Chad A. Landmon
Axinn
90 State House Square
Hartford, CT 06103

Re: Docket No. FDA-2021-P-1211 December 15, 2021

Dear Mr. Landmon:

This letter responds to the citizen petition you submitted on behalf of Par Sterile Products LLC (Par) received by the Food and Drug Administration (FDA, Agency, or we) on November 8, 2021 (Petition or Petitioner). In the Petition, you request that FDA:

(1) Refrain from approving [Eagle Pharmaceuticals, Inc.'s (Eagle)] [abbreviated new drug application (ANDA)] until it has either:

a Amended the stability specification and demonstrated that such amended stability specification does not pose any concerns with impurities or other safety issues; or

b Amended its release specification and demonstrated that a lower upper limit for the pH range in the release specification will ensure that Eagle's product will stay within the stability specification parameters during the entirety of its shelf-life.

(2) Refrain from approving any pending or future vasopressin ANDA referencing Vasostrict® if it has pH release specifications that are the same as or close to the pH stability specifications until it has either:

a Amended the stability specification and demonstrated that such amended stability specification does not pose any concerns with impurities or other safety issues;

b Amended its release specification and demonstrated that a lower upper limit for the pH range in the release specification will ensure that the ANDA product will stay within the stability specification parameters during the entirety of its shelf-life; or

c Demonstrated that such product will not experience any significant upward drift of pH such that any product released at the upper end of the pH release specification will not exceed the upper end of the pH stability specification during the entirety of the shelf life.

(Petition at 1-2).

We have carefully considered your Petition, the comment submitted by Eagle to the Petition docket, your reply to Eagle's comment (Reply), and other information available to the Agency. For the reasons stated below, the Petition is denied.

I. BACKGROUND

A. Section 505(q) of the FD&C Act

Section 505(q) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(q)) was added by section 914 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law 110-85, 121 Stat. 823) and was amended by the Food and Drug Administration Safety and Innovation Act (Public Law 112-144, 126 Stat. 993). Section 505(q) of the FD&C Act, as originally added by FDAAA, applies to certain citizen petitions and petitions for stay of Agency action that request that FDA take any form of action relating to a pending application submitted under section 505(b)(2) or (j) of the FD&C Act and governs the manner in which these petitions are treated. Section 505(q) directs FDA not to delay approval of a pending application submitted under section 505(b)(2) or (j) of the FD&C Act or section 351(k) of the Public Health Service Act (42 U.S.C. 262(k)) because of any request to take any form of action relating to the application unless the request is in the form of a citizen petition and FDA determines, upon reviewing the petition, that a delay is necessary to protect the public health.

The Agency has interpreted section 505(q) of the FD&C Act to apply to a petition, if among other things, the following statements apply:

(1) The petition is submitted in writing and pursuant to 21 CFR 10.30 or 10.35.

(2) An ANDA, a 505(b)(2) application, or a section 351(k) application related to the subject matter of the petition is pending at the time the petition is submitted to FDA.

(3) The application's user fee goal date is on or before the 150-day deadline for final Agency action on the petition.

(4) The petitioner requests an action that could delay approval of a pending ANDA, 505(b)(2) application, or 351(k) application.

(5) The petition does not fall within any of the exceptions described in section 505(q)(4).

Under section 505(q)(1)(E) of the FD&C Act, FDA may deny a petition at any point if the Agency determines that a petition or a supplement to the petition was submitted with the primary purpose of delaying the approval of an application and the petition does not on its face raise valid scientific or regulatory issues.

B. Vasopressin

Vasopressin has been marketed as a therapeutic agent for nearly a century. Pitressin, a natural vasopressin product developed as an extract of the bovine posterior pituitary, was first introduced in 1928. Pitressin tannate oil (new drug application (NDA) 003402) by subcutaneous or intramuscular administration was approved by FDA in 1941 and indicated for the control or

prevention of the symptoms and complications of diabetes insipidus due to a deficiency of endogenous posterior pituitary antidiuretic hormone.[1] Vasopressin injection also has been marketed as an unapproved product for the prevention and treatment of postoperative abdominal distention, in treatment of abdominal roentgenography to dispel interfering gas shadows, and in treatment of central diabetes insipidus. Intravenously administered vasopressin has been used off-label for treatment of cardiopulmonary resuscitation and for treatment of gastrointestinal hemorrhage and vasodilatory shock, as well as used diagnostically to provoke pituitary release of adrenocorticotropic hormone and growth hormone.

In June 2006, FDA announced a drug safety initiative to encourage unapproved drug manufacturers to obtain FDA approval.[2] In response to this initiative, Par submitted NDA 204485 for Vasostrict (vasopressin injection), which FDA approved on April 17, 2014. Vasostrict is a sterile, aqueous solution of synthetic arginine vasopressin for intravenous administration and is indicated to increase blood pressure in adults with vasodilatory shock who remain hypotensive despite fluids and catecholamines.[3]

II. DISCUSSION

Your Petition requests that FDA not approve Eagle's ANDA[4] or any other pending or future ANDA that references Vasostrict unless the applicant has demonstrated that the proposed vasopressin product will stay within the stability specification parameters with respect to pH throughout the product's shelf life (Petition at 1-2, 9). The Petition states that "if Eagle manufactures its product near the upper end of the pH range set forth in its release specification, the pH value of its product will drift upward during its shelf life and exceed Eagle's stability specification" (Petition at 9). We find that the Petition has not provided any evidence to support this claim of an "upward drift" in pH and has also failed to disclose relevant data and information which are unfavorable to the Petition and which directly rebut the Petition's claims concerning Eagle's ANDA. Accordingly, the Petition is denied. In addition, the Agency would have grounds to deny the Petition because it appears to have been submitted with the primary purpose of delaying approval of Eagle's ANDA and fails to raise valid scientific or regulatory issues.[5] The Agency intends to refer this matter to the Federal Trade Commission (FTC), which has the administrative tools and the expertise to investigate and address anticompetitive business practices.

A. The Petition Has Not Demonstrated the Likelihood of an "Upward Drift" in pH

[1] In a letter dated April 23, 1993, Parke-Davis, the application holder for Pitressin tannate oil, requested that FDA withdraw approval of this NDA (77 FR 29665 (May 18, 2012).
[2] This initiative was set forth in FDA's *Marketed Unapproved Drugs — Compliance Policy Guide* (CPG 440.100), which was withdrawn in December 2020 (85 FR 75331, November 25, 2020).
[3] See Vasostrict (vasopressin injection) labeling (4/2021), available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/204485Orig1s020lbl.pdf.
[4] ANDA 211538 for Vasopressin Injection, USP, 20 units/milliliter (mL), references Par's NDA 204485 for Vasostrict (vasopression injection, USP), 20 units/mL.
[5] See Section 505(q)(1)(E) of the FD&C Act.

Although the Petition cites, in passing, to the court decision in *Par Pharmaceutical, Inc. et al. v. Eagle Pharmaceuticals Inc.*, 2021 U.S. Dist. LEXIS 164739 (D. Del. Aug. 31, 2021) (the Court Decision) (Petition at 6), the Petition relies on proposed findings of fact submitted by the parties as its evidence and fails to address (or acknowledge) the court's actual findings of fact, including relevant findings by the court that squarely rejected an "upward drift" argument like the one presented in the Petition.[6]

The Court Decision concluded that "[d]uring the stability study of SVA001, Eagle recorded a pH level of 3.69 (which rounds to 3.7) at the 24-month mark—i.e., at the very end of SVA001's shelf life."[7] Importantly, it noted that "[t]he data show that Eagle has taken approximately 200 pH stability measurements since March 2017" and "[a]ll other pH measurements for SVA001 and all pH measurements for Eagle's other registration and characterization batches remained within the stability specification of 3.4-3.6 for the duration of those batches' shelf lives."[8] As Par acknowledged in the litigation, Eagle modified its manufacturing process to assure a tighter in-process control of pH in response to the one out-of-specification test result for batch SVA001.[9] In the litigation, Par made the same argument that it raises in the Petition; namely, that even after Eagle tightened its in-process control of pH, Eagle's product exhibits an upward pH drift after product release.[10,11] The court rejected Par's argument, finding that "the data do not establish that Eagle's ANDA has the 'drift problem' Par claims" and that "on every occasion that a pH measurement was taken since Eagle optimized its manufacturing process, the pH measurement has been within the stability pH specification in Eagle's ANDA and outside the pH limitation claimed in the asserted patents."[12] Most notably, the court found that "none of the pH measurements for the post-optimization batches approach the top end of Eagle's release specification (3.64). . . ."[13]

Although the Court Decision constitutes a legal opinion regarding Par's patent infringement allegations and not necessarily a scientific determination, the information in the decision is still relevant to the purported scientific and regulatory issues raised in the Petition because it is the material on which Par relies in support of its position. The Petition's claim that "product that is released nearer to the upper end of Eagle's release specification will exceed the stability specification during the product's shelf life" (Petition at 4), is directly at odds with the court's factual findings. The Agency has also evaluated the exhibits submitted with the Petition and reached the same conclusion as the court as to Par's drift theory. Specifically, there is no evidence that Eagle's vasopressin product will experience an "upward drift" in pH, such that the product is likely to be out of specification during its shelf life. The stability data for batches made after Eagle optimized its manufacturing process referenced in the court documents and included in support of the petition show that there is no "upward" trend in pH post-release, and

[6] No copy of this decision was submitted with the Petition. See 21 CFR 10.20(c)(1).
[7] 2021 U.S. Dist. LEXIS 164739 at *16.
[8] Id.
[9] Petition Exhibit C at 18-19.
[10] Court Decision at *19; Petition at 4-5.
[11] Court Decision at *20.
[12] Id. at *15, *20.
[13] Id. at *21.

none of the pH values on stability have exceeded the upper range of the pH stability specification.[14]

In its Reply to Eagle's comment, Par contends, without any support, that "Eagle's ANDA is overbroad and allows Eagle to use its original (not 'optimized') process" (Reply at 4). Par also claims that, unless Eagle amends the ANDA's release specification, Eagle will "have a right to release a product at a pH as high as 3.6 (and potentially 3.64) using the original process" (Reply at 3). This is incorrect, since, as Par should know, certain post-approval changes to an application, such as the manufacturing process change Par suggests, would have to be made in accordance with section 506A of the FD&C Act and §314.70 (21 CFR 314.70).[15]

Because the Petition has failed to provide any evidence to support its claim that Eagle's vasopressin product will experience an "upward drift" in the pH specifications during the product's shelf life, the Petition is denied.[16]

B. The Petition Appears to Have Been Submitted for the Primary Purpose of Delay and Fails To Raise Valid Scientific or Regulatory Issues

Your Petition is denied for the reasons stated in section I.A of this letter. Thus, we need not make an additional determination under section 505(q)(1)(E) of the FD&C Act (21 USC 355(q)(1)(E)). At the same time, your Petition could alternatively be denied because it: (1) appears to have been submitted with the primary purpose of delaying approval of Eagle's ANDA and (2) fails to raise valid scientific or regulatory issues. Id.; see Guidance For Industry, *Citizen Petitions and Petitions for Stay of Action Subject to Section 505(q) of the Federal Food, Drug, and Cosmetic Act* (September 2019) (505(q) Guidance).[17] As discussed in the 505(q) Guidance, we find the following factors relevant here:

- Submission of a petition when it appears, based on the date that relevant information relied upon in the petition became known to the petitioner (or reasonably should have been known to the petitioner), that the petitioner has taken an unreasonable length of time to submit the petition[18]

- Submission of a petition close in time to a known, first date upon which an ANDA, a 505(b)(2) application, or a 351(k) application could be approved (e.g., submission close in time to the expiration of exclusivity or, for 505(b)(2) applications and ANDAs, a patent that may affect the timing of an application's final approval)

[14] Exhibit D at 18 (Table of stability data for batches after optimized manufacturing was implemented).
[15] See guidance for Industry, *Changes to an Approved NDA or ANDA* (April 2004). We update guidances periodically. 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.
[16] The Agency's determination that the Petition fails to identify evidence to support Par's "upward drift" theory is independent of the Agency's determination that Eagle's ANDA meets the ANDA approval standards. Eagle's ANDA was approved on December 15, 2021, on the basis of the Agency's determination that the ANDA meets all of the relevant legal and regulatory requirements. See, e.g., section 505(j)(4) of the FD&C Act and 21 CFR 314.127.
[17] We update guidances periodically. 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.
[18] 505(q) Guidance at 15-16.

- Submission of a petition with little or no data or information in support of the scientific positions set forth in the petition[19]

The Petition relies on information that Petitioner asserts became public during a July 7-9, 2021, trial (Petition at 1-2) and certifies that the information upon which the Petitioner based the action requested in the Petition became known on or about July 28, 2021, with the filing of the post-trial briefs in the patent litigation *Par Pharmaceutical, Inc. et al. v. Eagle Pharmaceuticals Inc.*, No. 1-18-cv-00823-CFC-JLH (D. Del.). And yet, the Petition was not submitted until 3 months later, on November 8, 2021, approximately a month before the goal date for FDA to act on Eagle's ANDA—a date Par acknowledges it is aware of.[20]

Although section 505(q)(1)(A) of the FD&C Act directs FDA not to delay approval of a pending application submitted under section 505(j) (i.e., an ANDA) because of any request to take any form of action relating to the application unless the request is in the form of a citizen petition,[21] Par sent a letter to FDA on September 10, 2021, asking that FDA refrain from approving Eagle's ANDA in its current form. This letter, which was sent more than six weeks after Par claims it became aware of the information it relies on in the Petition, raises identical arguments as in the Petition. As its rationale for waiting until November 8 to submit its CP, Par claims that FDA sent a response letter on October 27, 2021, "directing Par to submit its request as a citizen petition" (Petition at 2). FDA did not "direct" Par to submit a petition. Rather, the Agency informed Par that a letter raising such concerns was not appropriate because it does not allow for these issues to be considered in a public manner.[22] A public process is the appropriate manner in which to raise such issues, including by giving the applicant of the ANDA, which such a letter seeks to delay, a chance to comment.

Par's Reply asserts that "[p]rivate correspondence is proper when the issues raised impact a single ANDA." (Reply at 7). We do not agree. Section 505(q) of the FD&C Act does not distinguish between requests that could delay the approval of a single ANDA and those that could delay the approval of multiple ANDAs.[23] By virtue of its statutory certification and verification requirements, the section 505(q) petition process is less vulnerable to misuse than private correspondence, and ensures prompt public access to allegations regarding follow-on applications that have the potential to delay approval and/or affect the public health. These provisions were added to shed light on, among other things, situations like the one here, and to ensure that petitioners submit information in their possession, including relevant information that contradicts their argument, in a timely manner. Accordingly, the Agency has stated that "communications with the Agency regarding any issues with the potential to delay the approval of an ANDA, 505(b)(2) application, or 351(k) application . . . are appropriately submitted

[19] Id.
[20] Petition at 1, citing a June 24, 2021, article.
[21] Par has on multiple occasions submitted 505(q) petitions (e.g., FDA-2019-P-6044, FDA-2017-P-1392, FDA-2016-P-2376).
[22] See Exhibit B (Letter from Sally Choe, Ph.D. to Chad A. Landmon dated October 27, 2021).
[23] See Section 505(q)(1)(A) of the FD&C Act (21 USC 355(q)(1)(A)). As stated in the 505(q) Guidance at 7, FDA interprets "section 505(q) to apply only to petitions for which, at the time the petition is submitted, *at least one* ANDA, 505(b)(2) application, or 351(k) application related to the subject matter of the petition is pending . . . ." (emphasis added).

through the petition process pursuant to § 10.30 or 10.35 rather than as correspondence to the new drug application (NDA), ANDA, 505(b)(2) application, 351(k) application, or another process."[24]

We further find that the Petition does not on its face raise valid scientific or regulatory issues for the reasons stated in section I.A of this letter.

C. The Petition Did Not Include All Information Referred to or Relied Upon

In addition to your Petition's failure to support its claims regarding Eagle's ANDA, FDA has identified other significant problems with the Petition. Under section 505(q)(1)(H) of the FD&C Act, the petitioner is required to provide all relevant information, both favorable and unfavorable, regarding the Petition's claims. The petition must include "all information and views upon which the petition relies" and "representative data and/or information known to the petitioner which are unfavorable to petition."[25] Additionally, the petitioner must certify that it has "taken reasonable steps to ensure that any representative data and/or information which are unfavorable to the petition were disclosed. . . ."[26]

In support of its requests, the Petition references trial exhibits identified as "DTX" and "PTX" that were not submitted with the Petition (Petition at 3, footnote 5).[27] As a result, we are unable to confirm the content of these exhibits. Under 21 CFR 10.20(c), "[i]nformation referred to or relied upon in a submission is to be included in full and may not be incorporated by reference, unless previously submitted in the same proceeding." Moreover, the failure to submit these trial exhibits, which were directly referenced in the Petition, contradicts the signed certification that states, "this [P]etition includes all information and views upon which the [P]etition relies."[28] As discussed, the Petition also failed to acknowledge or address the court's findings of fact, including several directly relevant to, and inconsistent with, arguments made in the Petition. This silence contradicts the signed certification stating that, "this petition includes representative data and/or information known to the [P]etitioner which are unfavorable to the [P]etition" (Petition at 10). While citing an opinion in passing for an unrelated proposition without providing a copy of that opinion or acknowledging its contents unfavorable to the Petition might arguably fall within the literal meaning of "including" that information in the Petition, it is not consistent with the candor and transparency expected of petitioners under section 505(q)(1)(H).

[24] 505(q) Guidance at 6.
[25] Section 505(q)(1)(H) of the FD&C Act.
[26] Id.
[27] The Petition's reliance on trial exhibits includes direct citations within the Petition as well as within the parties' Findings of Fact (Exhibits C and D) cited in the Petition.
[28] 505(q) Guidance at 6.

III. CONCLUSION

In summary, we find that the Petition has not provided any evidence to support its "upward drift" claim, and therefore, the Petition is denied. FDA intends to refer this matter to the FTC, which has the administrative tools and the expertise to investigate and address anticompetitive business practices.

Sincerely,

Douglas C. Throckmorton -S

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Director
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