Michelle R. Ryder
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1600 Stewart Avenue, Suite 604
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September 6, 2024

Re: Docket No. FDA-2022-P-0476

Dear Ms. Ryder:

This letter responds to your citizen petition (Petition) that was received by the Food and Drug Administration (FDA, Agency, or we) on March 29, 2022. The Petition requests that FDA

> . . . determine whether the original formulation submitted for the Reference Listed Drug (RLD), ADRENALIN (Epinephrine Injection [(United States Pharmacopeia)] USP, 30 [(milligrams)] mg/ 30 [(milliliters)] mL) (1 mg/ mL) (Multiple Dose Vials); New Drug Application (NDA) 204640, held by PAR STERILE PRODUCTS LLC, has been voluntarily withdrawn from the commercial market or withdrawn from sale for reasons of safety or efficacy.[1]

We have carefully considered the Petition and other information available to us. Based on our review of these materials and for the reasons stated below, the Petition is granted.

I. BACKGROUND

A. Adrenalin

Endo Operations Ltd.[2] (Endo) is the applicant for Adrenalin (epinephrine injection) 1 mg/mL (NDA 204640). FDA approved NDA 204640 for a 30 mL multiple dose vial of Adrenalin on December 18, 2013, for emergency treatment of allergic reactions (Type 1), including anaphylaxis.[3] FDA approved an additional indication to increase mean arterial blood pressure in

[1] Petition at 1. The Petition states "a sponsor wishing to submit an [abbreviated new drug application]referencing the *original* formulation [approved on 12/18/2013]" of NDA 204640 must submit a citizen petition seeking a determination on whether the original formulation of the drug was withdrawn from sale for reasons of safety or efficacy. Id. at 2 (emphasis in original).

[2] We note that the Petition identified NDA 204640 as being held by Par Sterile Products, LLC (Par). Although this used to be the case,Endo is currently identified as the applicant for NDA 204640 in FDA's *Approved Drug Products With Therapeutic Equivalence Evaluations* (commonly known as the Orange Book), available at https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm.

[3] See Adrenalin NDA 204640 product labeling, approved on Dec 18, 2013, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/204640s000lbl.pdf.

adult patients with hypotension associated with septic shock on January 29, 2019 (NDA 204640/S-009).[4]

FDA approved Adrenalin with an overage[5] of 14 percent (1.14 mg/mL) of the active pharmaceutical ingredient (API) epinephrine due to the observed instability of epinephrine and its degradation over time.[6] Epinephrine has two optical isomers: the naturally occurring endogenous form, L-epinephrine; and its isomer, D-epinephrine. L-epinephrine has approximately 10 to 15 times more systemic activity (when measured by systemic effects on blood pressure, etc.) than D-epinephrine.[7,8] The Adrenalin drug substance is manufactured as L-epinephrine.[9] Generally, aqueous formulations of L-epinephrine are chemically unstable as epinephrine is readily oxidized. The inactive ingredient sodium metabisulfite is included in the formulation to help stabilize L-epinephrine and decrease the rate of oxidation. L-epinephrine can degrade over time in aqueous formulations and form D-epinephrine. In addition, L-epinephrine can interact with sodium metabisulfite to form epinephrine sulfonic acid (ESA). As L-epinephrine degrades over time, the potency of the drug product gradually decreases, and higher levels of D-epinephrine and ESA are formed.

FDA has approved applications for epinephrine products that currently specify overages to account for the decrease in potency over the drug products' shelf life due to the inherent instability of epinephrine in aqueous formulations. The purpose of the overage is to ensure that the delivered dose of epinephrine is within the labeled dose throughout the approved expiry dating period for the drug product. Furthermore, the instability of L-epinephrine in aqueous formulations is accounted for in the USP epinephrine injection monograph, which specifies that the drug product contain not less than 90 percent and not more than 115 percent of the labeled amount of epinephrine (i.e., a product that has a labeled amount of 1 mg/mL of epinephrine may have not more than 1.15 mg of epinephrine in 1 mL of the formulation).[10] Both the current

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[4] See Adrenalin NDA 204640/S-009 product labeling, approved on Jan 29, 2019, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/204200Orig1s009,204640Orig1s009lbl.pdf.

[5] The term *overage* is often used in different ways in the context of pharmaceutical drug design and the manufacturing process. For the purpose of this letter, the term *overage* is an amount of an active ingredient in excess of the claim on the label added to compensate for degradation during manufacture or a product's shelf life, or to extend the shelf life. See FDA guidance for industry *Q8(R2) Pharmaceutical Development* (November 2009) at 5–6. We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[6] See Apr 24, 2020, letter from Janet Woodcock, Director, Center for Drug Evaluation and Research, to J. Ben Haas, Docket No. FDA-2019-P-6044.

[7] Patil PN, Miller DD, and Trendelenburg U, 1974, Molecular Geometry and Adrenergic Drug Activity, Pharmacol Rev, 26(4):323–392.

[8] Westfall TC and Westfall DP, 2011, Adrenergic Agonists and Antagonists. In: Brunton LL, Chabner BA, and Knollmann BC, editors, Goodman & Gilman's The Pharmacological Basis of Therapeutics, 12e, New York: McGraw-Hill Professional, 257–295.

[9] A *drug substance* is "an active ingredient that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or any function of the human body, but does not include intermediates used in the synthesis of such ingredient" (§ 314.3(b) (21 CFR 314.3(b)).

[10] See U.S. Pharmacopeia (USP), *United States Pharmacopeia and National Formulary* (USP-NF) (USP43-NF38 at 1648; USP42-NF37 at 1616; USP41-NF36 at 1530) (currently official on April 10, 2020).

formulation of NDA 204640/S-012 and the prior formulations of the product comply with the USP epinephrine injection monograph.[11]

On December 23, 2015, FDA approved a supplement, NDA 204640/S-002, which changed the drug product's formulation and provided for a 24-month expiry period.[12] The overage of epinephrine remained unchanged at 14 percent.[13]

On September 13, 2019, FDA received another supplement, NDA 204640/S-012, that proposed, among other things, to remove the 14 percent overage of epinephrine (from 1.14 mg to 1 mg).[14] FDA approved this supplement on August 17, 2021.

B. Legal and Regulatory Background

1. Abbreviated New Drug Applications, Generally

The Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417) (the Hatch-Waxman Amendments) created section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(j)), which established the current abbreviated new drug application (ANDA) approval process. To obtain approval, an ANDA applicant is not required to provide independent evidence of the safety and effectiveness of its proposed drug product. Instead, an ANDA applicant relies on FDA's previous finding that the RLD is safe and effective.[15] To rely on this finding, an ANDA applicant must provide sufficient information to show, among other things, that its drug product has the same active ingredient(s), conditions of use, route of administration, dosage form, strength, and, with certain permissible differences, labeling as the RLD (section 505(j)(2)(A) and (j)(4) of the FD&C Act). An ANDA applicant must also demonstrate that its proposed drug product is bioequivalent to the RLD (section 505(j)(2)(A)(iv) of the FD&C Act).[16] FDA must approve an ANDA unless it finds that, among other things, the ANDA applicant has not provided sufficient evidence of the foregoing, or if the methods used in, or the facilities and controls used for, the manufacture, processing, and packing

[11] When official USP-NF monograph(s) are available for the drug substance and/or drug product named in the application, FDA compares the quality standards found within the official USP-NF monograph with the quality attributes found in the application as part of the evaluation process. See the draft guidance for industry *Harmonizing Compendial Standards With Drug Application Approval Using the USP Pending Monograph Process* (July 2019) at 2. When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[12] See Apr 24, 2020, letter from Janet Woodcock, Director, Center for Drug Evaluation and Research, to J. Ben Haas, Docket No. FDA-2019-P-6044.

[13] See id.

[14] See id.

[15] An *RLD* is "the listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its ANDA" (§ 314.3(b)). RLDs are identified in the Orange Book.

[16] *Bioequivalence* is "the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study" (21 CFR 314.3(b)).

of the drug product are inadequate to assure and preserve its identity, strength, quality, and purity (section 505(j)(4) of the FD&C Act).

2. ANDAs for Parenteral Drug Products

Section 505(j)(4)(H) of the FD&C Act provides that FDA shall approve an ANDA unless, among other things,

> information submitted in the application or any other information available to the Secretary shows that
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> > (i) the inactive ingredients of the drug are unsafe for use under the conditions prescribed, recommended, or suggested in the labeling proposed for the drug, or
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> > (ii) the composition of the drug is unsafe under such conditions because of the type or quantity of inactive ingredients included or the manner in which the inactive ingredients are included.

Consistent with the statute, FDA has issued implementing regulations on inactive ingredients in drug products proposed in ANDAs. In general, a drug product approved in an ANDA may have different inactive ingredients from the RLD if the ANDA demonstrates that the different inactive ingredients do not affect the safety or efficacy of the proposed drug product (§ 314.94(a)(9)(ii) (21 CFR 314.94(a)(9)(ii)). However, for ANDAs for parenteral drug products, the only differences in inactive ingredients that are routinely permitted are changes in preservatives, buffers, and antioxidants. FDA's regulation at § 314.94(a)(9)(iii) concerning the content and format of an ANDA states

> [g]enerally, a drug product intended for parenteral use must contain the same inactive ingredients and in the same concentration as the reference listed drug identified by the applicant . . . . However, an applicant may seek approval of a drug product that differs from the reference listed drug in preservative, buffer, or antioxidant provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product.

The corresponding provision that addresses the refusal to approve an ANDA, § 314.127(a)(8)(ii)(B), provides that

> FDA will consider an inactive ingredient in, or the composition of, a drug product intended for parenteral use to be unsafe and will refuse to approve the ANDA unless it contains the same inactive ingredients, other than preservatives, buffers, and antioxidants, in the same concentration as the listed drug, and, if it differs from the listed drug in a preservative, buffer, or antioxidant, the ANDA contains sufficient information to demonstrate that the difference does not affect the safety or efficacy of the drug product.

In addressing comments on proposed § 314.127 regarding changes in preservatives, buffers, and antioxidants, the Agency noted in the preamble of the final rule that under the statute, the inquiry is whether these inactive ingredients are "safe under the conditions prescribed, recommended, or

suggested in the labeling" and that the regulation "reflects this concern, which is particularly acute for parenteral drug products."[17]

When an ANDA applicant seeks approval for a parenteral product with a formulation that is qualitatively and quantitatively the same as that of a previously approved and marketed version of the RLD it references,[18] FDA has determined that, in appropriate circumstances, it may waive the requirement in the regulation that the inactive ingredients in a parenteral drug product approved under an ANDA be the same inactive ingredients in the same concentrations as those in the RLD (except for preservatives, buffers, and antioxidants), insofar as the statutory requirement regarding safety of inactive ingredients has been met (§ 314.99).[19]

FDA's regulations also require an ANDA that refers to a listed drug that has been voluntarily withdrawn from sale to be accompanied by a citizen petition seeking a determination whether the listed drug was withdrawn for safety or effectiveness reasons (§ 314.122(a)). The regulations further require FDA to determine whether a listed drug that has been voluntarily withdrawn from sale was withdrawn for safety or effectiveness reasons prior to approving an ANDA that refers to the listed drug (§ 314.161(a)(1)). Where an applicant proposes a generic formulation for a parenteral product that differs from its RLD in inactive ingredients other than preservatives, buffers, and antioxidants, but is the same as a previously approved formulation of the RLD (except for preservatives, buffers, and antioxidants), FDA conducts this same type of analysis to determine whether the previously approved formulation was discontinued from sale for reasons of safety or effectiveness.[20]

II. DISCUSSION

The Petition requests that FDA determine whether the original formulation of Adrenalin (epinephrine injection) (30 mg/30 mL, multiple dose) 1 mg/mL, approved under NDA 204640, was voluntarily withdrawn from sale for safety or effectiveness reasons.[21]

A. Active Ingredient Overages

The Agency generally discourages the use of overages.[22] FDA generally encourages applicants to address major degradation pathways of the active ingredient(s) in their drug products through

[17] 57 FR 17950 at 17970, April 28, 1992.
[18] See guidance for industry *ANDA Submissions — Refuse-to-Receive Standards* at 8, n. 46 (December 2016) ("[Q]uantitative sameness generally is interpreted by [the Office of Generic Drugs] to mean a concentration that is within 95–105% of the RLD concentration.").
[19] See, e.g., May 4, 2018, letter from Janet Woodcock, Director, Center for Drug Evaluation and Research, to Kurt Karst, Docket No. FDA-2017-P-0866; and § 314.94(a)(9)(iii). We additionally note that FDA has described how an applicant may request and how the agency intends to evaluate a request for a waiver, with regard to a pH adjuster, of the requirement in § 314.94(a)(9)(iii) that a parenteral product have the same inactive ingredients in the same concentration as the RLD. See FDA Draft Guidance: Considerations for Waiver Requests for pH Adjusters in Generic Drug Products Intended for Parenteral, Ophthalmic, or Otic Use (April 2022), available at https://www.fda.gov/media/157655/download.
[20] See, e.g., Dec 11, 2017, letter from Janet Woodcock, Director, Center for Drug Evaluation and Research, to Terri Nataline, Docket No. FDA-2016-P-1825.
[21] Petition at 1.
[22] See FDA guidance for industry *Q8(R2) Pharmaceutical Development* (November 2009) at 5–6.

appropriate formulation design, manufacturing process, and container closure system selection.[23] Any overage in the manufacture of a drug product should be justified considering the safety and efficacy of the drug product.[24] When an applicant believes that an overage is necessary, the applicant should provide FDA with information regarding the amount of the overage, reason for the overage, and justification for the amount of overage.[25]

In an April 2010 response to a citizen petition (2010 response), FDA stated that the Agency "does not intend to approve an ANDA with an overage that exceeds the approved active ingredient overage level in the RLD."[26] The 2010 response addressed the issue of an overage in a proposed ANDA where its RLD was approved with an overage and was not reformulated to eliminate the overage. The 2010 response did not address a scenario where an RLD was approved as safe and effective by FDA with an overage, the RLD was subsequently reformulated to eliminate the overage, and an ANDA applicant sought to duplicate the original formulation of the RLD containing the overage. Consequently, the Petition before the Agency presents an issue that was not contemplated by the 2010 response.

As explained in section I.B.2., when FDA considers whether to approve an ANDA for a parenteral product with a formulation that differs from the formulation of the RLD (*i.e.*, the currently approved product) but is the same as a formulation that was previously approved for that listed drug, FDA undertakes a case-by-case, product-specific inquiry that examines, among other things, whether the previously approved formulation was discontinued for safety or effectiveness reasons. If the ANDA seeks approval for a product that duplicates a previously approved formulation and that formulation differs from the formulation of the currently approved RLD qualitatively or quantitatively with respect to inactive ingredients (other than preservatives, buffers, or antioxidants), an ANDA applicant could seek a waiver of the regulatory requirement that the generic product have the same inactive ingredients in the same concentrations as the currently approved RLD (except for preservatives, buffers, and antioxidants). An ANDA applicant that sought to duplicate the previously approved formulation that included an overage would still rely on the currently approved product without the overage as its RLD. In this scenario, an ANDA that sought to duplicate the previous formulation that included an overage may have a higher overage than its RLD. Permitting an ANDA to have a higher overage than its RLD in this scenario is appropriate where FDA determines that the previously approved formulation that included an overage was not discontinued for reasons of safety or effectiveness and the applicant has submitted information justifying the overage.[27]

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[23] See Apr 19, 2010, letter from Janet Woodcock, Director, Center for Drug Evaluation and Research, to Kate C. Beardsley and James A. Boiani, Docket No. FDA-2009-P-0522.

[24] See FDA guidance for industry *Q8(R2) Pharmaceutical Development* (November 2009) at 5–6.

[25] Id.

[26] See Apr 19, 2010, letter from Janet Woodcock, Director, Center for Drug Evaluation and Research, to Kate C. Beardsley and James A. Boiani, Docket No. FDA-2009-P-0522, at 4. Unlike the current Petition, this citizen petition addressed a situation where the RLD was approved with one overage (i.e., an overage of 5%), and there were no previously approved versions of the product using a formulation with an overage in a higher amount.

[27] We note that an ANDA applicant would not be required to "match" the overage in the previously approved formulation of the RLD that included an overage; a proposed ANDA product may have an overage that is the same as or less than the overage in the previously approved formulation of the RLD.

B. Overages and Analysis of Strength

Although the Petition does not raise the issue of whether overage affects strength (and potentially effectiveness), FDA nonetheless considered this issue. Under section 505(j)(4) of the FD&C Act, FDA "shall approve" an ANDA for a drug product that, among other things, is bioequivalent to the RLD and has the same active ingredient(s), conditions of use, route of administration, dosage form, strength, and with certain permissible differences, labeling as the RLD.

In the context of an application for FDA approval to market a new drug product, *strength* means:

> the amount of drug substance contained in, delivered, or deliverable from a drug product, which includes:
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> (1)
>
> (i) The total quantity of drug substance in mass or units of activity in a dosage unit or container closure (e.g., weight/unit dose, weight/volume or weight/weight in a container closure, or units/volume or units/weight in a container closure); and/or, as applicable.
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> (ii) The concentration of the drug substance in mass or units of activity per unit volume or mass (e.g., weight/weight, weight/volume, or units/volume); or
>
> (2) Such other criteria the Agency establishes for determining the amount of drug substance contained in, delivered, or deliverable from a drug product if the weights and measures described in paragraph (i) of this definition do not apply (e.g., certain drug-device combination products for which the amount of drug substance is emitted per use or unit time).[28]

FDA has explained that the Agency "has a longstanding history of considering a difference in the total quantity of drug substance of a parenteral product (*e.g.*, a single or multiple dose vial) or a difference in the concentration of a parenteral product to be a difference in the 'strength' of the product for purposes of section 505(j)(2)(A)(iii) of the FD&C Act. FDA considers it important to review proposed differences in the total drug content or the concentration of a parenteral product because such changes can result in medication errors and incorrect dosing of patients."[29] Accordingly, the strength of a liquid parenteral drug product, such as epinephrine injection, is determined by both criteria in the definition of *strength* under § 314.3(b) — i.e., the total quantity of drug substance in a container closure and the concentration of the drug substance.[30]

We note that the USP General Chapter <1> Injections provides that each container of an injectable product is filled with a volume that slightly exceeds the content indicated in the labeling.[31] This allowable excess volume, also referred to as *overfill*, is meant to be sufficient to

[28] § 314.3(b).
[29] 80 FR 6802 at 6816 (Feb 6, 2015).
[30] See id.
[31] See guidance for industry *Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products* (June 2015) at 2.

permit withdrawal and administration of the labeled volume.[32] However, the amount of drug substance "deliverable from" a drug product is intended to exclude the excess volume allowed by the USP (to permit withdrawal and administration of the labeled volume of an injectable product) from the description of the "strength" of the drug product.[33] Generally, the amount of overfill is not declared on the product labeling.[34]

Similarly, FDA generally does not consider overages in excess of the labeled amount of API, added to compensate for degradation during manufacture or a drug product's shelf life, or to extend the shelf life, when determining a drug product's strength in accordance with § 314.3(b). Such overages are generally small and are used to ensure a drug product's potency (i.e., therapeutic activity) typically due to manufacturing and quality considerations particular to the specific drug product that generally cannot be addressed through other means.[35] Some overages do not appear in the final formulated product, for example, when an overage is used during the manufacturing process to address loss of the API during manufacture. Other overages appear in the final formulated product, but decrease over time, for example, when the overage addresses degradation of the API during the product's shelf life. Allowable overages are an amount that is sufficient to provide the potency described in the drug product's labeling and are not large enough to cause the potency of the drug product to deviate from what is described in the labeling. As such, these overages are generally not declared in the approved products' labeling, and FDA may appropriately consider applicable drug products to have the same strength when one product has an overage and the other does not, or the products have overages in different amounts.[36]

C. No Safety Concerns with the Overage in Previously Approved Formulations of the RLD

Adrenalin is approved for intramuscular and subcutaneous administration for treatment of anaphylaxis and for intravenous (IV) administration for treatment of hypotension associated with septic shock.[37]

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[32] Id. We note that such allowable excess volume, or "overfill," is different from an overage, which as stated above, is an amount of an active ingredient in excess of the claim on the label added to compensate for degradation during manufacture or a product's shelf life, or to extend the shelf life. Supra n.5.

[33] See 80 FR 6802, 6816 (Feb 6, 2015) and 21 CFR 201.51(g).

[34] FDA guidance for industry *Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products* (June 2015) at 2.

[35] *Potency* is the therapeutic activity of the drug product as indicated by appropriate laboratory tests or by adequately developed and controlled clinical data. See 21 CFR 210.3(b)(16).

[36] We note that section 505(j)(2)(C) of the FD&C Act provides that "if a person wants to submit an abbreviated application for a new drug which has a different active ingredient or whose route of administration, dosage form, or strength differ from that of a listed drug, such person shall submit a petition to the Secretary seeking permission to file such an application." Such a petition is commonly referred to as a *suitability petition*. See also § 314.93. FDA regulations state that the only changes from an RLD for which the Agency will accept such a petition are (1) route of administration, (2) dosage form, (3) strength, and (4) an active ingredient substituted for one of the active ingredients in a listed combination drug (§ 314.93(a) and (b)). Because differences in overages are not considered to be differences in strength, an ANDA applicant seeking approval for the same strength as its RLD and proposing a difference in overage from that of its RLD would not submit a petition pursuant to section 505(j)(2)(C) of the FD&C Act.

[37] See Adrenalin NDA 204640 product labeling, approved on Jan 5, 2023, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/204640Orig1s018lbl.pdf.

The safety of epinephrine for use in anaphylaxis is well known based on more than 100 years of clinical experience.[38] Common self-limiting[39] adverse reactions associated with epinephrine use include tremor, dizziness, palpitations, and headache.[40] Serious adverse events include cardiotoxicity (i.e., myocardial ischemia and arrhythmias) and cerebral hemorrhages due to the rapid rise in blood pressure associated with epinephrine use.[41] Cardiac adverse events are rare and generally occur with IV administration, which is done in a monitored hospital setting. Overdosage of epinephrine can occur with the use of vial and syringe epinephrine products due to human error from potentially using a vial with the wrong concentration (e.g., using an intramuscular vial when an intravenous vial should have been used) or potentially drawing the incorrect amount for the indicated route of administration. However, if the epinephrine product is administered consistent with its approved labeling, an overdosage is unlikely. Epinephrine is rapidly inactivated in the body, and treatment following overdose with epinephrine is primarily supportive.[42]

The original formulation of Adrenalin was approved with a 14 percent epinephrine overage to ensure that an adequate dose of epinephrine was available to treat anaphylaxis in life-threatening situations despite the ongoing decrease in epinephrine content throughout the drug product's shelf life due to the general instability of epinephrine in aqueous formulations. The epinephrine doses approved for anaphylaxis are 0.3 mg and 0.5 mg, and the doses for hypotension associated with septic shock are diluted and titrated to achieve the desired effect.[43] If epinephrine was dosed at full potency with overage (i.e., 1.14 mg/mL) for anaphylaxis, at the start of the original formulation shelf life, the administered doses would be 0.34 mg and 0.57 mg, respectively. These are small increases relative to the total doses of epinephrine and are not considered to be super potent.

Moreover, the USP epinephrine injection monograph includes an upper assay limit of 15 percent, and the original Adrenalin formulation's 14 percent epinephrine overage falls within this upper assay limit. Consistent with this upper assay limit, FDA has approved other epinephrine injection products with overages similar to the overage in the original Adrenalin formulation.

FDA determined that the original Adrenalin formulation with a 14 percent overage had an acceptable safety profile when FDA approved Adrenalin in 2013. In addition, there were no postmarketing events or relevant literature in the Adrenalin Annual Reports and Periodic Adverse Drug Experience Reports for the periods in which the original formulation was approved (December 18, 2013 to December 23, 2015) that have changed the known benefit-risk profile of Adrenalin since its approval. Further, we consider Adrenalin, as reformulated in 2015,

[38] See Apr 24, 2020, letter from Janet Woodcock, Director, Center for Drug Evaluation and Research, to J. Ben Haas, Docket No. FDA-2019-P-6044.
[39] The term *self-limiting* refers to symptoms that resolve on their own without the need for medical treatment or intervention.
[40] See Adrenalin NDA 204640 product labeling, approved on Jan 29, 2019, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/204200Orig1s009,204640Orig1s009lbl.pdf.
[41] Id.
[42] Id.
[43] Id.

to be relevant because it contained the same 14 percent overage as the original formulation.[44] There were no postmarketing events or relevant literature in the Adrenalin Annual Reports and Periodic Adverse Drug Experience Reports for the periods in which this version was approved (December 23, 2015 to August 17, 2021) that have changed the known benefit-risk profile of Adrenalin. Given the noted lack of reported postmarketing events or relevant literature and the clinical history of safe use described above, FDA has determined that the safety risks of the original Adrenalin formulation with a 14 percent epinephrine overage are acceptable, and we expect that the original Adrenalin formulation and the currently approved Adrenalin product would have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling.

D. Differences in the Levels of Degradants and Impurities Between the Original Formulation of NDA 204640 and the RLD Will Not Affect Safety or Effectiveness

Adrenalin's drug substance is manufactured as L-epinephrine. Generally, aqueous formulations of L-epinephrine, such as Adrenalin injection, are chemically unstable because epinephrine is readily oxidized. As L-epinephrine degrades over time, the potency of the drug product gradually decreases, and higher levels of impurities (usually D-epinephrine and ESA) are formed.

Specifications for degradants and other impurities ensure drug product quality. These specifications are one of the factors used to determine a drug product's shelf life, which is the total time that the drug product is expected to be safe and effective when used as prescribed in its labeling. The general degradation of epinephrine in aqueous formulations is accounted for in the USP epinephrine injection monograph, which sets an upper assay limit of 15 percent. The original Adrenalin formulation accounted for the unique degradation process of epinephrine for that formulation and provided the necessary overage, which falls within the USP assay range, to ensure that an adequate dose of epinephrine was present throughout the drug product's shelf life.

For the original Adrenalin formulation, patient exposure to D-epinephrine and ESA is expected to be minimal since Adrenalin is administered infrequently and in small doses (e.g., 0.3 mg and 0.5 mg for anaphylaxis). Moreover, there is no toxicologic information suggesting that D-epinephrine and ESA are harmful impurities. Finally, there is no toxicologic information that would lead FDA to conclude that the levels of D-epinephrine and ESA in the original formulation make it less safe or effective than the currently approved Adrenalin product with the overage-free formulation. As a general matter, impurities are assessed by FDA during the normal course of ANDA review.

[44] Adrenalin was reformulated in 2015 (NDA 204640/S-002). However, the 14 percent overage remained the same. See Apr 24, 2020, letter from Janet Woodcock, Director, Center for Drug Evaluation and Research, to J. Ben Haas, Docket No. FDA-2019-P-6044. Considering the fact that the overage in the 2015 formulation was the same as the overage in the original formulation, we believe that adverse events associated with the 2015 formulation are informative regarding the safety of Adrenalin with a 14 percent epinephrine overage.

E. The Original Formulation of Adrenalin Was Not Discontinued From Sale for Safety or Effectiveness Reasons

The Petition requests that FDA determine whether the original formulation of Adrenalin (epinephrine injection) (30 mg/30 mL, multiple dose) 1 mg/mL (NDA 204640) was voluntarily withdrawn from sale for reasons of safety or effectiveness. As explained in section I.B.2. of this letter, where an applicant proposes a generic formulation that differs from its RLD in inactive ingredients other than preservatives, buffers, and antioxidants, but is the same as a previously approved formulation of the RLD (except for preservatives, buffers, and antioxidants), FDA will determine whether the previously approved formulation was discontinued from sale for reasons of safety or effectiveness.

We have carefully reviewed our files for records concerning the discontinuance from sale of the original Adrenalin formulation. We have also examined the relevant Adrenalin Annual Reports and Periodic Adverse Drug Experience Reports for postmarketing events or relevant literature. We have found no information that would indicate that the original Adrenalin formulation was discontinued from sale for reasons of safety or effectiveness. Therefore, we have determined that the original Adrenalin formulation was not discontinued from sale for reasons of safety or effectiveness. In making this determination, we also specifically considered the fact that the original Adrenalin formulation has an overage and the current Adrenalin formulation does not.

Because FDA has determined that the original formulation of Adrenalin was not discontinued from sale for reasons of safety or effectiveness, the Agency may, under § 314.99(b), grant a waiver of the regulatory requirement that the ANDA formulation contain the same inactive ingredients in the same concentration as the RLD, with the limited exceptions for preservatives, buffers, and antioxidants. This conclusion is supported by FDA regulations and by FDA's scientific determination that the original formulation was not discontinued for reasons of safety or effectiveness and is consistent with the statutory requirements for ANDA approval and with the Agency's previous decisions. Therefore, FDA may receive ANDAs that refer to Adrenalin as the RLD and propose to duplicate the original formulation of Adrenalin that include a request to waive the requirements of § 314.94(a)(9)(iii) under § 314.99(b), and FDA may approve such ANDAs if all other requirements are met.[45]

III. CONCLUSION

For the reasons stated above, we have determined that the original Adrenalin formulation was not discontinued from sale for reasons of safety or effectiveness. We have also determined that FDA may receive and approve ANDAs that refer to Adrenalin as the RLD and propose to

[45] We note that, ultimately, whether FDA will receive an ANDA for substantive review will be determined during the filing review of the submission. The approvability of the ANDA will be determined during the scientific review of the submission.

duplicate the original Adrenalin formulation if all other applicable requirements are met. Accordingly, the Petition is granted.

Sincerely,

Douglas C. Throckmorton -S

Digitally signed by Douglas C. Throckmorton -S
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Patrizia Cavazzoni, M.D.
Director
Center for Drug Evaluation and Research