Direct Dial: 202.637.1084
Ben.Haas@lw.com

555 Eleventh Street, N.W., Suite 1000
Washington, D.C. 20004-1304
Tel: +1.202.637.2200 Fax: +1.202.637.2201
www.lw.com

December 20, 2019

VIA ELECTRONIC DELIVERY

Division of Dockets Management
Food and Drug Administration
5360 Fishers Lane, Room 1061
Rockville, Maryland 20852

CITIZEN PETITION

On behalf of Par Sterile Products, LLC ("Par" or the "Company"), the undersigned submits this petition pursuant to sections 505(b), 505(j), and 505(q) of the Federal Food, Drug, and Cosmetic Act ("FDCA") and the Food and Drug Administration's ("FDA's" or the "Agency's") regulations at 21 C.F.R. § 10.30. In this petition, Par requests that FDA expedite its review of Par's pending Prior Approval Supplements ("PASes") that seek to eliminate an overage of the active ingredient in Adrenalin® and to make attendant changes to the product's shelf life. Until the Agency takes final action on each PAS, Par asks that it refrain from approving any abbreviated new drug application ("ANDA") submitted under Section 505(j) of the FDCA for an epinephrine injection product that cites Par's Adrenalin® as the reference listed drug ("RLD"). If and when FDA approves Par's pending PASes, Par requests that FDA refrain from approving any ANDA for generic Adrenalin® that contains an epinephrine overage.

Par markets Adrenalin® (epinephrine injection) 1 mg/mL under New Drug Application ("NDA") Nos. 204200 and 204640, which FDA approved in 2012 and 2013, respectively.[1] The currently-approved formulation of Adrenalin® contains an overage of the active ingredient epinephrine, due to the fact that epinephrine degrades over time. Par has endeavored to address, and potentially eliminate, the overage since the original approval, in addition to taking other actions intended to address concerns expressed by FDA during the Agency's review of the NDA (*i.e.*, concerns related to the impurity profile in the originally-approved product). It wasn't until May 2019, when Par initiated an investigation of an "out of specification" result on a manufacturing lot of Adrenalin® that exceeded the product specification for epinephrine, that the Company determined that certain formulation changes previously made to Adrenalin® in 2015-2016 made elimination of the epinephrine overage in Adrenalin® feasible. Given the company's long-standing effort to address the overage, as well as FDA's policy disfavoring overages due to

[1] NDA 204640 was approved by FDA for a 30 mL multiple dose vial of Adrenalin® on December 18, 2013, after the approval of NDA 204200 for a 1 mL single dose vial of Adrenalin® on December 7, 2012.

the concern that patients may receive super-therapeutic doses of the active ingredient, Par immediately initiated efforts to develop a new formulation of Adrenalin® without an overage.

On September 13, 2019, Par submitted a Changes Being Effected in 30 Days ("CBE-30") NDA supplement notifying FDA that it was planning to market a new formulation of Adrenalin® with no overage for its 30 mL presentation. Shortly thereafter, FDA determined that this change required the Agency's approval pursuant to a PAS, which FDA's regulations establish is required for changes with the substantial potential to adversely affect certain characteristics of the drug as they may relate to its safety or effectiveness.[2] On December 13, 2019, Par submitted a similar PAS to the NDA for its 1 mL Adrenalin® product to allow for a formulation that bears no overage.

Par's pending PASes have significant implications for FDA's review of pending or future ANDAs that cite to Adrenalin® as the RLD. Indeed, FDA's determination that removing the epinephrine overage requires prior FDA review and approval pursuant to a PAS underscores the critical safety and effectiveness concerns implicated by this overage. As a result, upon submission of the CBE-30, and in subsequent written communications, Par and its representatives have attempted to engage the Agency to understand the extent to which Par's pending elimination of the overage will be accounted for in the Agency's review of ANDAs for generic versions of Adrenalin®, yet has not received any substantive response to date.

Par is therefore filing this petition and requesting that FDA expedite its review of Par's pending PASes and take final action as soon as possible. Until FDA has completed its review of the PASes, Par asks that FDA refrain from approving any ANDA for a generic version of Adrenalin®. Further, if and when FDA approves the PASes and the Adrenalin® labeling is modified, Par requests that FDA refrain from approving any ANDA for a generic Adrenalin® product that contains an epinephrine overage (or that otherwise fails to demonstrate that it is the "same as" the new Adrenalin® formulation, whether 1 mL or 30 mL).

I. ACTION REQUESTED

Par requests that FDA expedite its review and take final action as soon as possible on Par's pending PASes proposing to remove the epinephrine overage from Adrenalin®.[3] Par further requests that until FDA has completed its review of the pending PASes, FDA refrain from approving any ANDA for an epinephrine injection product citing Par's Adrenalin® as the RLD. In addition, if FDA approves Par's pending PASes, Par requests that FDA refrain from approving any ANDA for an epinephrine injection product that cites Par's Adrenalin® as the RLD and that contains an epinephrine overage (or that otherwise fails to demonstrate that it is the "same as" the new Adrenalin® formulation).

---

2 *See* 21 C.F.R. § 314.70(b)(1).

3 This citizen petition addresses both the 30 mL multiple dose vial and 1 mL single dose vial of Adrenalin®. Any references to "Adrenalin®" are intended to cover both presentations of the product.

II. STATEMENT OF GROUNDS

A. Legal Background

An ANDA submitted to FDA for approval of a generic drug must demonstrate that the proposed generic is the "same as" a drug approved under Section 505(b) of the FDCA and listed in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations*.[4] FDA approves ANDAs pursuant to a demonstration that the proposed generic drug is the same as the already approved and listed drug, known as the RLD, relying on the Agency's prior determination that the RLD is safe and effective for the approved intended use.

To demonstrate that the proposed generic product is the "same as" the RLD, FDA regulations require that the proposed generic be "identical" to the RLD in a number of respects, including "strength."[5] "Strength" is defined as the concentration of active ingredient in the drug and/or its potency.[6] The requirement that a proposed generic have the same strength as the RLD reflects the scientific presumption that if the drug that is the subject of an ANDA has the same strength as the RLD (and shares other relevant attributes identified in the statute), it will have the same safety and efficacy as the RLD, and will be substitutable for the RLD.[7] An ANDA for a different strength product than the RLD can only be received by FDA if the applicant submits, and FDA approves, a suitability petition allowing the change.[8]

In the case of parenteral products, such as Adrenalin®, a proposed generic must generally contain "the same inactive ingredients and in the same concentration as the [RLD]."[9] There is a potential exception to this requirement for products that differ from the RLD only with respect to preservatives, buffers and antioxidants; however, for this exception to apply, the regulation requires 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."[10]

Additionally, FDA has a clear and consistent policy discouraging active ingredient overages in drug products, where an additional amount of active ingredient is present in the finished product in excess of the labeled amount. As FDA has explained, "[i]n general, a drug

---

4 21 U.S.C. § 355(j)(2)(A)(i); 21 C.F.R. §§ 314.92(a)(1), 314.94(a)(3).

5 21 C.F.R. § 314.92(a)(1).

6 *Id.* § 210.3(b)(16).

7 57 Fed. Reg. 17950, 17953 (Apr. 28, 1992); Letter from Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research ("CDER") to Katherine M. Sanzo, Esq., Morgan, Lewis & Bockius LLP, Docket Nos. 2001 P-0323/CP1 & C5 et al., 7 (Oct. 14, 2003), available at http://www.fda.gov/ohrms/dockets/dailys/03/oct03/102303/02p-0447-pdn0001-vol1.pdf.

8 21 C.F.R. § 314.93. A product with different strength will not be substitutable with previously approved products.

9 *Id.* § 314.94(a)(9)(iii).

10 *Id.*

product should be formulated with the labeled amount of active ingredient throughout its shelf life."[11] While FDA may permit a small active ingredient overage in certain cases where necessary to compensate for the degradation of the active ingredient over time, FDA disfavors such overages and allows their use only "where necessary."[12] This longstanding policy reflects the fact that overages put patients at risk of receiving "super-potent" doses of an active ingredient, above the strength reflected in the approved label for the product.[13]

To that end, FDA has taken the position that "in general, the only acceptable justification for an overage in the final [ANDA] drug product formulation is the demonstration of the same overage in the RLD."[14] An ANDA applicant must justify any active ingredient overage contained in its proposed generic product, which may be less than, but cannot exceed, the overage in the RLD.[15] If the generic product has an overage where the RLD does not, or the overage exceeds the active ingredient levels in the RLD, the strength of the product would be different than that of the RLD, raising questions about the safety and substitutability of the product and failing to satisfy the necessary conditions for ANDA approval.

B. Factual Background

Par (previously known as JHP Pharmaceuticals, LLC) submitted NDA 204200 to the Agency on March 7, 2012, seeking approval for Adrenalin® to treat severe acute anaphylactic reactions including anaphylactic shock. Adrenalin® is a clear, colorless, sterile parenteral solution containing the active ingredient L-epinephrine, and is intended for intramuscular or subcutaneous administration. L-epinephrine is a hormone and neurotransmitter with many functions in the body, including regulating heart rate, respiratory rate and metabolic shifts.

Throughout its review of NDA 204200, FDA expressed concern regarding the potency of Adrenalin® in connection with the levels of certain impurities found therein.[16] Each 1 mL of

---

11 FDA/ICH Guidance for Industry: QS(Rl) Pharmaceutical Development, at 4.

12 *Id*. at 5; Letter from Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research, to Kate C. Beardsley, Bue & Beardsley, LLP, Docket No. FDA-2009-P-0522 (Apr. 19, 2010) at 3.

13 *See e.g.*, 10/4/2006 Advisory Committee Regarding Levothyroxine, 20 (Jane Axelrad, Esq., Associate Director for Policy, CDER, *available at* http://www.fda.gov/ohrms/dockets/ac/06/transcripts/2006- 4228TI .pdf (stating, "[a]II manufacturers have to target 100% potency [(i.e., with no overage)] at release" because it "eliminates the risk of a patient obtaining a super potent product").

14 *See* FDA, Office of Generic Drugs, Question-based Review ("QbR") Frequently Asked Questions, at 16 (June 4, 2007), *available at* https://web.archive.org/web/20100307010900/http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/ucm120980.pdf; FDA Guidance for Industry, Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products- Chemistry, Manufacturing, and Controls Documentation, at 5 (July 2002).

15 *Id*.

16 FDA's review summary for NDA 204200 notes that the "major challenge with this application has been the concern about the proposed potency of the product [redacted] and the proposed specification for total impurities/degradants at expiry [redacted] raised by the CMC review staff." NDA 204-200, Summary

Adrenalin® is designed to deliver 1 mg of epinephrine; however, L-epinephrine can degrade through a variety of routes. One such route is oxidation, which can result in the formation of colored products and particulates. To suppress oxidation, sodium metabisulfite (which dissolves in water to form sodium bisulfite) was included in the Adrenalin® formulation. However, while sodium bisulfite is effective at preventing the formation of epinephrine oxidation products, it also reacts with epinephrine to form epinephrine sulfonic acid ("ESA"), an inactive impurity. The formation of ESA results in a decrease in the effective concentration of active epinephrine in the product. Similarly, L-epinephrine can racemize to form D-epinephrine, which results in a net loss of potency because D-epinephrine is inactive, and equilibrium is stable only for the 50/50 (racemic) mixture.[17]

To account for the potential degradation of L-epinephrine over the course of the product's 24-month shelf life, Par formulated Adrenalin® to contain slightly more than 1 mg of epinephrine per 1 mL (an overage). Indeed, this overage is accounted for in the USP epinephrine injection monograph upper assay limit of 115%.[18] Thus, at the time of submission and approval of NDA 204200, the product assay was set to 114% of the specified amount of epinephrine intended to be delivered to patients, resulting in each unit of product containing 1.14 mg of epinephrine per mL immediately after manufacturing was completed (i.e., prior to any degradation).[19]

Following the approval of NDA 204200 for the 1 mL vial of Adrenalin® in 2012, FDA approved NDA 204640 for the 30 mL vial of Adrenalin® in 2013. The approved 30 mL vial contained the same epinephrine overage as the approved 1 mL vial. Subsequent to these approvals, and pursuant to certain post-marketing commitments, Par investigated the underlying cause of the impurity formation in Adrenalin® and implemented formulation changes to the product in an effort to yield an improved degradant profile. In March 2015 and January 2016, Par submitted a NDA supplement for the 30 mL and 1 mL products, respectively, seeking approval for a formulation change to provide a more stable Adrenalin® product. FDA approved these supplements in December 2015 and September 2016.[20]

In parallel to these efforts, Par had long considered the feasibility of removing the epinephrine overage from Adrenalin®, and its pending PASes to do just that reflect a culmination

---

Review, at 15 (December 7, 2012), *available at* http://www.accessdata.fda.gov/drugsatfda _ docs/nda/20 12/2042000rig 1 Orig2s000SumR.pdf.

17 As initially approved, the active L-epinephrine isomer in Adrenalin® was observed to be lost at an average rate of 6% per month under accelerated conditions.

18 U.S. Pharmacopeia, *United States Pharmacopeia and National Formulary* (USP43-NF38 – 1648; USP42-NF37 – 1616; USP41-NF36 – 1530) (official as of December 19, 2019).

19 *See* NDA 204200, 3.2.P.2.3 Manufacturing Process Development, at 3 ("Both the 1 mL and 30 mL vial presentations contain a 14% overage for the drug substance, Epinephrine USP. Because of epinephrine degradation, primarily due to sulfonation and racemization, the overage is essential to meet specification requirements through an 18 month shelf-life.").

20 Indeed, as FDA is aware, Par previously submitted two citizen petitions asking FDA to require any epinephrine injection 1mg/1mL product to have the same or lower levels of impurities as the version of Adrenalin® that Par reformulated following its FDA-required postmarket testing. *See* Docket No. FDA-20160P-2376 and Docket No. FDA-2017-P-1392.

of those efforts. On May 20, 2019, Par discovered a manufacturing lot of Adrenalin® that contained epinephrine above the upper limit of 115.0% and was thus out of specification ("OOS"). In response to this finding, Par considered, among other options, reducing the specification for the overage in Adrenalin® from 114% to 113%. It was believed that such a change would reduce the potential incidence of further OOS results involving too much epinephrine, without significantly impacting the product formulation. Ultimately, it was determined that the cause of the OOS result related to the pH of a buffer used in the test assay, and was not due to method variability that resulted in exceeding the 114% overage. However, in exploring the possibility of reducing the overage, Par discovered that in light of the 2015-2016 reformulation of Adrenalin®, it may be possible to eliminate the epinephrine overage entirely. Specifically, the reformulation resulted in less sodium metabisulfite in the product. As a result, Adrenalin® became less susceptible to epinephrine degradation, potentially negating the need for an epinephrine overage.

Following a meeting on June 20, 2019 among Par manufacturing personnel, Par began conducting stability studies on a commercial-scale formulation of the product containing 100% epinephrine (1 mg/mL). The formulation also contained less hydrochloric acid, as hydrochloric acid is used to solubilize epinephrine, and a reduction in epinephrine thus permits a reduction in the hydrochloric acid content as well. On September 13, 2019, after one month stability data had been obtained, Par submitted a CBE-30 supplement notifying FDA that Par planned to manufacture the 30 mL single dose vial of Adrenalin® with no overage, along with other related changes (including a reduction in the product shelf-life from 24 months to 18 months pending additional data to support a longer shelf-life). This CBE-30 supplement contained in vitro stability data demonstrating that the reformulated product retained nearly 99% of the active ingredient L-epinephrine at one month of testing, conducted at 25° C and 60% relative humidity with an upright orientation. The CBE-30 supplement also contained data showing that the degradation of L-epinephrine in the current formulation of Adrenalin® (containing the overage) exhibits zero order kinetics. These data, and the observed rate of degradation of L-epinephrine in the product, suggested that a product that contains 1.0 mg/mL of epinephrine (i.e., no overage) would retain greater than 90% of the intended amount of the active ingredient for roughly 18 months.

On September 24, 2019, FDA notified Par that the changes proposed in the CBE-30 supplement required FDA's premarket review and approval, and that the Agency therefore considered this supplement to be a PAS. On November 18, 2019, Par amended its now PAS to provide stability data at the three-month interval for the overage-free formulation under long-term and accelerated conditions. These data underscore that an epinephrine overage is not needed to ensure that Adrenalin® is safe and effective. Moreover, by eliminating the overage, the reformulated product will significantly reduce, if not eliminate, any potential for a super-potent dose of the active ingredient to be administered to patients. On December 13, 2019, Par submitted an additional PAS seeking approval for an overage-free formulation of the 1 mL Adrenalin® product as well.

Because Par's efforts to eliminate the epinephrine overage from Adrenalin® have significant implications for FDA's review of any currently-pending or future ANDAs that cite Adrenalin® as the RLD, Par and its representatives have contacted the Agency in writing on multiple occasions regarding these efforts. Among other things, Par's outside counsel sent an

initial letter to FDA on September 16, 2019 concurrent with Par's submission of its CBE-30, and re-engaged on November 19, 2019 when Par amended its PAS to include additional stability data. Par has not received a substantive response from the Agency to this outreach. In light of the significant patient benefit that will derive from this formulation change and the resultant need for expedient action, Par submits this citizen petition.

C. FDA Should Expedite Its Review of Par's Pending PASes to Eliminate the Epinephrine Overage in Adrenalin®, Refrain from Approving Any ANDA for a Generic Adrenalin® Product Until Such Review Is Complete, and, if the PASes are Approved, Refrain from Approving any Generic Adrenalin® Product With an Epinephrine Overage.

As described above, Par sought to update its label and commercialize an overage-free version of its 30 mL Adrenalin® product in October 2019 by submitting a CBE-30 supplement one month prior, in September 2019. Par submitted a CBE-30 supplement pursuant to Par's understanding that this change had a "moderate" potential to affect the safety or effectiveness of the product, consistent with the criteria for a CBE-30 supplement established under FDA's regulations,[21] and because Par recognized the significant benefit to patient safety that would come from introducing an overage-free formulation as quickly as possible.

Indeed, Par's historical and current efforts to eliminate the epinephrine overage from Adrenalin® were driven by the potentially significant safety risks associated with administering too high a dose of epinephrine. The potential safety issues associated with an epinephrine overage are described in detail in the attached document titled "Safety of Epinephrine in Higher Doses".[22] This document reports that even small amounts of epinephrine can cause severe side effects, and certain patient populations are at higher risk for epinephrine toxicity. An overdose of epinephrine may lead to, among other things, cerebrovascular hemorrhage, pulmonary edema, and cardiac arrhythmias that may be fatal.[23] Cases of epinephrine overdoses have indeed been reported in the literature. As just one example, a case study published in the Journal of Medical Case Reports in 2017 described the occurrence of an adrenaline overdose in a nine-year-old child to whom adrenaline was administered following the onset of anaphylaxis.[24] The authors reported that "[w]hile delaying and under-dosing adrenaline in anaphylaxis is widely recognized as detrimental, one should remain vigilant for adrenaline overdose because the risk of adverse effects, such as ventricular arrhythmias, hypertensive crises, pulmonary edema, and associated mortality is significant."[25] A more recent case report similarly noted that "inadvertent and accidental

---

21 21 C.F.R. § 314.70(c).

22 Provided as Exhibit 1.

23 Adrenalin® Labeling (Jan. 2019), available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/204200Orig1s009,204640Orig1s009lbl.pdf.

24 Pui Yi Lily Liew and John Andrew Craven, *Adrenaline overdose in pediatric anaphylaxis: a case report*, Journal of Medical Case Reports (2017) 11:129.

25 *Id.*

epinephrine overdosing is probably an under-recognized event, which can result in potentially lethal complications."[26]

In light of these safety risks, Par requests that FDA expedite its review of Par's pending PASes and take final action on the PASes as soon as possible. This request is buttressed by FDA's longstanding position disfavoring overages and permitting them only when strictly required to account for the characteristics of the product. To that end, Par also requests that until the Agency's review of the PASes is complete, FDA refrain from approving a pending or future ANDA citing Adrenalin® as the RLD. Were FDA to deny this request and approve such an ANDA while Par's PASes are pending, FDA would be approving a generic product that raises safety concerns that, in short order, would no longer be associated with the brand product (assuming FDA's approval of the PASes). Indeed, Par notes that FDA's determination that the changes described in Par's September 2019 CBE-30 supplement required submission of a PAS reflects the Agency's conclusion that the changes have "substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product."[27] Consequently, for a generic product seeking to be the "same as" Adrenalin®, the presence or absence of an epinephrine overage in the proposed generic product may likewise have a substantial potential to affect the safety and effectiveness of that generic product, and FDA should not approve such ANDA until these safety and effectiveness issues are resolved.

In addition, if FDA approves Par's PASes, FDA should refrain from approving any generic version of Adrenalin® with an epinephrine overage. In that event, a generic product with an overage would fail to meet FDA's requirement that a generic product have the same strength as the RLD. FDA may only receive an ANDA for a different strength product than the RLD if the applicant submits, and FDA approves, a suitability petition allowing the change.[28] Even then, such an approval would conflict with FDA's stated position that the only acceptable justification for an overage in a generic product is the presence of the same overage in the RLD. Accordingly, if FDA approves Par's PASes permitting the elimination of the epinephrine overage from Adrenalin®, FDA should require the same of any proposed generic product.

III. ENVIRONMENTAL IMPACT

Par Sterile Products, LLC claims a categorical exclusion from the requirement to submit an environmental assessment pursuant to 21 C.F.R. § 25.31(a).

---

26 Maya Caroline André and Jürg Hammer, *Life-Threatening Accidental Intravenous Epinephrine Overdose in a 12-Year-Old Boy*, Pediatric Emergency Care (2019) 35:6.

27 21 C.F.R. § 314.70(b)(1).

28 *Id*. at § 314.93.

IV. ECONOMIC IMPACT

Information regarding the economic impact of this petition will be submitted at the request of the Commissioner.

V. 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: June 19, 2019 (when Par first received stability data supporting the stability of an Adrenalin® formulation with no overage). 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: Par Sterile Products, LLC. 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,

J. Ben Haas
of LATHAM & WATKINS LLP