 to 0.5 mg for patients weighing 30 kg or more. For Ana-Kit, the recommended dosage was by age rather than by weight, but the reader will note the relative similarity in dosage to the currently approved products: 0.3 mL (0.3 mg) for 12 years of age and older, 0.2 mL (0.2 mg) for 6-12 years, 0.15 mL (0.15 mg) for 2-6 years, and 0.05 to 0.1 mL (0.05 to 0.1 mg) for infants to 2 years of age.

As such there was historical precedent to support approval of the EAI products with fixed doses of 0.15 mg for patients who weigh 15 to 30 kg (33 to 66 pounds) and 0.3 mg for patients who weigh 30 kg or more (starting with EpiPen in 1987, Twinject in 2003, and Auvi-Q in 2012), as well as to support approval of marketing applications of the various epinephrine products in vials that had previously been marketed unapproved products (starting with Adrenalin in 2012).

Since the first EAI products were approved, several pharmacokinetic and pharmacodynamic studies have been conducted and published that have evaluated the dosing, PK, and PD effects of epinephrine in adults (Simons, Gu et al. 2001) and children (Fisher, Schwartz et al. 1993) (Simons, Roberts et al. 1998) (Simons, Gu et al. 2002). These pharmacokinetic evaluations show linear clearance of epinephrine in all age ranges, and the pharmacodynamic evaluations demonstrate a similar pharmacologic response, including effects on BP, HR, etc., in both children and adults. Similarly, the underlying disease process is considered the same regardless of age, lending support for use in all pediatric age groups. Based on this information, PK/PD modeling has allowed the Agency to confirm both the historically-based dosing of epinephrine for treatment of anaphylaxis as well as the dosage strengths contained in the approved fixed-dose epinephrine auto-injector products. For example, during the review of the Adrenalin applications, this modeling allowed the Agency to confirm that the dosages of 0.01 mg/kg up to 0.3 mg, with a maximum of 0.5 mg for patients in the supervised medical setting, and of up to 0.3 mg for patients in the unsupervised medical setting, is appropriate for treatment of anaphylaxis.

With this supplement, Kaléo is proposing the first fixed-dose epinephrine auto-injector with a dose of 0.1 mg for use in patients who weigh 7.5 to 15 kg, which corresponds to approximately 1 to 3 years of age. The same literature-based PK/PD modeling previously performed by the Agency also supports that a fixed dose of 0.1 mg may be administered to patients who weigh between 7.5 and 15 kg in the outpatient setting while seeking further medical care.

4.2.4 Support for the 0.1 mg Dosage Strength: PK/PD Modeling

The Office of Clinical Pharmacology recommends approval of the proposed fixed-dose of 0.1 mg epinephrine for children with a body weight between 7.5 kg to <15 kg. Please see Section 3.4 of this review for details.

4.3 Safety

4.3.1 Summary of Safety

The safety assessment for this application is adequate and supports the safety of the proposed 0.1 mg dose of Auvi-Q with an exposed needle length of 0.29 inches (~7.27 mm) for treatment of anaphylaxis in patients who weigh 7.5 to 15 kg. No clinical trials were conducted. The safety of epinephrine use in this population comes from the literature, including many pharmacological studies in animals, pharmacokinetic, pharmacodynamic, and epidemiologic studies in humans, one clinical trial in patients with anaphylaxis, adverse event reports, and over 115 years of clinical experience. Epinephrine has been used to treat anaphylactic reactions in all age and weight ranges. The safety information to support the proposed exposed needle length of the new Auvi-Q dosage strength comes from an ultrasound study conducted under IND (see below).

That epinephrine has a narrow therapeutic index (therapeutic window) is well documented (Simons 2006). Having a narrow therapeutic index means that there is a very small window between the pharmacologic effects of epinephrine that are therapeutic and adverse effects that are associated with use. Since the therapeutic index of epinephrine is narrow, most patients experience side effects during treatment at recommended doses. It is also well documented that higher doses are associated with cardiac toxicity, which may even occur in some susceptible patients even at recommended dosages. Keeping the narrow therapeutic index of epinephrine in mind, PK and PD modeling performed by the Agency suggests that the proposed 0.1 mg dosage strength could be safely used in patients who weigh as low as 7.5 kg, and as high as 15 kg, but that a fixed 0.1 mg dosage would not be appropriate for patients who weigh less than 7.5 kg.

For a more detailed review of the specific safety issues related to the use of epinephrine for the treatment of anaphylaxis, please see my previous reviews of the Adrenalin applications (NDA 204200, and NDA 204640).

4.3.2 Exposed Needle Length

Historically, the determination of an appropriate exposed needle length for an auto-injector to deliver an intramuscular or subcutaneous dose of 0.3 mg or 0.15 mg of epinephrine into the midpoint of the vastus lateralis muscle in the antero-lateral thigh was not made based on specific data. In the case of EpiPen, for example, the exposed needle lengths for the two dosage strengths were proposed by the company and accepted by the Agency without any data other than historical precedent. The same is true for both Twinject/Adrenaclick and Auvi-Q, namely that the proposed exposed needle lengths were to a large extent based on historical precedent. In retrospect, these needle lengths appear appropriate to deliver epinephrine into either the intramuscular or subcutaneous compartment of the anterolateral thigh safely without hitting bone. The Agency is aware, however, of reports of needles hitting bone, with consequent bending and/or breaking, if the injection is delivered into another anatomical region other than the mid anterolateral thigh.

However, when the Agency first began considering how to help companies develop a new lower dosage EAI product for use in progressively younger patients, there was no historical precedent on which to rely. The main issue is ensuring that the injection reaches one of the two compartments (IM or SC) but does not hit bone. While there are multiple publications dealing with the appropriate needle length for injections into the legs of infants and young children, these data were not considered adequate to support use of an EAI because the typical needle and syringe is inserted after manually pinching the skin to ensure either IM or SC dosing, whereas the EAI devices only trigger once the skin has been compressed to a point where the force applied to the tip of the injector is sufficient to trigger the device. Further, injection via needle and syringe is typically performed by a healthcare professional who is experienced in the appropriate injection technique, whereas an EAI is intended to be used by even the most inexperienced user. Therefore, the longer needle lengths typically recommended for injections are not applicable to use of an EAI in this setting.

That the use of data from the compressed state is the most appropriate for an EAI product is supported by data from a study performed by Song et al. (Song, Nelson et al. 2005), which confirmed that tissue depth decreases when forces similar to those needed to trigger an EAI device are applied to the skin. In this study, mid-antero-lateral thigh ultrasound results were compared in the uncompressed state and after compression with 8 lb of force to mimic the approximate force to fire for EpiPen. A decrease in skin-to-muscle distance of 19% was noted in one man, and 25% in one woman after force was applied to the mid thigh. Therefore, the Agency considers that compressed state is most appropriate for making an assessment of the exposed needle length, as it more closely mimics the state at the time of epinephrine administration from an EAI.

The first instance that the Agency dealt with this was in the case of the Pediatric Research Equity Act (PREA) post-marketing commitment (PMC) for Twinject. The 0.3 mg dosage strength of Twinject (NDA 20-800) was approved on May 30, 2003, for the emergency treatment of anaphylaxis and severe allergic reactions in patients weighing 30 kg or more. Twinject was a two-dose epinephrine auto-injector that provided auto-injection of the first dose but required disassembly and manual injection of the second dose. At the time of approval, the Pediatric Rule was being challenged in court, so pediatric studies were encouraged but not required. Subsequently, supplement (S-001) was approved on May 28, 2004, for the 0.15 mg dosage strength to treat patients weighing 15-30 kg. The supplement triggered PREA, at which time the Division deferred pediatric assessments for Twinject (for the treatment of anaphylaxis in patients who weigh less than 15 kg) until May 28, 2007. Subsequently, a single-dose version of Twinject, called Adrenaclick, was approved in both 0.3 mg and 0.15 mg dosage presentation on November 25, 2009, after which marketing of Twinject was discontinued. All presentations of Twinject / Adrenaclick, including the 0.3 and 0.15 mg dosages, use (b) (4) gauge 5/8 inch needle with a needle penetration of 0.5 inch (spec range (b) (4) inch) (Note: Except for the second dose of the no-longer-marketed Twinject, needle penetration is controlled by a (b) (4) , which stops the needle hub from travelling at a predetermined depth under the skin).

What information would be required to fulfill the Twinject PREA PMC was discussed over several interactions with the previous Twinject NDA holders, and the data were subsequently submitted to the Agency over a period of multiple years. These included a literature-based pharmacokinetic and pharmacodynamic modeling report and a tissue thickness sonographic study to determine the appropriate exposed needle length for the proposed weight and age range.

The PK/PD modeling confirmed that a 0.1 mg dosage strength would be appropriate for the proposed weight range of 10 to 15 kg. The sonographic study measured of skin-to-muscle, muscle-to-bone, and skin-to-bone distances in the anterolateral thigh by ultrasound in both the uncompressed and fully compressed states in children who weighed both 7.5 to 15 kg, comparing the results to data generated in children 15 to 30 kg. In the cohort of children who weighed 7.5 to 15 kg (N=30), mean uncompressed and compressed skin-to-bone distances (STBD) were 31.98 and 17.74 mm, respectively, with the minimum measured STBD distance being 25.7 and 13.3 mm, respectively. Based on these data, the company proposed that (b) (4) [redacted]. However, atypical of PREA PMC submissions, the pediatric assessment for Twinject was not submitted as a supplement, and in fact a 0.1 mg dosage strength product was never developed.[2] As a result, while the Agency considered the PMC to be complete and issued a PMC fulfilled letter on January 30, 2014, the existence and results of the sonographic study were never made public.

When the Agency contacted the remaining companies recommending that they consider development of a 0.1 mg dosage strength, the Agency was aware of the type of sonographic data that might be needed to provide support for each of the products, realizing that the specifications for each product differ and therefore the sonographic studies might provide differing results. Kaléo provided this study, summarized below, and is proposing an exposed needle length based on the results of the study.

Auvi-Q Sonographic Study (MSC14123)

This was an open-label, multi-center, non-randomized, uncontrolled, single-arm sonographic study that was designed to determine the appropriate needle length for Auvi-Q when administered to a pediatric population weighing 7.5 kg (16.5 lbs) to less than 15 kg (33 lbs). Skin-to-bone distance (STBD) and skin-to-muscle distance (STMD) were measured in the anterolateral thigh (vastus lateralis muscle) midway between the hip and knee using a modified Auvi-Q device which contained no medication or needle. Specifically, an ultrasound probe was fitted into a modified Auvi-Q device in a manner such that the device would both mimic the surface area and the simulated needle

2 The issue of the Twinject PMC was discussed with the Pediatric Review Committee (PeRC) on several occasions before the PMC fulfillment letter was eventually issued in 2014. At the time, the Agency interpreted that PREA applied to drugs but not to devices. Since a lower dosage strength would require modification of the device, PeRC considered that under PREA the Agency could not require development of [a new device to support] a new dosage strength.

activation pressure of the actual Auvi-Q device. A dolorimeter was used to obtain sonographic measurements when a force of 10 lbf (pound-force), a force is similar to the maximum activation force for the device, was applied to the skin to simulate compression from and triggering of an actual Auvi-Q device. Sonographic measurements were obtained at baseline and with pressure applied. STBD and STMD were determined at baseline and with force application. The primary endpoint was the STBD at baseline and at simulated needle activation.

A total of 53 subjects were enrolled at two study sites, of whom 51 subjects who had at least one short-axis STBD ultrasound measurement were included in the analyses (all 51 had full image sets including both compressed and uncompressed, and short- and long-axis images). One subject discontinued due to an adverse event of pinching of the skin associated with mild discomfort during the ultrasound image acquisition, and one subject discontinued due to subject decision.

Study Population

The study population included 22 females (43.1%) and 29 males (56.9%) with a mean age of 19.1 (SD 9.8) months. The vast majority of subjects were Caucasian (82.4%). The study achieved the planned enrollment goal of a relative balance in enrolled subjects who weighed 7.5 to 11 kg, and 11 to 15 kg (non-inclusive); 28 (54.9%) of subjects were in the 7.5 to 11 kg weight category and 23 (45.1%) were in the 11 to 15 kg weight category. Mean BMI was 17.122 (SD 1.950) kg/m^2, and mean thigh circumference was 26.2 (SD 2.1) cm.

STBD

The mean (SD) STBDs (n=51) in the uncompressed state were 22.37 (±3.83) and 22.69 (±3.28) mm for short- and long-axis, respectively, whereas the mean (SD) STBD in the compressed state (i.e., with simulated needle activation) were 13.31 (±2.06) and 15.52 (±2.53) mm for short- and long-axis, respectively.

The weight-adjusted mean (SD) short-axis STBDs in the uncompressed state for subjects weighing 7.5, 11, and 15 kg were 19.64 (±3.51), 22.36 (±3.51), and 25.47 (±3.51) mm, respectively. The weight-adjusted mean (SD, range) short-axis STBDs in the compressed state for subjects weighing 7.5, 11, and 15 kg were 12.45 (±2.00, 8.46 to 17.91), 13.31 (±2.00, 9.32 to 18.77), and 14.30 (±2.00, 10.30 to 19.76) mm, respectively.

STMD

The mean (SD) short-axis STMDs (n=51) was 7.94 (±1.68) mm in the uncompressed state, and 6.29 (±1.23) mm in the compressed state. The weight-adjusted mean (SD) short-axis STMDs in the uncompressed state for subjects weighing 7.5, 11, and 15 kg were 8.88 (±1.60), 7.94 (±1.60), and 6.86 (±1.60) mm, respectively. The weight-adjusted mean (SD, range) short-axis STMDs in the compressed state for subjects weighing 7.5, 11, and 15 kg were 6.89 (±1.18, 4.23 to 9.46), 6.29 (±1.18, 3.63 to 8.86), and 5.60 (±1.18, 2.94 to 8.17) mm, respectively.

Combined STBD and STMD Analysis

Plots of the percent of subjects having a STBD greater than and a STMD lower than a threshold (short axis compression) for the 7.5, 11, and 15 kg groups are shown in Figure 3, Figure 5, and Figure 5, respectively. Combined STBD and STMD plots for all weights are shown in Figure 7 and Figure 8, respectively. Kaléo used the plots to determine the optimal needle length. It will be seen that the proposed needle length is short enough that it is highly unlikely to hit bone in any weight group (Figure 7), yet would still provide IM dosing (as opposed to SC dosing) in about 55% of patients in the lowest weight group of 7.5 kg, whereas in patients who weigh 15 kg the likelihood of achieving an IM dose is reduced to between 10-15% (Figure 8).

Summary and Recommendation

Based on the data submitted, the proposed exposed needle length of 0.29 inches (~7.27 mm) will provide an acceptable margin for safety with regard to hitting bone. Since both IM and SC dosing are acceptable, the proposed exposed needle length is acceptable.

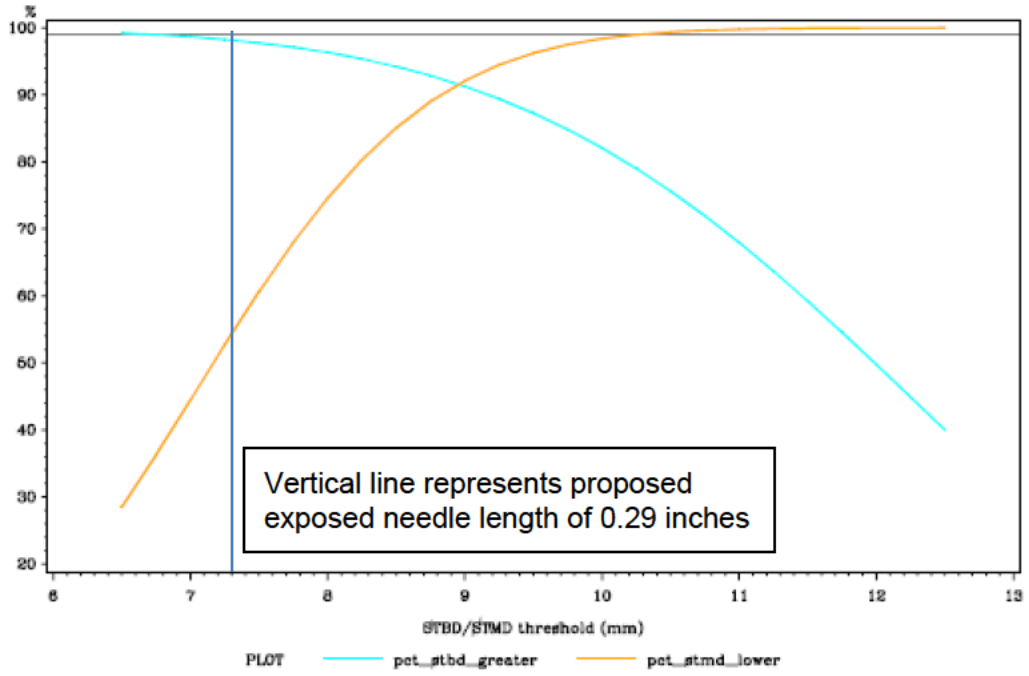


Figure 4. Study MSC14123. Percent of subjects weighing 7.5 kg having a STBD greater and STMD lower than a threshold (short axis compression)
Source: msc14123-report-body.pdf, F1, p27

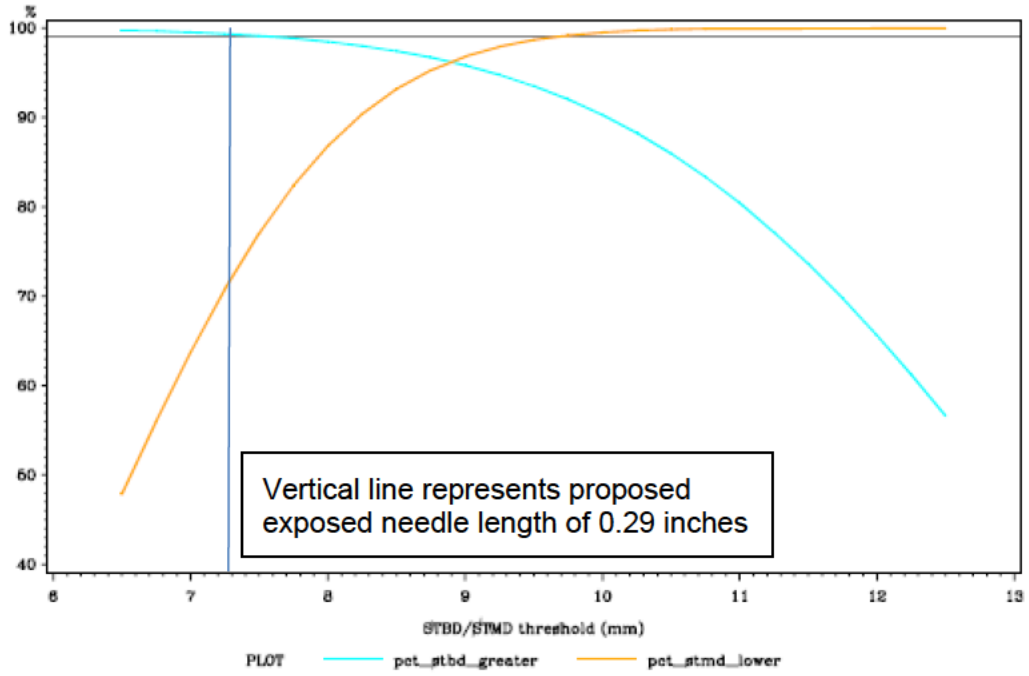


Figure 5. Study MSC14123. Percent of subjects weighing 11 kg having a STBD greater and STMD lower than a threshold (short axis compression)
Source: msc14123-report-body.pdf, F2, p28

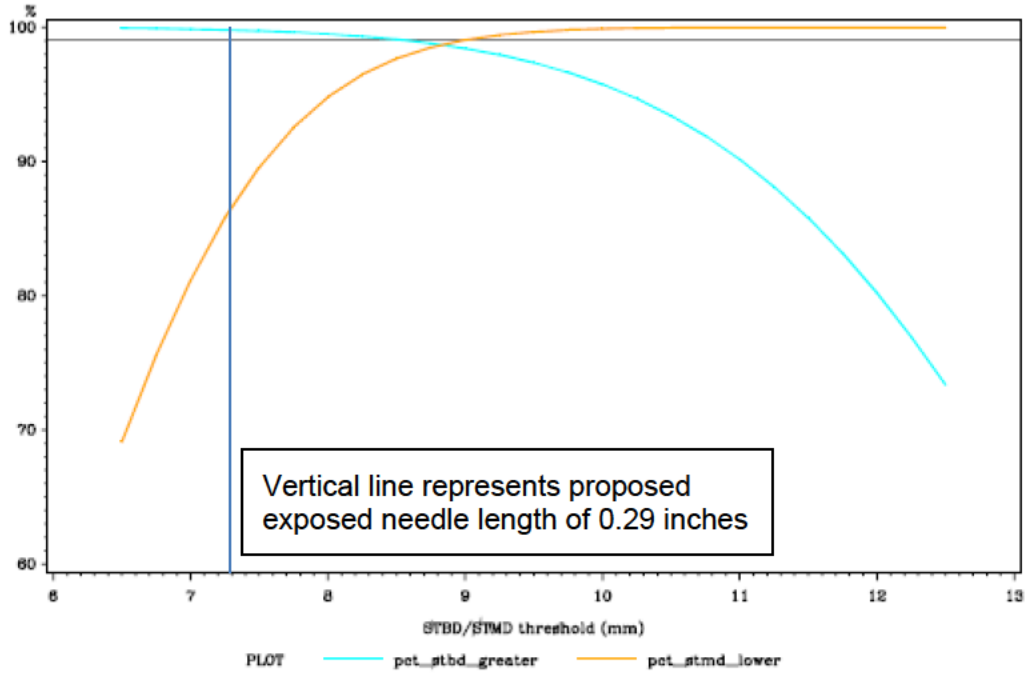


Figure 6. Study MSC14123. Plot of the percent of subjects weighing 15 kg having a STBD greater and STMD lower than a threshold (short axis compression)
Source: msc14123-report-body.pdf, F3, p29

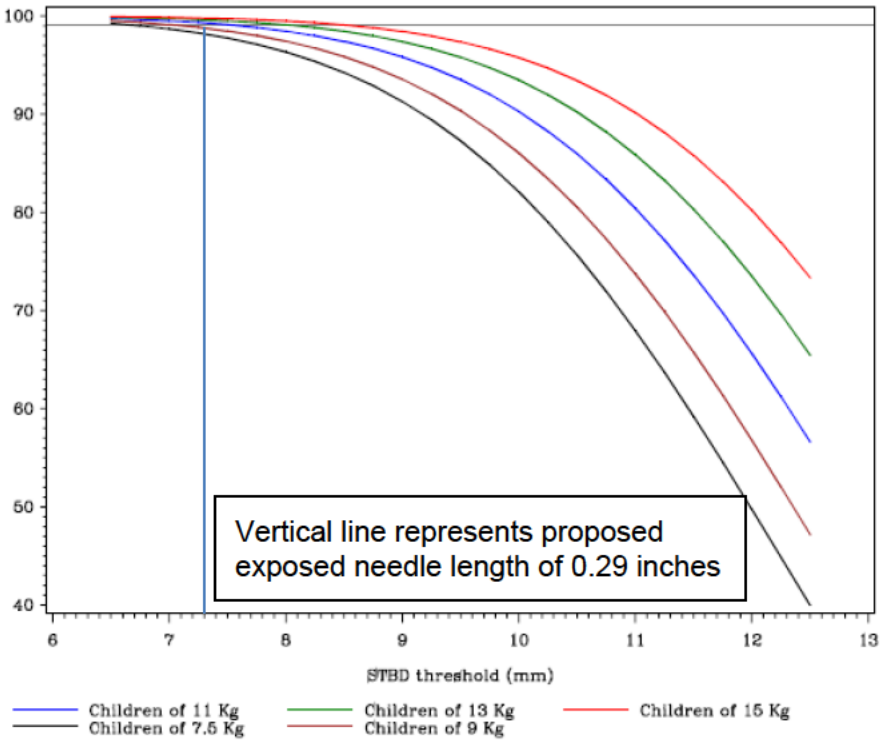


Figure 7. Study MSC14123. Plot of the percentage of subjects with a STBD greater than a given threshold by weight (short axis compression)
Source: msc14123-report-body.pdf, F7, p46

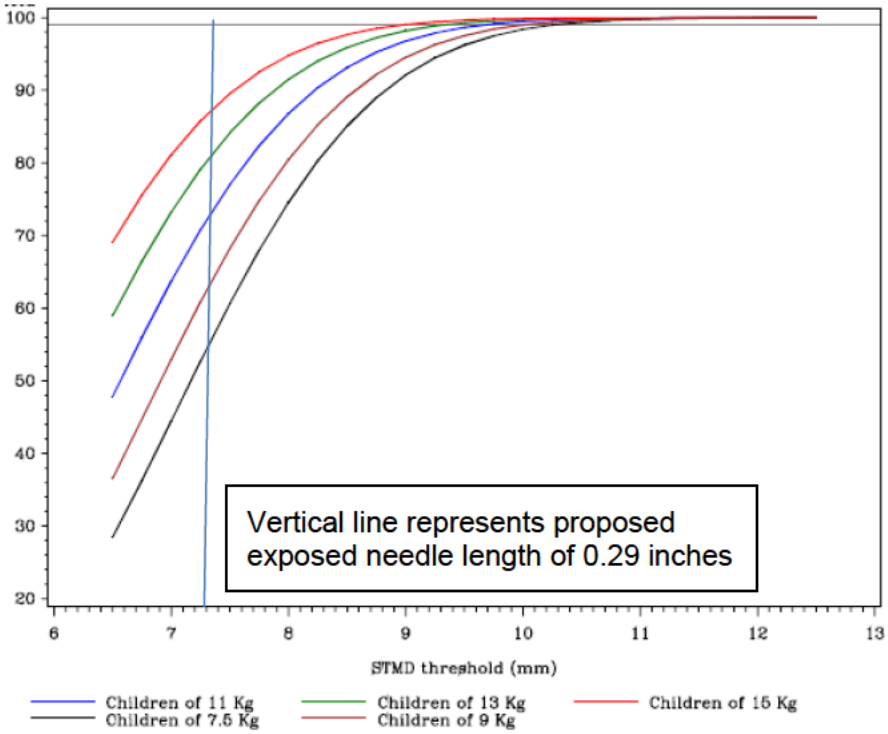


Figure 8. Study MSC14123. Plot of the percentage of subjects with a STMD lower than a given threshold by weight (short axis compression)
Source: msc14123-report-body.pdf, F8, p47

5 Appendices

5.1 Labeling Recommendations

With approval of these supplements, the labeling for Auvi-Q will not substantially change. Supplement S-008 includes changes to the Prescribing Information to describe the new dosage strength in the appropriate sections of the labeling, along with corresponding changes to the Patient Information Leaflet (PIL). Supplement S-009 includes changes to the Instructions for Use (IFU), along with corresponding changes to the voice prompts embedded in the device. The proposed changes were reviewed and determined to be acceptable.

5.1.1 Prescribing Information

The Prescribing Information will remain similar to the current labeling, except for adding the new dosage strength in the appropriate sections of the labeling and other changes noted below.

Of note, on July 12, 2017, Kaléo submitted a CBE supplement (S-010) to add stress cardiomyopathy to the Adverse Reaction section (Section 6) of the PI. Stress cardiomyopathy, sometimes referred to as 'Takotsubo cardiomyopathy', is a relatively recent but well-recognized adverse reaction to epinephrine, with at least one published

systematic review and meta-analysis of multiple cases in the literature. (Nazir, Lohani et al. 2017) It is therefore reasonable to add this to the Adverse Reactions section of the labeling, and the new labeling to be approved with these supplements will include this information.

A waiver under PREA will be granted for patients who weigh less than 7.5 kg, corresponding to children who are less than approximately 1 year of age, because a standardized (fixed) dose is not appropriate for patients who weigh less than 7.5 kg, and vial formulations of epinephrine that allow for appropriate weight-based dosing are available. Since a fixed-dose EAI product such as Auvi-Q would be ineffective and/or unsafe in the pediatric group(s) for which a waiver is being requested, PREA requires that information describing the safety concern be included in the pediatric use section (Section 8.4) of labeling. Section 8.4 will read as follows (new wording in blue and underlined):

> "AUVI-Q may be administered to pediatric patients at a dosage appropriate to body weight [*see DOSAGE AND ADMINISTRATION (2)*]. Clinical experience with the use of epinephrine suggests that the adverse reactions seen in children are similar in nature and extent to those both expected and reported in adults. Since the doses of epinephrine delivered from AUVI-Q are fixed, consider using other forms of injectable epinephrine if doses lower than 0.1 mg are deemed necessary."

The Division believes that the proposed language is appropriate and is in line with the previous labeling of these products when discussing epinephrine doses lower than what are available in a fixed-dose auto-injector presentation.

5.1.2 Carton and Container Labeling

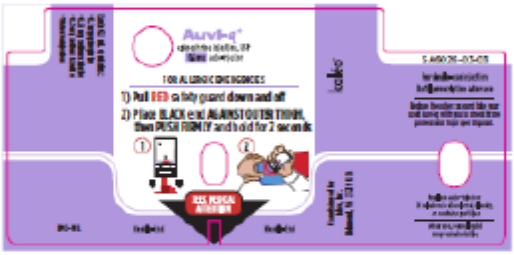
The Division of Medication Error Prevention and Analysis (DMEPA) provided comments about the proposed carton and container labeling for the 0.1 mg dosage strength that were sent to Kaléo shortly prior to submission of the supplements. At the same time, the Division also sent a comment about the proposed carton/container labeling.

Kaléo has proposed that the 'Q' not be capitalized in the proprietary name for the 0.1 mg dosage strength. In other words, the new dosage strength product would be depicted on the carton/container labels as 'Auvi-q', not 'Auvi-Q'. DMEPA considered this change to be acceptable.

Kaléo initially proposed a teal color for the 0.1 mg device, but the Agency recommended that Kaléo consider a different color scheme because the teal color scheme for the 0.1 mg dosage strength might be confused with the blue color of the approved 0.15 mg dosage strength, especially by patients/caregivers with blue-green color blindness. In response, Kaléo changed the proposed color scheme for the 0.1 mg dosage strength to lavender. The new color scheme, shown below, is acceptable to the Agency.

Revised AUVI-Q 0.1 mg Outer Case Label

Revised AUVI-Q 0.1 mg Device Label



CAD rendering of AUVI-Q 0.1 mg

The Agency also requested that Kaléo simplify the graphic on the device that depicts the 0.1 mg device being administered while holding the leg of the child. The original graphic was visually complicated due to inclusion of a second leg in the background. Kaléo revised the graphic to show only the one leg that is being held during the injection. The new graphic, shown below, is acceptable to the Agency.

The revised labeling proposed by Kaléo is acceptable.

5.1.3 Instructions for Use

Supplement S-009 contains changes to the Instructions for Use and auditory device prompts. These changes were reviewed by the Division and by CDRH and found to be acceptable.

5.2 Advisory Committee Meeting

No advisory committee was convened to discuss this application.

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