

January 16, 2015

[BY ELECTRONIC SUBMISSION]

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

CITIZEN PETITION

The undersigned respectfully submits this citizen petition on behalf of Mylan Specialty, L.P. (Mylan Specialty) under 21 USC 355 and 21 CFR 10.30, among other provisions of law, to request that the Commissioner of Food and Drugs (the Commissioner) take certain actions with respect to abbreviated new drug application (ANDA) 90-589, submitted by Teva Pharmaceuticals (Teva), for an epinephrine auto-injector. Teva's ANDA relies on Mylan Specialty's EpiPen[®] (epinephrine injection) as the reference listed drug (RLD). Among other things, Mylan Specialty asks that the Commissioner refrain from approving the Teva ANDA unless, after conducting an appropriately rigorous review under the established standards for proposed generic emergency use auto-injectors, the agency concludes that the proposed product is the "same as" the EpiPen[®] auto-injector. This includes that patients, caregivers, and other relevant user groups trained in the use of the EpiPen[®] auto-injector who face an emergency situation are able to safely and effectively use the proposed product in accordance with the EpiPen[®] auto-injector instructions for use, without additional physician interaction or training. As discussed herein, Mylan Specialty believes that, because of the nature and scope of differences in design and operating principles, EpiPen[®]-trained users will not be able to safely and effectively use the Teva proposed product in accordance with the FDA-approved EpiPen[®] auto-injector instructions for use.

Epinephrine auto-injectors are used for the emergency treatment of allergic reactions, including potentially fatal anaphylaxis, which can progress from exposure to cardiorespiratory arrest in as little as five minutes. These products are used primarily by patients, including children, and caregivers (not medical professionals) under highly stressful, time-sensitive conditions where they must recognize the signs and symptoms of anaphylaxis and execute a successful injection. Thus, it is imperative that the users understand how to quickly and properly administer the product in an emergency. In that regard, the Food and Drug Administration (FDA or the agency) has concluded that proposed generic epinephrine auto-injectors pose unique issues of sameness that are essential to safety and effectiveness, and that involve both the drug and device components of this combination product.¹

¹ See Docket No. FDA-2009-P-0578, PDN (May 27, 2010) (Dey Petition Response) (Tab 1). Dey was renamed Mylan Specialty in 2012 and is a subsidiary of Mylan Inc.

By way of example, the FDCA generally requires that, in order to be approved, a proposed generic product must be the “same as” the RLD, which results in an “A”-rating in the Orange Book, reflecting the agency’s judgment that the two products are therapeutically equivalent and may be substituted one for the other.² With regard to epinephrine auto-injectors, FDA has more specifically said that evaluating whether a proposed generic meets this sameness requirement involves determining whether “patients in an emergency situation can use the [proposed generic] product safely and effectively in accordance with instructions provided for the RLD without additional physician intervention or retraining prior to use.”³ Moreover, FDA has recognized that the data necessary to demonstrate that two products are the same, notwithstanding differences in auto-injector design and operating principles, may fall outside that which is permitted in an ANDA and necessitate a new drug application (NDA) submitted in accordance with section 505(b)(2) of the Food, Drug, and Cosmetic Act (FDCA) (a 505(b)(2) NDA). The agency has established general principles for evaluating the approvability of a proposed generic epinephrine auto-injector, and said it will consider the safety and effectiveness issues raised by such products on a case-by-case basis. None of the other epinephrine auto-injectors on the market, each of which represents a distinct design and operating principles, is rated as therapeutically equivalent to another.

This petition is submitted with regard to one such specific case, and seeks to have FDA carefully apply the demanding standards it has said govern here. Publicly available (and recently confirmed) information indicates that the design and operating principles of the Teva proposed product differ significantly from those of the EpiPen® auto-injector. With that in mind, experts have analyzed the differences between the Teva proposed product and the EpiPen® auto-injector and the likely implications for safe and effective use of the proposed generic. As noted above, FDA has said the question to ask in considering whether to approve a proposed generic product such as Teva’s is whether “patients in an emergency situation can use the product safely and effectively in accordance with instructions provided for the RLD without additional physician intervention or retraining prior to use.”⁴ The experts’ unequivocal answer to that question is a resounding “no.”

As discussed herein and in the experts’ reports, the differences in design and operating principles of the EpiPen® and Teva auto-injectors are of a nature and magnitude that, without retraining or physician intervention, likely will prevent patients and caregivers trained on the EpiPen® auto-injector from safely and effectively using the Teva product in an emergency.

² The agency has explained that “[a]n ‘A’ rating reflects FDA’s judgment that the products generally may be substituted for each other without physician intervention with the expectation that the substituted product will produce the same clinical effect and safety profile as the RLD when used for the labeled uses.” Dey Petition Response at 5; *Orange Book*, Preface at vii.

³ Docket Nos. FDA-2007-P-0128, FDA-2009-P-0040, PPAD (July 29, 2009) (King Petition Response) at 6 (Tab 2). At the time the EpiPen auto-injector NDA was approved, the NDA sponsor was Meridian Medical Technologies, Inc., a wholly-owned subsidiary of King Pharmaceuticals. Mylan Specialty currently holds the EpiPen NDA.

⁴ *Id.*

Moreover, patients and caregivers will not be able to use the Teva product “in accordance with instructions provided for” the EpiPen® auto-injector because, among other things, the EpiPen® auto-injector instructions expressly warn users *not* to touch the needle end of the device and the Teva product requires users to remove a safety cap covering the *needle end of the device* and flip a safety clip at the other end to be in a position to administer an injection and the EpiPen® auto-injector instructions (reflecting the fact that the EpiPen® auto-injector has a different mechanism for shielding the needle before use and locking mechanism) require only that the user pull off the safety cap. Even if a patient following the EpiPen® auto-injector instructions with the Teva product manages to remove the safety clip, no injection will be delivered. The user must then, under stressful and time-sensitive conditions, recognize that there was a failure, successfully diagnose the problem, and then work to complete the injection.

These and other differences in design and operation can be expected to result in failed treatments, delays, and user injury. The significance of these errors cannot be overstated, because (1) anaphylaxis is life-threatening, (2) the onset can be rapid (and can move from exposure to cardiorespiratory arrest in as little as five minutes), which means that quick and effective injection is essential, and (3) the product typically is used not by medical professionals but by patients and caregivers who are extremely agitated and possibly experiencing the start of physical effects in a typical use scenario, and therefore need to react with instinct based on training in use of the auto-injector.

In accordance with the requirements placed on applicants by the approval standards for ANDAs generally, as well as the specific principles the agency has enunciated with regard to auto-injectors intended for emergency use, FDA must require, among other things, that Teva demonstrate that patients and caregivers trained on the EpiPen® auto-injector can, without physician intervention or training, safely and effectively use the proposed generic product in an emergency. Meeting that burden of proof requires, at a minimum, very carefully designed human factors studies that would demonstrate the Teva product’s safety and effectiveness and its comparability to the EpiPen® auto-injector in that regard, as well as technical performance data. As the agency has recognized, such human factors data are beyond the scope of what may be submitted in an ANDA.⁵ For that reason, the Teva ANDA may not be approved and must be withdrawn and, if sufficient data are generated, resubmitted as a 505(b)(2) NDA. Further, the differences between the two auto-injectors mean that the labeling for the Teva product must fall outside the limited exceptions to the statutory requirement for a generic product to have the same labeling as the RLD, which also precludes approval of the ANDA.

The issues raised by the proposed Teva device and its submission under an ANDA are novel and involve significant potential health risks to patients. The agency has addressed in general terms the safety and efficacy implications of auto-injector design, and more specifically of differences in design and operation for emergency use auto-injectors, in its response to the Dey petition and petitions submitted by King Pharmaceuticals, as well as in a draft guidance.⁶

⁵ King Petition Response at 7.

⁶ See *Guidance for Industry and Staff: Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products* (June 2013) (Injector Guidance).

FDA has not, however, issued guidance or otherwise provided detail on how to apply the applicable standards to epinephrine auto-injectors. Among other things, the agency has not articulated how to distinguish between differences in emergency-use auto-injector design and operating principles that merit a “BX”-rating (*i.e.*, a determination that the products are not therapeutically equivalent) and those differences that may, with appropriate data, permit approval of an ANDA (with its concomitant finding of therapeutic equivalence). Moreover, beyond stating that human factor studies may be needed and in this context cannot be submitted in ANDA, FDA has not said what data are required to establish that two products with design and operating differences are therapeutically equivalent.

By this petition, Mylan Specialty asks the agency to perform a thorough analysis, consult with technical and medical experts, patient representatives, and members of industry to provide clarity on the appropriate principles and data-driven standards for sameness and apply those enunciated principles and standards to the specific factual scenario presented by Teva’s proposed product. The EpiPen® auto-injector has been serving patients at risk of anaphylaxis for decades, and Mylan employees have developed significant knowledge regarding both the condition and epinephrine auto-injectors, and we look forward to actively participating and supporting the agency’s scientific and regulatory deliberations. Further, we believe that the following actions should be taken.

I. ACTIONS REQUESTED

Mylan Specialty asks that:

1. FDA refrain from approving the Teva ANDA unless the agency affirmatively finds that the proposed generic product is the same as the EpiPen® auto-injector such that:
 - a. Patients, caregivers, and other relevant user groups who were trained in the use of the EpiPen® auto-injector and who face an emergency situation are able to safely and effectively use the Teva product in accordance with the instructions for the EpiPen® auto-injector without additional retraining or physician interaction;
 - b. No human factors or other clinical testing is required to demonstrate the Teva product’s safety or effectiveness in actual use by patients or their caregivers who were trained in the use of the EpiPen® auto-injector, or that the Teva product has the same safety and effectiveness profile as the EpiPen® auto-injector;
 - c. The instructions for use and related aspects of the label and labeling of the Teva product do not differ from the the EpiPen® auto-injector label and labeling beyond differences permitted by the statute and applicable regulations, which require that a generic product generally have the same labeling as the RLD;

- d. Considering the EpiPen® auto-injector as a whole and its individual constituent parts, differences between the Teva product and the EpiPen® auto-injector do not introduce new risks, taking into account both risks intrinsic to the Teva product and risks associated with switching from one epinephrine auto-injector to another without training or physician intervention; and
 - e. The Teva product is shown to be bioequivalent to the EpiPen® auto-injector through appropriately designed bioequivalence testing to examine potential performance differences resulting from design differences and assure equivalent clinical outcomes in the context of generic substitution.
2. FDA require Teva to provide the information necessary to make the above determinations, including specific information regarding product design and operating principles, as well as the results of comparative performance tests between the Teva product and the EpiPen® auto-injector, as detailed herein.
 3. Because human factors or other clinical testing is required to demonstrate the Teva product's safety or effectiveness in actual use, FDA require withdrawal of the ANDA and submission of an NDA under FDCA § 505(b)(2).
 4. If the Teva product is approved under a 505(b)(2) NDA, FDA not assign a therapeutic equivalence code to the Teva product indicating its therapeutic equivalence to the EpiPen® auto-injector unless the agency finds that the two products are bioequivalent and can be expected to have the same clinical effect and safety profile when administered for the approved use and substituted without retraining.
 5. FDA convene a joint meeting of the appropriate advisory committees to provide expert advice and clarity to the agency on the complex scientific, technical, regulatory, and policy issues implicated by the data-driven evaluation of the "sameness" of the Teva proposed generic epinephrine auto-injector and the EpiPen® auto-injector.

II. FACTUAL BACKGROUND

A. Anaphylaxis

Anaphylaxis has been defined as "a serious allergic reaction that is rapid in onset and may cause death."⁷ The onset of anaphylaxis is extremely rapid, and immediate epinephrine

⁷ Sampson HA, Munoz-Furlong A, Campbell R, Adkinson NF, Bock SA, Branum A, *et al.*, Second symposium on the definition and management of anaphylaxis: summary report, *J Allergy Clin Immunol* (2006) 117:391-397 (Tab 3).

intervention to arrest the reaction is essential. Failure to inject epinephrine promptly has been identified as the most significant factor contributing to death.⁸ To that end, the World Health Organization classifies epinephrine as an essential medication for the treatment of anaphylaxis, and all published national guidelines emphasize prompt injection of epinephrine as the only first-line therapy for an acute episode.⁹

Rapid and adequate intervention with epinephrine relieves upper airway obstruction, alleviates shock, and can prevent cardiopulmonary arrest.¹⁰ Cardiorespiratory arrest may occur in as little as five minutes after exposure to an allergen, and delayed administration may result in death. This is amply demonstrated in studies of fatal or near-fatal anaphylaxis. For example, in a UK registry study of 164 people with fatal anaphylaxis, the median time to cardiorespiratory arrest was five minutes after iatrogenic exposure (e.g., anesthesia or antibiotic), 15 minutes after insect sting, and 30 minutes after food allergen ingestion.¹¹ Other studies have shown similar results.¹²

The literature shows that, after a patient with a life-threatening allergy has been exposed to a triggering allergen, there may be an extremely short window for effective pharmacological intervention. For this reason, international guidelines, supported by multiple peer-reviewed publications, recommend the administration of epinephrine as the first-line treatment of choice

⁸ Bock SA, Munuz-Furlong A, Sampson HA. Fatalities due to anaphylactic reactions to foods. *J Allergy Clin Immunol* 2001;107:191-193 (Tab 4); Bock SA, *et al.*, Further fatalities caused by anaphylactic reactions to food, 2001-2006, *J Allergy Clin Immunol* (2007) 119: 1016-18 (Tab 5); Leiberman P, *et al.*, The diagnosis and management of anaphylaxis practice parameter: 2010 Update, *J Allergy Clin Immunol* (2010) 126: 477 (Tab 6).

⁹ Simons FER, *et al.*, World Allergy Organization Guidelines for the Assessment and Management of Anaphylaxis, *WAO Journal* (2011) 4:13-37 (WAO Guidelines) (Tab 7); Simons FER, Anaphylaxis, *J Allergy Clin Immunol* (2010) 125:S161-181(Tab 8).

¹⁰ Simons FER, Anaphylaxis: recent advances in assessment and treatment, *J Allergy Clin Immunol* (2009) 124:625-36 (Tab 9).

¹¹ Pumphrey RSH, Lessons for management of anaphylaxis from a study of fatal reactions, *Clin Exp Allergy*. (2000) 30:1144-1150, Summary, Table 3 (Tab 10).

¹² A US observational study reporting fatal and near-fatal reactions to food in children and adolescents conducted over a 14-month period identified six fatal and seven near-fatal cases of food-induced anaphylaxis in children and adolescents. All cases had symptoms within 30 minutes of food ingestion. Two of the six who died received epinephrine within the first hour, whereas six of the seven who survived the episode received epinephrine within 30 minutes. Sampson HA, *et al.*, Fatal and near-fatal anaphylactic reactions to food in children and adolescents, *N Engl J Med*. (1992) 327:380-384 (Tab 11). Another study documented 25 unselected cases of fatal anaphylaxis in adults between 1989 and 2001. The majority of patients had symptoms within 30 minutes of exposure. The time to death was 0-60 minutes in 13 cases, 1-6 hours in 4 cases, 24-96 hours in 4 cases and unknown in 4 cases. Greenberger PA, *et al.*, Fatal anaphylaxis: postmortem findings and associated comorbid diseases, *Ann Allergy Asthma Immunol* (2007) 98:252-257 (Tab 12).

for anaphylaxis as soon as possible to “achieve[] peak plasma and tissue concentrations rapidly.”¹³

B. EpiPen® (epinephrine auto-injector)

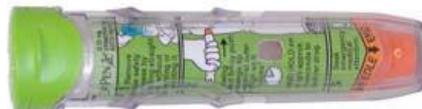
Mylan Specialty holds approved NDA 19-430, for EpiPen (epinephrine auto-injector), a drug-device combination product. The product is indicated in the emergency treatment of allergic reactions (Type I) including anaphylaxis of various origins.¹⁴ The EpiPen® auto-injector is intended for immediate administration in patients who are at increased risk of anaphylaxis, as emergency supportive therapy; patients are directed to seek immediate medical or hospital care in conjunction with use of the EpiPen® auto-injector.¹⁵ It is available in two strengths, 0.3 mg/delivery (the EpiPen® auto-injector) (yellow carrier cap and label) and 0.15 mg/delivery (the EpiPen Jr® auto-injector) (green carrier cap and label).

The EpiPen® auto-injector is specifically designed to facilitate the administration of epinephrine under stressful conditions, in a variety of environments, and on an irregular basis by a wide range of patients and caregivers who are not healthcare professionals. The device features a needle end that is orange and a safety release end that is blue. Further, the operational mechanisms of the EpiPen® auto-injector, such as its spring tension, ensure safe and effective drug administration when used properly. Once removed from the carrier tube, use of EpiPen® auto-injector involves: (1) removing the safety release, and (2) swinging and pushing the tip of the device against the outer thigh.

EpiPen Auto-Injector in Carrier Tube



EpiPen Jr Auto-Injector in Carrier Tube



EpiPen Auto-Injector removed from Carrier Tube



EpiPen Jr Auto-Injector removed from Carrier Tube

¹³ WAO Guidelines at 13, 21-22.

¹⁴ EpiPen Labeling at 2 (Tab 13).

¹⁵ *Id.* at 2-3.



Trainer

Because the EpiPen® auto-injector is intended for administration by a patient or a caregiver in irregular emergency situations that may be fatal, it is imperative that those who would administer the product are thoroughly familiar with it and its operation, and can use it properly under stressful circumstances. Since its launch, the key goal has been to prepare users to promptly and properly inject the EpiPen® auto-injector. Today, to that end:

- The product labeling includes a Patient Insert with easy-to-read instructions for use.
- The Prescribing Information directs healthcare providers to “review the patient instructions and operation of EpiPen . . . in detail, with the patient or caregiver,” and provides that “[p]atients and/or caregivers should be instructed in the appropriate use of EpiPen and EpiPen Jr.”¹⁶
- The Patient Insert states that “[y]our healthcare provider will show you how to safely use the EpiPen or EpiPen Jr Auto-Injector” and instructs patients to “[u]se your EpiPen or EpiPen Jr exactly as your healthcare provider tells you to use it.”¹⁷
- The product is packaged with a trainer device and related instructions so patients and caregivers can practice using the product. As stated in the Prescribing Information, “[p]atients and/or caregivers should be instructed to use the Trainer to familiarize themselves with the use of the EpiPen® auto-injector in an allergic emergency.”¹⁸
- There is a training DVD on how to use the EpiPen® auto-injector.
- Healthcare professionals receive hands-on training, so they can better assist patients and caregivers.

¹⁶ *Id.* at 8.

¹⁷ *Id.* at 11.

¹⁸ *Id.* at 8.

- The device itself is designed to be intuitive to use, and there are clear instructions for use on the device itself.

As the Patient Insert explains, the safe and effective use of the EpiPen® auto-injector requires patients and caregivers to be familiar and comfortable with use of the product in emergency situations.¹⁹

C. The Teva Proposed Product

The Teva proposed product utilizes the Vibex™ auto-injector designed by Antares Pharma.²⁰ The Vibex auto-injector used in the Teva proposed product has a yellow or green needle cap and a blue safety clip at the other end.²¹



The presentation above, exemplar directions on the Antares website, and the use instructions for a non-emergency use product using the Vibex platform indicate that Teva's proposed product generally is used by (1) removing the needle cap; (2) removing the safety clip; and (3) pressing the auto-injector into the thigh.

In addition to differences in how the product is used, Teva has publicly acknowledged that the device design and operating principles of its proposed auto-injector incorporate other meaningful differences from the EpiPen® auto-injector. For example, an Antares report notes the differences between Vibex and the EpiPen® auto-injector and states the following: "EpiPen requires a higher beginning and ending spring force than the [Vibex] device does to accomplish this because the EpiPen device is using the stored energy within its main spring to perform multiple functions, whereas the [Vibex] device uses the stored energy within its main spring to

¹⁹ EpiPen Labeling at 9.

²⁰ See Antares Pharma, *Pipeline Chart*, <http://www.antareshpharma.com/investors/pipeline> (last visited Jan. 16, 2015) (identifying the "Vibex™ EPI" as being used on a Teva product for which an ANDA has been filed) (Tab 14). "EPI" presumably refers to an auto-injector intended for use with epinephrine.

²¹ Investor Presentation by P. Wotton, President and CEO, Antares Pharma (Sept. 2012) (Tab 15).

perform just one function.”²² As described below, this and other differences, including the distinct use instructions, have significant regulatory implications and negatively impact patient health and safety.

III. LEGAL STANDARDS

A. ANDA Approval Standards

Under Section 505(j) of the FDCA, an ANDA applicant must demonstrate, among other things, that its proposed product is the same as the RLD with regard to active ingredient, dosage form, route of administration, strength, labeling, and conditions of use, and that it is bioequivalent, as well.²³ A product that meets these standards may be approved and receive an “A” rating in the *Orange Book*, connoting therapeutic equivalence. The agency has explained that “[a]n ‘A’ rating reflects FDA’s judgment that the products generally may be substituted for each other without physician intervention with the expectation that the substituted product will produce the same clinical effect and safety profile as the RLD when used for the labeled uses.”²⁴

Generally, a proposed generic product that is pharmaceutically equivalent²⁵ and bioequivalent to, and has the same labeling as, the RLD will be approved under an ANDA and receive an “A” rating.²⁶ There are circumstances, however, where a proposed product, even though bioequivalent and pharmaceutically equivalent, differs from the RLD in therapeutically significant ways that preclude approval via an ANDA.

In some instances, product differences may require changes in labeling that go beyond the permitted exceptions to the “same labeling” requirement for generic products. Generally, exceptions are permitted if they are required because of minor product differences approved in a suitability petition (*e.g.*, change in dosage strength) or because the proposed generic and reference listed drugs are produced or distributed by different manufacturers.²⁷ Permitted differences include minor labeling variations, such as in expiration date, formulation, bioavailability, or pharmacokinetics; labeling revisions to comply with FDA guidance, and omission of an aspect of labeling that is protected by patent or regulatory exclusivity.²⁸ The

²² Transcript of Testimony of Peter Sadowski, Defense Expert Witness, at 428, from *King Pharmaceuticals, et al. v. Teva Parenteral Medicines, Inc., et al.* (D. Del.; 1:09-cv-00652) (Tab 16).

²³ FDCA 505(j)(2)(A)(i)-(v); *see, e.g.*, 21 CFR 314.94(a)(4)-(8).

²⁴ Dey Petition Response at 5; *Orange Book*, Preface at vii.

²⁵ Products are considered pharmaceutical equivalents if they contain the same active ingredient in the same strength or concentration, are in the same dosage form, have the same route of administration, and meet the same compendial or other applicable standards of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. *See* 21 CFR 320.1(c); *Orange Book*, Preface at vii.

²⁶ *See Orange Book*, Preface at vi-vii.

²⁷ FDCA 505(j)(2)(A)(v).

²⁸ 21 CFR 314.94(a)(8)(iv).

exception has been construed as narrow by Congress and FDA.²⁹ Relatedly, even when accommodating variations in labeling resulting from patent or exclusivity provisions, FDA has not tolerated those variations if they resulted in a substitutable generic product that is less safe and effective than the reference drug.

In other cases, the products may differ in ways that require clinical data to demonstrate the proposed product's safety and effectiveness, and such data are beyond the scope of what may be reviewed and approved in an ANDA.³⁰ In such circumstances, the proposed product may be submitted with such data via an NDA submitted in accordance with FDCA 505(b)(2).³¹ Even if approvable via a 505(b)(2) NDA, the product or its labeling may nonetheless differ from the RLD in ways that preclude an "A" rating.

B. Application of Standards to a Proposed Generic Auto-Injector

The agency has acknowledged the potential significance of these issues in the context of drug-device combination products generally, and with regard to auto-injectors specifically.³² The agency's "sameness" analysis necessarily involves the delivery device, where FDA examines "whether any difference in materials, design, or operating principles introduces a new risk."³³ In that regard, FDA considers "both risks intrinsic to the new product and risks associated with switching from one product to the other without additional physician intervention or training, and looks at both the RLD as a whole and its constituent parts."³⁴

FDA has acknowledged that, when reviewing an ANDA for an auto-injector combination product, the agency must evaluate the auto-injector component "to ensure that its performance characteristics and critical design attributes will result in a product that will perform the same as the RLD." The key inquiry is whether there are design differences that "significantly alter

²⁹ H.R. Rep. No. 98-857, pt. 1, at 22 (1984) (stating that the labels must be the same, except for small changes such as a difference in manufacturer's address); ANDA Proposed Rule, 54 FR 28872, 288884 (July 10, 1989); ANDA Final Rule, 57 FR 17950, 17953, 17955, 17957, 17961 (Apr. 28, 1992).

³⁰ See FDCA 505(j)(2)(A).

³¹ See *Guidance for Industry: Applications Covered by Section 505(b)(2)* (Oct. 1999 draft) at 3 ("An applicant should file a 505(b)(2) application if it is seeking approval of a change to an approved drug that would not be permitted under section 505(j), because approval will require the review of clinical data."); Docket No. FDA-2009-P-0123, PPAD (August 26, 2009) (Auxilium Petition Response) at 5 (requiring clinical data from follow-on products because differences from RLD raise the risk of "potentially severe and irreversible" health effects, and finding that the need for such data precludes submission of an ANDA and necessitates a 505(b)(2) NDA) (Tab 17).

³² See generally King Petition Response, Dey Petition Response.

³³ King Petition Response at 6.

³⁴ *Id.*

product performance or operating principles” or “result in impermissible differences in labeling” (*i.e.*, labeling differences beyond what is permitted in an ANDA).³⁵

Specifically with regard to auto-injectors that require training for unsupervised use by patients, the agency has said:

For ANDAs for a product with labeling that describes use by patients without physician supervision and further requires training of patients by a physician prior to initial unsupervised use, FDA considers whether patients can be safely switched to a new product without retraining by a physician or health care professional. ***For an ANDA for a product intended for emergency use by patients without professional supervision (such as a prefilled auto-injector indicated for emergency treatment of allergic reactions), it is particularly important to ensure that patients in an emergency situation can use the product safely and effectively in accordance with instructions provided for the RLD without additional physician intervention or retraining prior to use.***³⁶

The ability of users trained on the EpiPen® Auto-Injector to use the proposed product to administer epinephrine promptly and properly in an emergency cannot be over-emphasized. Even without the added complication of substitution – which is often unknown to the prescriber and patient – user error related to devices like epinephrine auto-injectors is not uncommon.³⁷

Further, in order to allow the agency to conduct the necessary evaluation, an applicant seeking approval of an ANDA for such a product must provide detailed information on the proposed product, including the design, materials, and operating principles of the auto-injector, as well as performance tests comparing the auto-injectors of the RLD and the proposed generic product.³⁸ Comparative performance testing that would demonstrate therapeutic equivalence includes extended needle length, needle integrity, activation force, dispensing time, dispensed volume, injection force, breakloose force, extrusion force, needle gauge, needle protrusion, and needle penetration depth.³⁹

Additionally, differences between auto-injectors (including but not limited to needle hub assembly, operating principles, and ergonomics) “may require further clinical data” to determine

³⁵ King Petition Response at 6.

³⁶ *Id.* (emphasis added); *see also id.* at 10-11 (“For products that require physician training before unsupervised patient use, differences in operation [between the proposed generic and RLD] that require retraining prior to use are not expected to be acceptable in an ANDA.”); Dey Petition Response at 8.

³⁷ Bonds RS, *et al.*, Misuse of medical devices: a persistent problem in self-management of asthma and allergic disease, *Ann Allergy Asthma Immunol* (2014) 114: 74-76.e2 (Tab 18); Sicherer SH, *et al.*, Use assessment of self-administered epinephrine among food-allergic children and pediatricians, *Pediatrics* (2000) 105: 359-62 (Tab 19).

³⁸ King Petition Response at 7.

³⁹ *Id.* at 8-9, 11.

that there is no clinical impact.⁴⁰ Because proper use by the target population (patients and caregivers in stressful emergency situations) is essential to the product's safe and effective use, demonstrating that the proposed product is safe and effective may also require human factor analysis, actual use studies and labeling comprehension studies.⁴¹ Importantly, the agency has acknowledged that, if clinical data or human factor studies are necessary to answer these critical questions of sameness or safety and efficacy, "such studies are beyond the scope of studies that can be reviewed and approved in an ANDA", and would require the product to be submitted for review as an NDA under FDCA 505(b)(2).⁴²

IV. ANALYSIS

The agency has stated that "the emergency-use situations under which an EpiPen auto-injector is used calls for particular vigilance in assuring that patients would be able to use a generic version of the EpiPen auto-injector as safely and effectively as they would the RLD."⁴³ Further, this analysis must take into account "not only . . . the individual attributes of one or several auto-injector differences, but also the *combined* effects of those differences."⁴⁴ And one of the specific factors identified to be evaluated is the "impact of unexpected change in [the] product during emergency use."⁴⁵ In that regard, the purpose of the analysis is to "ensure that patients in an emergency situation can use the product safely and effectively in accordance with instructions provided for the RLD without additional physician intervention or retraining prior to use."⁴⁶

The petition submitted by Dey Pharma sought relief with regard to all proposed generic versions of the EpiPen® auto-injector. In large part, the agency denied the requested relief because it was categorical, and the relevant issues require case-by-case analysis and decision-making.⁴⁷ In its response to the Dey petition, FDA said it would instead conduct a careful product-specific analysis of each proposed generic product that seeks to rely on the EpiPen® auto-injector as the reference listed drug:

We will evaluate any device design change to determine what, if any, methods, bench testing data, and type of studies are necessary to validate the safety and effectiveness of those changes. We also will evaluate the combined effect of any

⁴⁰ *Id.* at 8.

⁴¹ *Id.*

⁴² *Id.* at 7; *see also* Dey Petition Response at 5.

⁴³ Dey Petition Response at 8.

⁴⁴ *Id.* at 9 (emphasis in original).

⁴⁵ *Id.* at 7.

⁴⁶ *Id.* at 8, *quoting* King Petition Response at 7.

⁴⁷ *See, e.g.*, Dey Petition Response at 13 ("[W]e decline to adopt a categorical approach to design changes Instead, we will evaluate any changes to the auto-injector design in a generic version of the EpiPen auto-injector on a case-by-case basis.").

differences in the auto-injector that could affect the overall safety and effectiveness (including ease of use, impact of unexpected change in product during emergency use, interpretability of labeling instructions, and likelihood of timely training before use) of a particular proposed generic version of EpiPen auto-injector. To the extent such changes could affect safe and effective use of epinephrine therapy for treatment of anaphylaxis, the Agency may require further study or human factors studies, recommend an alternative regulatory pathway, or decline to approve the application under section 505(j) of the Act.⁴⁸

By this petition, Mylan Specialty is asking FDA to confirm that, specifically with regard to the Teva proposed product, the agency is conducting the probing inquiry required for products such as these, which are used by patients and caregivers in potentially life-threatening situations.

A. There are Significant Differences Between the Teva Product and the EpiPen® auto-injector

Attached as Tab 20 is an Expert Comparative Analysis conducted by Interface Analysis Associates (IAA) comparing the design features and operating principles of the EpiPen® auto-injector and the Teva product. IAA was founded and is headed by Anthony Andre, Ph.D., CPE, whose credentials are attached as Tab 21. As the report makes clear, IAA's analysis led to the conclusion that there are significant differences between the products, and that those differences would prevent a patient or caregiver trained on the EpiPen® auto-injector from being able to use the Teva product safely and effectively in an emergency, or in accordance with the EpiPen® auto-injector instructions for use.

Notably, the Teva product requires users to perform two steps (remove a safety cap covering the needle and flip a safety clip at the other end) to be in a position to administer an injection, but the EpiPen® auto-injector instructions (reflecting the fact that the EpiPen® auto-injector has a different mechanism for shielding the needle before use and locking mechanism) require only that the user pull off the safety cap and, moreover, expressly warn users *not* to touch the needle end of the device. Additionally, the mechanical actions required to perform the steps required for each device are distinct; for example, EpiPen® auto-injector users are instructed to pull the safety cap straight up and off without bending or twisting, while the Teva product requires flipping the safety clip off to enable the device for administration.

Having analyzed the differences between the EpiPen® auto-injector and the Teva proposed product and considered the implications for safety and effectiveness, IAA came to this conclusion:

There are numerous significant differences in the design and use procedure between the EpiPen Auto-Injector and [Teva] Proposed Generic Auto-Injector. If the latter was substituted as a generic for the former, these differences would likely results in negative transfer, such that the learned habits and expectations of

⁴⁸ *Id.*

EpiPen-trained users would thwart effective and safe use of the Proposed Generic device (without physician intervention and training). Further, the differences are such that the Proposed Generic device cannot (or would not) be used safely and effectively in strict accordance with the instructions for use for EpiPen Auto-Injector, which, most significantly, does not provide for removing a needle cap, and in fact warns against touching the needle end of the device. The use errors likely to occur include potential delayed therapy, partial or complete failure to delivery therapy, and possible injury due to unintentional or inverted injection.⁴⁹

Also attached (as Exhibit 22) is the declaration of Eli O. Meltzer, M.D. Dr. Meltzer, whose CV is attached to his declaration, has decades of experience in the fields of allergy and immunology, both as a practicing physician treating patients at risk of anaphylaxis and as a faculty member, and has been a member of FDA's Pulmonary/Allergy Advisory Committee and a consultant to the Center for Drug Evaluation and Research. It is Dr. Meltzer's view that:

[T]here are clinically significant – in fact, life-threatening –risks to having patients and caregivers (who are trained and familiar with the EpiPen[®]/EpiPen Jr[®] epinephrine auto-injector) use, without physician intervention or retraining, a generic epinephrine auto-injector with different instructions for use and different administration techniques. I do not believe that a user trained on the EpiPen[®]/EpiPen Jr[®] platform will be able to reliably use a different operational platform in an emergency situation as safely and effectively.⁵⁰

Perhaps most importantly, Dr. Meltzer further concludes, “based on the description of the design and operating principles of the Vibex auto-injector contained in the comparison analysis prepared by Dr. Andre, I do not believe that EpiPen[®] patients could be safely switched to any generic epinephrine auto-injector that utilizes the Vibex platform without retraining by a physician or other healthcare professional.”⁵¹

1. Differences in Design and Operating Principles

The differences in design and operating principles between the EpiPen[®] auto-injector and the Teva product, discussed in some detail in the IAA report, are summarized below.⁵²

⁴⁹ IAA Report at 16.

⁵⁰ Declaration of E.O. Meltzer (Meltzer Declaration) at ¶ 77.

⁵¹ *Id.*

⁵² The product characteristics discussed below are taken from the FDA-approved labeling for Otrexup[™] (methotrexate) (available at <http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=9ab8ce16-f7de-41d4-a4c8-1c742621b6d5>) (Tab 23) and Investor Presentation by P. Wotton, President and CEO, Antares Pharma (Sept. 2012) (Tab 15).

**EpiPen® Auto-Injector and Proposed Teva Product:
 Design and Operational Differences**⁵³

	EpiPen® auto-injector	Teva
Steps to Operation	1. Remove safety cap (to enable injection).	1. Remove needle guard.
	2. Inject drug.	2. Remove safety clip (to enable injection).
		3. Inject drug.
Remove Safety Cap/Clip	Hold device body in one hand, and with other hand, pull safety cap straight up, without bending or twisting it.	Grasp device in one hand and use the thumb of that hand to flip up the safety clip.
Prepare Needle	No preparation is necessary. Patient is trained and warned not to touch the needle end.	Patient must grasp the needle end and twist off a needle cap.
Method of Injection	The EpiPen® auto-injector is swung and pushed against the thigh until it clicks.	Vibex is held against the thigh, and then pressed into the leg.

As the preceding table indicates, there are significant differences in the two products' design and operating principles, including:

- **The manner in which the safety is released:** The first step with the EpiPen® auto-injector is to remove the safety cap. To do that, a patient or caregiver grasps the unit in one hand, and pulls off the safety release with the other hand, pulling straight up without bending or twisting the cap. The Teva product has a safety clip, and its removal is the second step in that product's preparation for use. The safety clip is released by holding the device body in one hand and flipping the safety clip with the thumb of the same hand.

⁵³ See IAA Report at 6-8.

EpiPen® Auto-Injector

1. Grasp unit with the orange tip pointing downward.
2. Form fist around the unit (orange tip down).



3. With your other hand, pull off the blue safety release.

Vibex



- **Preparation of the needle:** Importantly, the method of preparing the Teva product's needle for injection is directly contrary to the instructions for the EpiPen® auto-injector. Once the EpiPen® auto-injector's safety cap has been removed, the auto-injector is ready for use; the next step is injection. The needle is recessed within the tip of the unit and no further action is needed to prepare the device for injection.

In fact, EpiPen® auto-injector users are specifically trained not to touch the needle cap. The EpiPen® auto-injector labeling warns in several places not to touch the tip that contains the needle because it could result in an accidental injection. For example, the Prescribing Information states: “**Caution: Never put your thumb, fingers, or hand over the orange tip. Never press or push the orange tip with your thumb, fingers, or hand.** The needle comes out of the orange tip. Accidental injection into finger, hands or feet may cause a loss of blood flow to these areas. **If this happens, go immediately to the nearest emergency room.**”⁵⁴

In contrast, the Teva proposed product requires that a patient grasp the needle tip to twist and pull off a needle cap. This is different than the instructions for use of the EpiPen® auto-injector, which requires no needle preparation and prominently warns users not to touch the needle end of the device. This fundamental difference means that a patient or caregiver trained in use of the EpiPen® auto-injector could not safely and effectively operate the Teva product in accordance with the EpiPen® instructions for use, because those instructions do not provide for removal of a needle cap, and expressly warn against touching that end of the device.

EpiPen® Auto-Injector

Vibex

Do not to touch the needle tip

⁵⁴ EpiPen Labeling at 13 (emphasis in the original).



- **Method of injection:** The EpiPen® auto-injector and the Teva product achieve injection through different operational principles, which would be reflected in different instructions for injection. The EpiPen® auto-injector is injected by grasping the unit with the hand, holding the tip near the outer thigh, and then swinging and jabbing the unit against the thigh, holding it there for approximately ten seconds. The Vibex device incorporated into the Teva product is operated by holding the device against the thigh at a 90° angle, and then pushing the device into the leg.

EpiPen® Auto-Injector

Vibex



4. Hold orange tip near outer thigh.

DO NOT INJECT INTO BUTTOCK.



5. Swing and **firmly push** against outer thigh until it clicks so that unit is perpendicular (at 90° angle) to the thigh.

(Auto-injector is designed to work through clothing.)



2. Possible Misuse Resulting from Product Differences

The IAA Report catalogs the myriad ways in which these differences can lead to misuse that puts patients at risk:

- **Failure to Remove the Needle Cap.** Because the EpiPen® auto-injector needs no needle preparation and the instructions for use reflect that, many EpiPen-trained users would not expect to have to remove a needle cap in order to use the product and likely would skip that step. Additionally, the Teva needle cap has a hole in it that resembles the hole through which the EpiPen® needle extends, which might also suggest to users that the needle cap is simply the needle end of the device and not something to be removed. Failure to remove to needle cap will result in treatment failure, as the device will not fire.
- **Delay in Removing the Needle Cap.** If the device fails to fire because the needle cap is still in place, some users may eventually figure out that the needle cap needs to be removed. This process of discovery will result in delay in administering treatment, as might the removal process itself, because the cap must be twisted off, which is not a movement used with the EpiPen® auto-injector. In fact, the EpiPen® labeling specifically instructs users not to twist the safety cap off, which may make twisting the needle cap off of the Teva device counterintuitive to users trained on the EpiPen® auto-injector. Additionally, if performed after the safety has been released (which would be expected to be the case with users who follow EpiPen® procedures), the process of removing the needle cap presents the risk of the user accidentally firing the auto-injector into his or her finger or hand. This represents not only a treatment failure but also a medical situation requiring treatment.
- **Failure/Delay in Removing the Safety Cap.** As noted above, the EpiPen® auto-injector and Teva product have different methods for removing the safety. The EpiPen® method (grasp device in one hand, pull cap straight off with the other) will not work with the Teva product, which requires grasping the device in one hand and flipping off the safety clip. This could lead to delay in use of the device, and given the stressful circumstances may even result in a complete failure to deliver treatment.
- **Inversion of the Device.** An EpiPen®-trained user may confuse the needle cap on the Teva product with the safety clip, given that he or she would be only be expecting to remove one cap before using the device. This may lead the user to hold the Teva device upside down, because the end of the EpiPen® auto-injector from which the safety clip is removed is held away from the body. If this is done with the safety clip in place, the device will not fire. If it is done after the safety has been removed, however, there is a risk of accidental injection into the hand.
- **Delay or Failure in Injection.** The EpiPen® auto-injector is injected into the thigh by swinging the device into the leg and pushing, which causes a spring to inject the needle and drug. The Teva product, by contrast, is held against the leg at a 90 degree angle and then pushed. An EpiPen®-trained user who “swings and

jabs” the Teva product may not extend the needle fully or may not have the device properly positioned to operate to its full potential.

- **Delay in Operation.** The Teva product, with its clear plastic body and safety clip on one end that is flipped up, resembles the EpiPen® auto-injector carrying case, which has a clear body and a clip at one end that is flipped up. This could lead an EpiPen®-trained user to mistake the Teva device for a device in a carrying case, and to spend time trying to extract the device from its case. This would lead to delay in treatment and, if the user is manipulating the device after removing the safety clip, presents a risk of accidental injection into the hand.
- **Device Reuse.** After the EpiPen® auto-injector has been fired, the needle guard is more fully extended, and the product cannot fit back into its carrying case. The needle guard on the Teva product also extends to cover the extended needle, but the needle cap can still be placed over that end of the device, which makes it look much like an unused device. Although both auto-injectors also have a window that shows whether the device has been used, they are different, and an EpiPen®-trained patient or caregiver might not see or look at the window on the Teva product and, reaching for an auto-injector in an emergency, may mistake the used device for a new one. This could result in a delay or failure of treatment.

3. Safety and Effectiveness Implications of Misuse

Dr. Meltzer has been treating patients at risk of anaphylaxis, and prescribing the EpiPen® auto-injector, for decades.⁵⁵ He is intimately familiar with the product’s operation, and instructs patients, caregivers and healthcare professionals in its use.⁵⁶ As an expert in anaphylaxis, Dr. Meltzer recognizes “the potential for life-threatening consequences” if anaphylaxis is not promptly and properly treated.⁵⁷ As he acknowledges, the “[f]ailure to administer epinephrine promptly is the most important factor contributing to death in children and adolescents with anaphylaxis.”⁵⁸ Further, “epinephrine auto-injectors are used in emergency situations to treat anaphylactic reactions that, if remain untreated, or are treated too late, can result in death. As a result, *any* confusion caused by a change in the design and operating principles of the auto-injector could contribute to life-threatening delay.”⁵⁹

It is in that context that Dr. Meltzer considered the implications of generic substitution for the EpiPen® auto-injector. Consistent with the assumptions underlying FDA’s enunciated standard for approval of generic emergency auto-injectors, Dr. Meltzer is well aware that

⁵⁵ Meltzer Declaration at ¶¶ 8, 37, 38.

⁵⁶ *Id.* at ¶ 38.

⁵⁷ *Id.* at ¶ 23.

⁵⁸ *Id.*

⁵⁹ *Id.* at ¶ 75.

patients who are dispensed a generic epinephrine auto-injector are highly unlikely to receive training in the generic product's use.⁶⁰ For that reason, it is essential that any generic product that would be substituted for the prescribed auto-injector have the same design, operating principles, and instructions for use.⁶¹ Having read the IAA analysis of the differences between the EpiPen® auto-injector and the Teva proposed product, Dr. Meltzer has concluded that "there is a clinically significant risk that EpiPen®-trained users will experience at least some delay in attempting to figure out the operating differences in a proposed generic epinephrine auto-injector using [the Vibex] platform, if not complete failure."⁶²

Dr. Meltzer agrees with the safety risks identified by IAA, and speaks to the implications of those risks for the analysis that FDA has said underlies its review of a proposed generic epinephrine auto-injector:

As a result of these significant safety risks, I believe that, due to the specific differences between the way the Vibex auto-injector is understood to be designed and operates (as presented in Dr. Andre's report), and the way the EpiPen® auto-injector is designed and operates, an EpiPen®-trained user could not be safely switched to a generic epinephrine auto-injector using the Vibex platform without additional clinician intervention and training. Furthermore, I do not believe that patients can be expected to use the Vibex auto-injector in an emergency situation safely and effectively in accordance with the EpiPen® instructions for use without additional clinician intervention and retraining prior to use.⁶³

4. Implications for Approvability of the Teva ANDA

EpiPen® auto-injector patients are specifically instructed to "[u]se your EpiPen or EpiPen Jr exactly as your healthcare provider tells you to use it"⁶⁴. If a patient who has been trained to use EpiPen® Auto-Injector uses the proposed Teva product as trained, the Teva product will not work. The combined effect of the differences described above has the potential to result in significant patient confusion. As noted above, the agency's analysis must recognize that the EpiPen® auto-injector is intended for emergency use by patients and caregivers, not medical professionals, on an irregular basis and is essential to treating a time sensitive life-threatening condition. Anaphylaxis is an acute systemic reaction with serious effects, including death, that can occur within minutes of exposure to the triggering allergen (typically, a food, an insect sting, medication, or latex). It is well recognized that epinephrine is the cornerstone of treatment, considered the first-line medication choice in anaphylaxis because it may help relieve

⁶⁰ *Id.* at ¶¶ 47-50.

⁶¹ *Id.* at § IV.

⁶² *Id.* at ¶ 74.

⁶³ *Id.* at ¶ 76.

⁶⁴ EpiPen Labeling at 11.

all symptoms and signs, and should be given immediately.⁶⁵ That is why it is critical that any epinephrine auto-injector be able to be used quickly and correctly.

As the agency has recognized, “[u]nder high stress levels, the user is distracted and will have less time to make decisions, consider multiple device outputs, follow complex operating logic, or physically manipulate device components.”⁶⁶ Accordingly, it is imperative not only that the device be appropriately designed, but also that the patient or caregiver be familiar with, and well-trained in using, the auto-injector.⁶⁷ It is for this reason that the EpiPen® auto-injector is approved with an extensive and continuing program to perpetually educate and train patients and caregivers in the use of the EpiPen® auto-injector. Patients who are prescribed an EpiPen® auto-injector (and their caregivers) are trained by a healthcare professional in the specific use of the EpiPen® auto-injector, receive detailed patient-focused labeling with instructions on use of the product, and are furnished a trainer device in order to practice using the EpiPen® auto-injector. The purpose is for the patient or caregiver to be prepared to safely and effectively use the product in an emergency.

If a patient or caregiver in an emergency situation is presented with an auto-injector with which he or she is not familiar – and, perhaps more importantly, that differs in design and operation from that with which he or she has been trained – there is a real risk that the device will be misused, and that delivery of the drug will be delayed or completely missed, which can have lethal results. Alternatively, patients that are switched back to the EpiPen® auto-injector from Teva’s proposed product may attempt to twist off the needle cap, which could result in an accidental injection. Accidental injection can lead to “intense local vasoconstriction and irreversible tissue ischemia” in the digit, as well as the “lost dose hazard,” where the dose is either injected into the caregiver and completely lost or delayed in absorption into the patient’s system.

The significant differences in design and operation between the Teva product and the EpiPen® auto-injector, described above, will necessarily require differences in labeling; the instructions for use of the Teva product cannot be the same as those for the EpiPen® auto-

⁶⁵ See, e.g., The Merck Manual, “Anaphylaxis,” available at http://www.merckmanuals.com/home/immune_disorders/allergic_reactions_and_other_hypersensitivity_disorders/anaphylactic_reactions.html (rev. May 2014) (Tab 24); see also, e.g., Simons F, et al., World Allergy Organization Guidelines for the Assessment and Management of Anaphylaxis, *J. Allergy Clin. Immunol* (2011) 127(3):593.e1-e22 (Tab 25).

⁶⁶ *Guidance for Industry and FDA Premarket and Design Control Reviewers: Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management* (July 18, 2000) at 10.

⁶⁷ See, e.g., Arkwright P, Farragher A, Factors Determining the Ability of Parents to Effectively Administer Intramuscular Adrenaline to Food Allergic Children, *Pediatr. Allergy Immunol* (2009) 17:227-229 (Tab 26) (“Appropriate education is essential if parents and caregivers are to be competent in the use of these auto-injectors.”); Soar J, et al., Emergency Treatment of Anaphylactic Reactions: Guidelines for Healthcare Providers, *Resuscitation* (2008) 77:157-169 (Tab 27) (“Patients and those close to them (e.g., family, friends, carers) should receive training in using the auto-injector and should practice regularly using a suitable training device, so that they will know what to do in an emergency.”).

injector. With that in mind, the agency's review of ANDA 90-589 must include careful consideration of whether patients and caregivers who are extensively trained on, and comfortable with, the EpiPen® auto-injector will be able to quickly and properly use the Teva product in accordance with the EpiPen® instructions, without any training on the proposed generic.⁶⁸ Unless FDA has a basis for concluding that patients and caregivers in an emergency will, without retraining, be able to safely and effectively use the Teva product, the agency must refuse to approve the ANDA.

B. Because Clinical or Human Factor Studies are Necessary to Demonstrate the Teva Product's Sameness and its Safety and Effectiveness, the Product Cannot be Submitted in an ANDA.

Moreover, the burden is on Teva to demonstrate that its product meets the standards for approval.⁶⁹ As the agency has explained, one of the central inquiries in determining whether a proposed generic auto-injector may be approved is whether design differences between the proposed product and the RLD "significantly alter product performance or operating principles."⁷⁰ To conduct that evaluation, FDA must have detailed information about the design, materials and operating principles of the proposed product, as well as comparative performance data. If the Teva ANDA does not contain the necessary information (*see* discussion above as to specific data required), or if the data do not demonstrate equivalence on these essential characteristics, the agency cannot approve the ANDA.⁷¹

In particular, Teva must provide a basis on which the agency can reasonably conclude that patients and caregivers will be able to use Teva's proposed product safely and effectively in a life-threatening emergency, without retraining. The nature and extent of the differences in design and operating principles between Teva's proposed product and the EpiPen® auto-injector may require supporting data before the agency can reach that conclusion.⁷² If data from human factor analysis, actual use studies, or usability studies are necessary for FDA to determine that

⁶⁸ The differences in design and operation will necessarily require differences in labeling, such that the instructions for use of the Teva product will not be the same as those for the EpiPen auto-injector. The labeling differences are important both to whether patients and caregivers can safely and effectively use the Teva product in an emergency, and whether the labeling is not the "same as" the EpiPen auto-injector labeling, as the law requires for approval of an ANDA.

⁶⁹ 21 USC 355(j)(2)(A); 21 CFR 314.94; 21 CFR 314.127(a).

⁷⁰ King Petition Response at 6.

⁷¹ Additionally, if Teva is seeking a waiver of the requirement to provide *in vivo* data of bioequivalence, the agency should require the drug product to have the same active and inactive ingredients in the same concentration as the EpiPen auto-injector, and Teva to provide data from performance testing to show that the Teva product's needle penetration depth, dispensing time, dispensed volume, and injection force are similar to those of the EpiPen auto-injector.

⁷² Moreover, the stated differences in design and operation between EpiPen® auto-injector and Teva's proposed ANDA also likely result in performance differences, which is why data from appropriately designed bioequivalence studies to examine these differences and assure equivalent clinical outcomes in the context of generic substitution are essential.

patients and caregivers do not require training to be able to safely and effectively use Teva's proposed product in an emergency (and the safety risks identified herein demonstrate that they are), the product cannot be reviewed or approved via an ANDA. Rather, Teva must withdraw the ANDA and submit a 505(b)(2) NDA.⁷³

C. Because the Teva Product's Labeling Would Differ from the EpiPen® Auto-Injector Labeling in Ways Beyond the Permitted Exceptions, the Teva Product Cannot be Approved in an ANDA.

Generic products generally are required to have the same labeling as the RLD. The statute permits differences in defined circumstances, and FDA's regulations provide further detail on those circumstances. These are exceptions, however, and therefore construed narrowly. Moreover, the agency has specifically acknowledged that, although "[c]ertain minor labeling changes," such as to identify a change in materials to make the proposed product lighter or more robust or durable, are acceptable, other changes are not.⁷⁴ In that regard, significant changes in the instructions for use – which would indicate a need for patient or caregiver retraining before the proposed generic auto-injector could be safely and effectively used – fall outside the permitted labeling differences.⁷⁵ Moreover, it is the applicant's responsibility to demonstrate that changes in the instructions for use do not require retraining.

Accordingly, FDA must determine whether the differences between the Teva product and the EpiPen® auto-injector require differences in labeling that exceed the exceptions laid out in the statute and regulations. This includes but is not limited to analyzing whether differences in instructions for use require retraining before patients or caregivers and or otherwise go beyond the narrow exceptions laid out in the statute and regulations. If FDA cannot answer those questions in the negative, or if it requires clinical or human factors data to be able to do so, the agency cannot approve the ANDA.

D. A Teva 505(b)(2) NDA Must Demonstrate Therapeutic Equivalence

Mylan Specialty recognizes that, even if Teva is required to submit a 505(b)(2) NDA, the Teva product may be a pharmaceutical equivalent to the EpiPen® auto-injector. Accordingly, if the product is also bioequivalent to the EpiPen® auto-injector, Teva may seek an "A" rating in the Orange Book, connoting therapeutic equivalence and signaling FDA's determination that the products are substitutable. To receive an "A" rating, however, it is not sufficient for the products to be merely bioequivalent pharmaceutical equivalents; FDA must conclude that the products

⁷³ See Dey Petition Response at 9-10 ("[I]n some instances, differences in specific aspects of an applicant's generic version of EpiPen auto-injector are significant enough that they require clinical studies, including human factors, to ensure the safety and effectiveness of the product. Further, some differences may be so significant that FDA may deny approval under section 505(j) of the Act and recommend an alternate regulatory pathway such as that found under section 505(b)(2).").

⁷⁴ King Petition Response at 10-11.

⁷⁵ See *id.* (differences in operation that require retraining are not permissible labeling changes for an ANDA).

“can be substituted with the full expectation that the substituted product will produce the same clinical effect and safety profile as the [RLD].”⁷⁶

Because a therapeutic equivalence determination for a prefilled auto-injector takes into account both the auto-injector component and the drug component of the combination product,⁷⁷ differences in auto-injector design, operating principles, or performance could preclude a finding of therapeutic equivalence, even if the Teva product is both pharmaceutically equivalent and bioequivalent to the EpiPen® auto-injector. Accordingly, if Teva submits a 505(b)(2) NDA for an epinephrine auto-injector that relies on the EpiPen® auto-injector as the RLD, the agency must carefully consider the differences between the auto-injectors, and cannot assign an “A” rating if the products cannot be expected to have the same clinical effect and safety profile if substituted one for the other.⁷⁸ This evaluation should proceed in accordance with well-articulated principles and standards and take into account the agency’s consistent precedent of approving epinephrine auto-injector products that present distinct design and operating principles under the 505(b)(2) pathway with a “B” rating, connoting that they are not therapeutically equivalent, as well as other similar approvals involving 505(b)(2)s for combination products that are pharmaceutically equivalent but not “A”-rated as therapeutically equivalent.

E. The Agency Should Convene an Advisory Committee Meeting to Address the Complex Scientific, Technical and Policy Issues Posed by The First Proposed Emergency Auto-Injector.

Mylan Specialty also asks that FDA engage in a searching analysis on these issues and convene a meeting of the appropriate advisory committees to consider the important and complex scientific, technical, and policy issues raised by the proposed Teva epinephrine auto-injector. The Teva ANDA presents a first-of-a-kind, first-in-class medical product, *i.e.*, the first proposed substitutable epinephrine auto-injector and, more broadly, the first proposed substitutable emergency use auto-injector, presented to the agency. In the King and Dey petition responses, FDA enunciated the policy issues raised by, and general standards for approval of, a generic auto-injector for emergency use by patients and caregivers. FDA has not, however, issued product-specific guidance for epinephrine auto-injectors or otherwise articulated its proposed principles for analyzing differences in design and operating principles or the design standards for generating data to inform FDA’s decision making with regard to those policy issues and general standards. At the very least, the agency must conform any such guidance or standards to the prior pronouncements regarding the safe and effective use of emergency-use

⁷⁶ *Orange Book*, Preface at vii; *see also* King Petition Response at 7 (To be therapeutically equivalent, products must be “expected to have the same clinical effect and safety profile when administered to patients for the labeled uses.”).

⁷⁷ King Petition Response at 7.

⁷⁸ The significance of the risks associated with improper substitution of one epinephrine auto-injector for another is made clear by the agency’s assigning a “BX” rating to all approved epinephrine auto-injectors in the *Orange Book* to clearly communicate that, despite being pharmaceutically equivalent, the products are not therapeutically equivalent.

auto-injectors, as expressed in the King and Dey petition responses. With the Teva ANDA, the agency must concretely address significant questions that arise in implementing that policy and applying those standards. Consistent with FDA's *Guidance for the Public and FDA Staff on Convening Advisory Committee Meetings* (Aug. 2008 draft) (the Advisory Committee Guidance), it is appropriate for those questions to be put before an advisory committee.

Because the EpiPen® auto-injector is intended for use in the emergency treatment of anaphylaxis, which can be fatal in a matter of minutes, the likely users – patients and caregivers, not medical professionals – must be able to use the product quickly and properly. With that in mind, approval of a proposed generic version of the EpiPen® auto-injector requires FDA to conclude that, notwithstanding the differences in auto-injector design and operating principles, patients and caregivers will be able to safely and effectively use the generic product without any training. As discussed in this petition, that determination requires careful consideration of a number of significant and complex issues, including:

- What is the significance of the design differences (*e.g.*, presence/absence of a carrying case; shape/profile of the injector barrel; number and shape of safety caps/clips; labeling)?
- What is the significance of differences in how the devices are operated (*e.g.*, removing two safety caps, not just one; the manner in which the safety caps are removed and the order of –such removal; the method of injection)?
- What is the significance of differences in performance characteristics (*e.g.*, injection force; needle penetration depth)?
- What data and information are necessary to allow for an informed decision on the above issues? How should those data be developed (*e.g.*, human factors studies; study design)?
- What are the implications of the fact that these products are administered by patients (including children) and caregivers, not medical professionals, and under emergency conditions?⁷⁹ How should they be addressed in terms of sponsors' developing data and the agency's consideration of the data?
- Recognizing the well-established need for rapid administration and drug uptake, should the bioequivalence evaluation take into account partial

⁷⁹ In this regard, the proposed Teva epinephrine auto-injector raises issues similar to those associated with the first product in a class that is proposed for a switch from prescription to over-the-counter (OTC) use.

AUC? If so, what should be the time endpoint for that measurement and comparison?

Given the risks to patient safety – from anaphylaxis, and therefore from delayed, improper, or failed use of the generic – these issues require careful consideration, and the agency would benefit from the advice of appropriate experts and the views of interested members of the public.

The stakes are high and the tolerance for error correspondingly low. Millions of Americans suffer from life-threatening allergies, and it is estimated that 63 to 99 deaths occur each year in the United States from anaphylaxis from allergic reactions to medicines, food, and/or insect stings.⁸⁰ Establishing appropriate standards to ensure the therapeutic equivalence of generic epinephrine auto-injectors involves questions of significant public interest, both generally and with regard to Teva's proposed epinephrine auto-injector in particular. Moreover, it involves the intersection of several scientific and technical disciplines, including the medical treatment of allergies, the prevention of anaphylaxis, the analysis of pharmacokinetics and pharmacodynamics, medical device design, and human factors analysis. Accordingly, it is particularly well-suited to advisory committee review.⁸¹

The interdisciplinary nature of the issues is reflected in the agency components with relevant expertise, which include the Office of Generic Drugs, the Division of Pulmonary, Allergy, and Rheumatology Products, the Office of Combination Products, and the General Hospital Devices Branch, which oversees auto-injectors within the Center for Devices and Radiological Health's Office of Device Evaluation. With that in mind, Mylan Specialty asks that FDA convene a joint meeting of the Pharmaceutical Science and Clinical Pharmacology Advisory Committee, the Pulmonary-Allergy Drugs Advisory Committee, and the General Hospital and Personal Use Devices Panel of the Medical Device Advisory Committee, in order to comprehensively address the issues raised by the proposed generic version of the EpiPen® auto-injector.

F. Conclusion

In the King Petition Response, FDA established clear standards for evaluating the approvability of an ANDA for a proposed generic auto-injector. In the Dey Petition Response, the agency explained the application of those standards to a proposed generic version of the EpiPen® auto-injector. With this petition, Mylan Specialty seeks merely to have the agency carefully apply those enunciated standards to the pending Teva ANDA. For the reasons discussed herein, Mylan Specialty believes application of the standards should lead FDA to not approve ANDA 90-589, and if Teva submits a 505(b)(2) NDA for the product, the standards

⁸⁰ Ma L., *et al.*, Case fatality and population mortality associated with anaphylaxis in the United States, *J. Allergy Clin Immunol* (2014) 133: 1075-83 (Tab 26).

⁸¹ See Advisory Committee Guidance at 5 (circumstances in which an advisory committee meeting is appropriate include where there are issues “involving the intersection of several scientific disciplines” or “significant questions . . . regarding the . . . implementation of a regulatory policy”).

preclude an “A” rating to the product if approved. Accordingly, Mylan Specialty asks that the Commissioner take the requested actions.

V. ENVIRONMENTAL IMPACT

The actions requested in this petition are subject to categorical exclusion under 21 CFR 25.31.

VI. ECONOMIC IMPACT

Information on the economic impact of this proposal will be submitted upon request of the Commissioner.

VII. CERTIFICATION

I certify that, to my best knowledge and belief: (a) this petition includes all information and views upon which the petition relies; (b) this petition includes representative data and/or information known to the petitioner which are unfavorable to the petition; and (c) I have taken reasonable steps to ensure that any representative data and/or information which are unfavorable to the petition were disclosed to me. I further certify that the information upon which I have based the action requested herein first became known to the party on whose behalf this petition is submitted on or about the following date: July 20, 2009 (information regarding Teva’s device); November 1, 2010 (information regarding Teva’s device); February 16, 2012 (information regarding Teva’s device); October 11, 2013 (information regarding Teva’s device); November 8, 2014 (information regarding Teva’s device); January 13, 2015 (information regarding Teva’s device); and January 15, 2015 (expert reports) through January 2015. If I received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, I received or expect to receive those payments from the following persons or organizations: None (however, as a Mylan employee, I receive compensation). I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

Respectfully submitted,

A handwritten signature in blue ink that reads "Frank Casty MD". The signature is cursive and includes the letters "MD" at the end.

Frank Casty, MD

HEAD GLOBAL MEDICAL AFFAIRS

Enclosures

Tabs 1 – 27