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December 6, 2021

VIA ELECTRONIC SUBMISSION

Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 2085

Re: Par Sterile Products, LLC's Reply to Eagle's Comment on Docket No. FDA-2021-P-1211

Dear Sir or Madam:

On behalf of Par Sterile Products LLC ("Par"), we respectfully submit this reply to Eagle Pharmaceuticals Inc.'s ("Eagle's") comment dated November 22, 2021 ("Eagle's Comment") to the above-referenced citizen petition and reiterate our request that the Commissioner of FDA take the actions described in the citizen petition.

Eagle's Comment is completely irrelevant to the issue raised in the citizen petition. Having no adequate response to the issue presented by Par, Eagle tries to distract by addressing a different, irrelevant issue – the stability of product made by its "optimized" process and released at a lower pH. As additional distraction, Eagle attacks Par directly. Eagle seems to believe that baseless accusations against Par and its counsel will win the day, and excuse Eagle's inability to engage on the merits of Par's concerns. Such is not the case.

Despite the defamatory accusations riddled throughout Eagle's Comment, Par did not file its citizen petition for an anticompetitive purpose and certainly did not delay filing. Rather, Par raised valid scientific and regulatory concerns that Eagle has still failed to address. Moreover, Par attempted to raise these concerns in a way that would not unduly delay Eagle's approval. It first became publicly known during the recent patent trial that Eagle's ANDA product experiences a problematic upward drift in pH after manufacture. This is an issue because Eagle's pH release specification has the identical range as its pH stability specification; if Eagle releases a batch of its ANDA product at the upper end of its pH release specification (as its ANDA would permit it to do), the pH will drift upward and outside the pH stability specification during its shelf life, as found by the court during the trial.

Eagle ignores this issue entirely, relying instead on the findings of a district court judge who acknowledged that he lacked the requisite expertise to evaluate the issue and did not have data for "optimized" batches released at the upper limit of the release specification. In fact, the district court's findings that Eagle so heavily relies on involve Eagle's "optimized" manufacturing process (which amounts to little more than additional stirring of a batch) for products released at pH levels near the middle of Eagle's pH release specification. But, as addressed in Par's citizen

petition, Eagle is seeking approval for a broader pH release specification that will allow Eagle to release product at the very upper limit of its pH release specification, which is identical to its stability specification, as well as product made outside its "optimized" process. The citizen petition raises concerns about any potential impact of an upward pH drift for product released at the upper end of Eagle's release specification. Eagle does not address this in its comment, and for good reason. There is no adequate response.

Par also feels obligated to address Eagle's smokescreen of baseless accusations of fraud and misconduct and its outrageous request for criminal prosecution. Eagle's inflammatory rhetoric is clearly designed to distract from the fact that it does not, and cannot, respond to the scientific and regulatory issue raised in Par's petition. Contrary to Eagle's accusations, Par and its counsel did not submit a fraudulent certification, and the citizen petition is not a "sham." Eagle's accusations are a product of its inability to distinguish the issue analyzed by the district court (i.e., "optimized" batches released at a lower level of the pH release specification) from the issue raised in the citizen petition (i.e., batches that may be made by a different process or released at the upper end of the pH release specification). Eagle's entire criticism hinges on Par's not reciting certain findings made by the district court. But, as noted above, the findings cited by Eagle are irrelevant to the present issue. Moreover, Par did not hide the district court's decision. To the contrary, Par not only cited it, but included the entire transcript from it, as well as multiple filings related to the court's decision (including Eagle's proposed findings of fact).

Par did not file its citizen petition for an anticompetitive purpose, but rather to raise with FDA real regulatory and scientific issues with Eagle's ANDA product. Nor did Par delay filing. As will be detailed below, Par expeditiously submitted its citizen petition after timely submitting private correspondence to FDA concerning Eagle's ANDA and being informed by FDA that other ANDA applicants may wish to comment.

In sum, despite all of Eagle's bluster and spurious, derogatory accusations, Par has raised meritorious issues regarding pH drift in Eagle's ANDA product that deserve serious consideration by FDA. Eagle, however, ignores those issues. FDA should therefore require Eagle to amend its pH stability specification and demonstrate that such amended stability specification does not pose any concerns with impurities or other safety issues. Alternatively, Eagle should be required to change its release specification and demonstrate that a lower upper limit for the pH range in the release specification will ensure that, even with an upward pH drift, its ANDA product will stay within the stability specification parameters during the entirety of its shelf-life.

I. EAGLE FAILS TO ADDRESS THE MERITS OF PAR'S CITIZEN PETITION AND INSTEAD MISTAKENLY RELIES ON THE DISTRICT COURT FINDINGS

Eagle falsely asserts that FDA does not need to review the issue presented in Par's citizen petition because the district court already did.[1] Eagle's Comment, Docket No. FDA-2021-P-1211-0007 ("Eagle's Comment") at 5 (November 22, 2021). This is wrong for three reasons. First, the district court never "thoroughly considered and expressly rejected" "the precise factual claims" in Par's citizen petition. *Id.* at 1-2. In fact, the district court was never presented data for optimized batches released at the upper end of Eagle's pH release

[1] Eagle fails to inform FDA that Par appealed the district court's decision and therefore the findings Eagle urges FDA to defer to will be further reviewed and may be overturned. *See* Notice of Appeal, *Par Pharm., Inc. et al. v. Eagle Pharm. Inc.,* 2021 WL 3886418 (Sept. 22, 2021) (No. 307).

specification. In other words, the concern raised by Par's citizen petition could not have been adequately reviewed by the court. Instead, the court reviewed data for optimized batches released below the upper limit of the pH release specification. *See Par Pharm., Inc. et al. v. Eagle Pharm. Inc.*,No. 1-18-cv-00823-CFC-JLH (consol.), 2021 WL 3886418 at *6 (D. Del Aug. 31 2021). Contrary to Eagle's position, however, an upward drift still occurred in the optimized batches. *See id.* at *7 ("[T]he pH fluctuations observed over the shelf lives of the post-optimized batches . . . are in the neighborhood of . . . [0].05.") (internal quotations omitted). Moreover, when the court considered data for the pre-optimized batches released at the upper end of the release specification, it found that they had a pH level of 3.69 at the 24-month mark, which was an out-of-specification result. *See id.* at *5.

> In fact, the court *specifically* questioned this during the trial:
>
> THE COURT: Is it your opinion that the FDA knows that SV[00]A1 does not meet the stability specification in the ANDA?
>
> THE WITNESS: Yes.
>
> THE COURT: So they do know?
>
> THE WITNESS: Yes. It has been presented to them. They know.
>
> THE COURT: So isn't a premise of your opinion is that the FDA is going to authorize Eagle to put on the market a drug that has the same characteristics as SVA[00]1?
>
> THE WITNESS: Yes, Your Honor.
>
> THE COURT: *How do you reconcile that? If they know SVA[00]1 doesn't meet the stability specification requirement, why would they ever allow that, an SVA[00]1 drug to be on the market?"*

See Trial Transcript, 321:1-15, *Par Pharm., Inc. et al. v. Eagle Pharm. Inc.*, No. 18-823-CFC-JLH (Consolidated) (D. Del.) (emphasis added) (attached as Exhibit B to Par's Petition).

If Eagle was only seeking approval for an ANDA with a narrower release specification limited to its optimized manufacturing process that mirrored its in-process specification, then the issue would be different and the district court's findings would be more on point here. *See* Par's Petition regarding Vasopressin, Docket No. FDA-2021-P-1211-0001 ("Par's Petition") at 4 (November 8, 2021) (explaining that Eagle's in-process pH specification has an upper limit of 3.54 but that its release specification is 3.6). But then, Eagle would no longer have a right to release a product at a pH as high as 3.6 (and potentially 3.64) using the original process, and with a lowered release specification there would be less of a concern that its pH would drift above the 3.6 upper limit of its stability specification during the product's shelf life. That is not the case. Instead, Eagle maintains that "there is no basis for requiring Eagle to modify its pH specifications" (Eagle's Comment at 8) even after the court found that product made according to the broad parameters in the ANDA drifted out of the stability specification. Rather, Eagle attempts to mislead by citing to statements by the district court that, after reviewing pH stability data for the "optimized" batches released far below the upper end of the release specification (*Par Pharm., Inc. et al. v. Eagle Pharms. Inc.*, 2021 WL 3886418 at *11, Appendix Table 1), "the pH measurement has been within the stability pH specification in Eagle's ANDA" (Eagle's Comment at 2, citing *Par Pharm., Inc. et al. v. Eagle Pharms. Inc.*, 2021 WL 3886418 at *6),

"the data for the optimized process shared by Eagle with the FDA demonstrate that that process results in products that comply with both the ANDA's release pH specification and its stability pH specification[,]" (*id*. citing *Par Pharm., Inc. et al. v. Eagle Pharms. Inc.*, 2021 WL 3886418 at *7), and "[t]he pH measurement data adduced at trial demonstrates that if Eagle uses its optimized process to manufacture its ANDA product, the product will have a pH that meets the ANDA's stability pH specification[]" (*id*. citing *Par Pharm., Inc. et al. v. Eagle Pharms. Inc.*, 2021 WL 3886418 at *7). Eagle neglects to mention two critical details that makes these findings irrelevant to the present issue. All of the data for the "optimized" batches were released at the middle of the release specification, not at the specification's upper end, and Eagle's ANDA is overbroad and allows Eagle to use its original (not "optimized") process. *See Par Pharm., Inc. et al. v. Eagle Pharms. Inc.*, 2021 WL 3886418 at *11.

Second, the court itself even "wonder[ed] whether a district court has the necessary expertise or constitutional authority to decide either while an ANDA is pending before the FDA or after FDA has approved the ANDA that the ANDA applicant employed faulty testing or screening procedures." *Par Pharm., Inc. et al. v. Eagle Pharms. Inc.*, 2021 WL 3886418 at *10 fn. 2. This doubt was not misplaced. The district court is not in a position to evaluate the sufficiency of ANDA applications, and that is not the court's role. In fact, the court has a very limited record before it that is restricted by the Federal Rules of Civil Procedure, the Federal Rules of Evidence, and the choices that the parties make as to what information they submit in evidence. Even judges who regularly preside over pharmaceutical cases lack the depth of technical knowledge and FDA's complement of highly technical support staff. Moreover, the court lacks the authority to request that an ANDA applicant perform further studies, and the court is not charged with ensuring the safety and efficacy of the ANDA product.

Finally, in issuing its opinion, the court presumed that FDA would ensure that Eagle's product would meet its stability specification:

> Eagle's ANDA product cannot [] lawfully be distributed for use and would not be approved for distribution by the FDA unless, at all periods during the product's shelf life, the product's pH is between 3.4 and 3.6 (i.e., before rounding between 3.35 and 3.64). Thus, to comply with its ANDA specifications, Eagle's generic version of Vasostrict® must have a pH of 3.4 and 3.6 at the time of its release for distribution and for its entire shelf life.

Par Pharm., Inc. et al. v. Eagle Pharm. Inc., 2021 WL 3886418 at *5; *see also* Par's Petition at 5-6. As such, FDA should not defer to a district court that deferred to FDA to ultimately decide approval.

II. EAGLE'S FALSE ALLEGATIONS OF FRAUD AND DELAY ARE BASELESS AND UNFOUNDED

Eagle attempts to hide the fact that it doesn't address the merits of Par's citizen petition by repeatedly calling it a "sham CP" and lodging baseless and false accusations[2] against Par

[2] One particularly false and misleading statement by Eagle is that "Endo's most recent SEC Form 10-Q openly warns that FDA's approval of a generic vasopressin product could force the company into bankruptcy . . . ." Eagle's Comment at 10. But nowhere in Endo's 10-Q does it make this statement. Instead, it provides language warning investors that "the introduction of

and its counsel. When all of Eagle's spurious accusations are set aside, it's clear that Par and its counsel did not submit a fraudulent certification and did not delay in filing its citizen petition. No additional administrative sanctions or external referrals are warranted because Par's petition raises a valid scientific and regulatory issue regarding Eagle's ANDA product in an appropriate and timely manner.

Par did not submit its citizen petition for any anticompetitive reason or to cause a delay, but submitted it to raise to FDA a valid scientific and regulatory issue still unaddressed by Eagle. As referenced in Eagle's comment, FDA has provided a "non-exclusive list [that] sets forth an array of substantive and procedural considerations that, even individually, can support a factual determination that a given petition fails to raise valid scientific or regulatory issues and instead was submitted with the primary purpose of delaying the approval of generic drugs." Eagle's Comment at 4, citing FDA, Guidance for Industry: Citizen Petitions and Petitions for Stay of Action Subject to Section 505(q) of the Federal Food, Drug, and Cosmetic Act (the "505(q) Guidance") (rev. 2, Sept. 2019). Although the 505(q) Guidance provides eight considerations (505(q) Guidance at 15-16), Eagle listed only four of them (Eagle's Comment at 5), and failed to support any. The considerations listed by Eagle are as follows:

1. Submission of a petition [where] 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;

2. 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;

3. Submission of a petition raising the same or substantially similar issues as a prior petition to which FDA has already substantively responded, particularly when the subsequent submission closely follows in time the earlier response; and

4. Submission of a petition requesting that other applicants be required to meet standards for testing, data, or labeling for their products that are more onerous or rigorous than the standards FDA has determined are necessary for the applicable listed drug and/or petitioner's version of the same product.

Eagle's Comment at 5. Consideration of these factors demonstrates that Par submitted its citizen petition, not to cause delay, but to raise substantive issues for FDA's consideration.

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any competing versions of Vasostrict® could result in significant reductions in our market share, revenue and cash flows, both in the short term and long term, and could have a material adverse effect on our business, financial condition, results of operations and cash flows." Endo International plc, SEC Form 10-Q, at 45. It later addresses the possibility of bankruptcy in similar language: "as a result of the possibility or occurrence of an unfavorable outcome with respect to any legal proceeding, we have engaged in and, at any given time, may further engage in strategic reviews of all or a portion of our business. Any such review or contingency planning could ultimately result in our pursuing one or more significant corporate transactions or other remedial measures, including on a preventative or proactive basis. These actions could include a bankruptcy . . . ." *Id*. at 49. The 10-Q is far from the smoking gun that Eagle falsely portrays it to be and only demonstrates the lengths that Eagle will go to cast Par in a negative light.

Considerations 1 and 4 are addressed below in sections B and C, respectively. Consideration 3 is inapplicable because the issue raised by Par had never been raised before.

Consideration 2, while never addressed explicitly in Eagle's comment, also does not support Eagle. Eagle filed its ANDA referencing Par's Vasostrict® Product with a Paragraph IV certification on March 23, 2018. *See* FDA, Paragraph IV Patent Certifications, at 75 (Nov. 29, 2021), shorturl.at/ajGQZ; s*ee also* Complaint at 7, *Par Pharm., Inc. et al. v. Eagle Pharm. Inc.*, 2021 WL 3886418 (May 31, 2018); Answer at 7, *Par Pharm., Inc. et al. v. Eagle Pharm. Inc.*, 2021 WL 3886418 (August 6, 2018). Eagle sent Par a notice letter on April 16, 2018. *See* Complaint at 7, *Par Pharm., Inc. et al. v. Eagle Pharm. Inc.*, 2021 WL 3886418 (May 31, 2018); Answer at 7, *Par Pharm., Inc. et al. v. Eagle Pharm. Inc.*, 2021 WL 3886418 (August 6, 2018). The first date the ANDA could have been approved would have been 30 months later, on October 16, 2020. *See* 21 C.F.R. § 314.107(b)(3)(i). But Par did not submit a petition just prior to that date. Nor did Eagle get approval by that date. Instead, as discussed herein and in the petition, Par raised the serious scientific and regulatory issue concerning Eagle's ANDA product shortly after such issue became public. Par has no reason to believe Eagle is any closer to approval now than it was a year ago.

Notably, Eagle knew that it could not plausibly allege the consideration listed in the 505(q) Guidance that the petition was submitted "with little or no data or information in support of the scientific positions set forth in the petition." 505(q) Guidance at 16. This omission by Eagle severely undercuts any argument that the petition lacks a valid scientific and regulatory concern and further highlights Eagle's attempt to obfuscate the petition's merits with defamatory accusations.

A. Par and its Counsel Did Not Submit a Fraudulent Certification

Eagle's accusation that Par did not cite unhelpful findings in the district court decision is unfounded given that the court did not address – and could not have addressed – the issue raised in the petition. *See* Eagle's Comment at 6. As discussed above, Par's citizen petition requests that FDA evaluate whether there are safety issues with the likely upward pH drift in Eagle's product, which can cause a batch that is released at the upper end of Eagle's pH release specification to drift above the pH stability specification during the product's shelf life. Because the district court was not provided with – and thus did not analyze – data from optimized batches released at the upper end of Eagle's release specification (*id.*), however, the court's findings are irrelevant to the requested action. As such, Par had no obligation to list findings by the court that were immaterial to the citizen petition. Nevertheless, Par in no manner hid the district court's decision from FDA and in fact cited the decision in its citizen petition to make FDA aware of it and allow FDA the opportunity to consider it.

B. Par Did Not Delay Filing its Citizen Petition and Did Not Improperly File Private Correspondence

Eagle baselessly asserts that "[t]he only possible rationale for Par's decision to violate the FDCA § 505(q) mandates, evade the citizen petition process, and ignore the Agency's repeated warnings against abusing confidential correspondence is that Par was seeking to engineer a delay between the July trial and the imminently expected approval of Eagle's ANDA." Eagle's Comment at 11-12. In fact, however, Par sought to avoid any delay. As noted in Par's citizen petition, the relevant information first became public during the patent trial on July 7 through July 9, 2021. *See* Par's Citizen Petition at 1. The post-trial briefs were filed on July 19 and 28. *Id*. at 2. Par reviewed the briefs and submitted private correspondence to FDA on

September 10, 2021 (just over a month after the post-trial briefs were filed). Private Correspondence from C. Landmon to FDA ("Private Correspondence") (September 10, 2021) (attached as Exhibit E). In contrast to the current citizen petition, the private correspondence was focused only on Eagle's ANDA. *See* Private Correspondence at 1 (requesting that FDA "refrain from approving Eagle's ANDA in its current form.") The facts thus demonstrate that Par wasted no time in raising these issues with FDA.

Nor was Par "ignor[ing] the Agency's repeated warnings against abusing confidential correspondence . . . ." Eagle's Comment at 11. Private correspondence is proper when the issues raised impact a single ANDA. In fact, FDA routinely considers issues raised in private correspondence. Notably, the very article cited by Eagle in its attempt to disparage Par for submitting private correspondence describes an example where FDA previously considered private correspondence and rendered a decision impacting the status of an ANDA. *See* Chad A. Landmon & William C. Rose, Using FDA's Citizen Petition Process and Litigation to Achieve Market Success, 34 BIOTECH L. REP. 197, 198 (Nov. 5, 2015) (attached as Exhibit D to Eagle's Comment). Further, Par was not attempting to "abus[e] the confidentiality protections afforded to private regulatory correspondence in order to evade the citizen petition process," but instead expected FDA to share the private correspondence with Eagle in a streamlined manner to the extent that FDA required input from Eagle on the issue. Eagle's Comment at 11. Further, unlike a with citizen petition, FDA is not required to respond to private correspondence before approval of an ANDA, allowing expeditious agency action. In fact, the Agency is not required to take any action at all in response to private correspondence. If it believes the correspondence is without merit, it can ignore the correspondence altogether.

On October 27, 2021, however, FDA sent a response letter directing Par to submit its request as a citizen petition to allow Eagle and "*others* the opportunity to comment and participate in the decision-making process." FDA Ltr. to C. Landmon at 1 (October 27, 2021) (emphasis added). FDA's statement that it wanted to allow "others the opportunity to comment," implied that Par's requested action would affect ANDAs other than Eagle's. As such, Par edited the private correspondence to conform to the requirements of a citizen petition as well as to address the other ANDA applicants, and refiled it as directed by FDA.

C. Par Did Not Request that Eagle's ANDA Products Meet Standards that are more Onerous or Rigorous than for Par's Vasostrict® NDA Products

Par is not requesting that FDA hold Eagle's ANDA product to "far stricter regulatory standards than the ones FDA applied to Vasostrict® itself . . . ." Eagle's Comment at 12. And in the same vein, the fact that Par has not "pull[ed] Vasostrict® off the market" does not demonstrate that the citizen petition is baseless and that there is no "genuine safety and immunogenicity risk from higher pH products . . . ." Eagle's Comment at 9. It's difficult to understand how Eagle can even make that comparison. Par has raised a serious scientific and regulatory concern that, if Eagle releases product at the upper end of its pH release specification, then the pH of that product will likely drift up and out of the stability specification during its shelf life, which could raise issues with safety and immunogenicity given that Eagle presumably has not thoroughly tested – and FDA thus has not vetted – the potential impact of a higher pH on Eagle's product. Eagle's product is not Par's product, and unless a direct comparison is made, there can be no assurance that Eagle's product will act the same way as Par's product at the same pH. If Eagle believes that there is no safety concern with uncontrolled changes in pH, then it can raise the stability specification in its ANDA to encompass the pH drift of its product. Par has already demonstrated that its Vasostrict® NDA Product has no safety issues at higher pH ranges; FDA should require Eagle to do the same or

to revise its release specification to ensure that the pH of its product will not exceed the pH stability specification during the entirety of the product's shelf life.

CONCLUSION

For the reasons stated in Par's citizen petition and above, FDA should refrain from approving Eagle's ANDA until either: (1) Eagle amends its stability specification and demonstrates that such amended stability specification does not pose any concerns with impurities or other safety issues; or (2) Eagle amends its release specification and demonstrates that a lowered upper limit for the pH range in the release specification will ensure that, even with an upward pH drift, Eagle's ANDA product will stay within the stability specification parameters during the entirety of its shelf life.

Verification

I certify that, to my best knowledge and belief: (a) I have not intentionally delayed submission of this document or its contents; and (b) the information upon which I have based the action requested herein first became known to me on or about July 28, 2021 (filing of the post-trial briefs discussed herein), October 27, 2021 (receipt of letter from FDA directing that the request sent to FDA on September 10, 2021 be submitted as a citizen petition), and December 1, 2021 (receipt of comment from Eagle Pharmaceuticals, Inc.). 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 Pharmaceutical Inc. – an Endo International Company. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this document.

Sincerely,

Chad A. Landmon

Exhibits

EXHIBIT E

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September 10, 2021

VIA E-MAIL AND REGULAR MAIL

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Re: Eagle Pharmaceuticals, Inc.'s Out of Specification Vasopressin ANDA Product Referencing Vasostrict® Should Not Be Approved

Dear Sir or Madam:

We write regarding Eagle Pharmaceuticals, Inc.'s ("Eagle") ANDA No. 211538 ("Eagle's ANDA") for a proposed generic vasopressin product referencing Vasostrict®. Eagle submitted its ANDA for a generic vasopressin product in 2018, and its June 2021 response to a Complete Response Letter has a GDUFA goal date of December 15, 2021.[1] During a recent patent trial over Eagle's ANDA, it came to light that, if Eagle manufacturers its product at the upper end of the pH release specification in its ANDA, then the pH of Eagle's product will likely increase above the upper limit set in its stability specification. The release specification and the stability specification for Eagle's ANDA product have a pH range of 3.4 to 3.6. Because the pH of Eagle's product is likely to increase during its shelf life, Eagle's ANDA product may be released within the release specification parameters, but the pH will drift upward and outside of the specification during the product's shelf life, creating potential issues for the stability and immunogenicity profile of Eagle's product. FDA should therefore refrain from approving Eagle's ANDA in its current form.

On July 7-9, 2021, a public three-day trial was held in the patent case *Par Pharmaceutical, Inc. et al. v. Eagle Pharmaceuticals Inc.*, No. 18-823-CFC-JLH (Consolidated) (D. Del.). During the trial, Eagle described the pH of its vasopressin product and admitted that

[1] *Eagle Pharmaceuticals Announces FDA Maintains Prioritization of ANDA for Vasopressin*, BUSINESS WIRE (June 24, 2021), https://www.businesswire.com/news/home/20210624005316/en/Eagle-Pharmaceuticals-Announces-FDA-Maintains-Prioritization-of-ANDA-for-Vasopressin.

its ANDA product can exceed the stability specification for pH during its shelf life even if the product's pH were within the release specification after manufacturing. Post-trial briefs and proposed findings of fact were filed on July 19, 2021, and July 28, 2021, which has contextualized and brought into focus certain aspects of what was revealed during the trial. It is our understanding that this is the first public disclosure of this information.

The regulations are clear that drug products that do not meet specifications must be rejected: "For each batch of drug product, there shall be appropriate laboratory determination of satisfactory conformance to final specifications for the drug product . . . prior to release," and products that fail to meet the release specifications "shall be rejected."[2] Among other things, FDA guidance requires release and stability specifications and data supporting those specifications.[3] Before approving Eagle's ANDA, FDA should require Eagle to amend the stability specification and demonstrate that such amended stability specification does not pose any concerns with impurities or other safety issues. Alternatively, Eagle should be required to change its release specification and demonstrate that a lower upper limit for the pH range in the release specification will ensure that, even with an upward pH drift, Eagle's product will stay within the stability specification parameters during the entirety of its shelf-life.

A. Eagle's Products Will Likely Be Outside the Stability Specification Even if They Are Within the pH Release Specification.

Vasopressin is an antidiuretic hormone that is most often used as a life-saving drug in emergency and intensive care medicine to increase and maintain systemic vascular resistance and arterial pressure.[4] Eagle's proposed ANDA product is packaged in one milliliter vials with a concentration of 20 units per milliliter. *See* Trial Transcript, 129:2-4, *Par Pharm., Inc. et al. v. Eagle Pharm. Inc.*, No. 18-823-CFC-JLH (Consolidated) (D. Del.) ("Tr.") (attached as Exhibit A). The proposed product will arrive refrigerated and will be stored in a refrigerator or at room temperature. Under refrigeration conditions, the proposed shelf life is 24 months. *Id.* at 134:18. When it is stored at room temperature, however, the proposed shelf life is 12 months from the time it is removed from refrigeration up to 24 months total. *Id.* at 128:13-21. Based on the different storage conditions, properties such as pH must be tested and controlled to ensure that the product stays within the prescribed specifications during its shelf life. Control of pH is one way to ensure optimal stability of vasopressin, and when the pH is not stable and controlled, the stability of the product is affected. *See, e.g.*, *id.* at 198:1-199:16.

According to the testimony at the patent trial, Eagle's release pH specification and its stability pH specification for its ANDA product are identical: 3.4 to 3.6. This means that the ANDA product must have a pH of 3.4 to 3.6 before it is released and during the entirety of its shelf life. *See id.* at 349:8-350:16 (Kinam Park, Ph.D., expert for Eagle); DTX-327[5] (ANDA document, stability specifications) at 1; Par's Proposed Findings of Fact Regarding Eagle's Infringement of the '209 and '785 Patents ("Par's FOF"), ¶ 86 (attached as Exhibit B); Defendants' Proposed Findings of Fact Regarding Noninfringement ("Eagle's FOF"), ¶¶ 334-45 (attached as Exhibit C); PTX-1427 (ANDA Module 3.2.P.5.1, description of specifications). As

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[2] 21 C.F.R. §§ 211.165(a), (f).

[3] *See generally* ANDA Submissions – Content and Format, Guidance for Industry (June 2019); ANDAs: Stability Testing of Drug Substances and Products, Guidance for Industry (June 2013).

[4] *See generally* Aviral Roy & Richard Phillip Dellinger, *Attempting to define and refine vasopressin use in septic shock: the VANISH trial*, 4 ANN. OF TRANSLATIONAL MED. 501 (2016).

[5] Reference herein to documents with "DTX" and "PTX" designations refer to trial exhibits introduced into evidence from the defendant and plaintiff, respectively, in Eagle's patent trial. Although such documents do not appear on the court's PACER system, they were discussed in open court during the course of the trial, are referenced in transcript pages discussed herein, and can be located in Eagle's ANDA. Where possible, we have provided a sufficient description of such documents to enable FDA to locate the documents within Eagle's ANDA.

will be discussed further below, the evidence during the patent trial demonstrated that the pH of Eagle's ANDA product increases over time. As a result, 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. This is because the release and stability specifications are identical. FDA should therefore not approve Eagle's ANDA under the current specifications and should require Eagle to demonstrate that no impurity or other safety-related issues will result even under revised pH specifications. Eagle's specifications should be changed to ensure all product released will remain within stability specifications throughout its shelf-life.

1. Eagle's Batch SVA001 Was Released and Fell Outside the Stability Specification for pH.

Batch SVA001, for example, was released at the top end of the release specification (3.4-3.6) with a pH of 3.64. *See* Tr. 362:7-9; *id.* at 226:2-12 (Lee Kirsch, Ph.D., Par's expert); Par's FOF, ¶ 100; *see also* PTX-1435 (ANDA Module 3.2.P.8.1), at 9. During 24-month stability testing of this batch, the pH values were measured at 3.7, 3.8, and 3.7 when stored upright and under refrigeration conditions. *See* Par's FOF, ¶ 98; PTX-208 (ANDA document, stability data for registration batch SVA001); Tr. 220:19-23, 221:15-222:8 (Kirsch). Three values were recorded "because the original measurement of 3.69 was out of specification" ("OOS"). Par's FOF, ¶ 98; *see* Tr. 357:11-358:2 (Park); DTX-993 (ANDA document, pH measurements under various conditions); *see also* Eagle's FOF, ¶ 358 ("the 24-month upright sample result was 3.69 (rounded to 3.7)" which "fell just outside the upper pH limit of 3.64 at proposed expiry").

Eagle undertook an investigation to determine the root cause of the OOS result and found that the high pH values occurred because batch SVA001 "was released at the upper limit of the pH specification (the release value was 3.64, which rounds to 3.6)." Par's FOF, ¶ 100; *see* Eagle's FOF, ¶ 360; *see also* PTX-1435 (ANDA Module 3.2.P.8.1), at 9; Tr. 227:2-16 (Kirsch). In addition, Eagle also concluded that "[t]he product is the likely root cause of the high pH." Par's FOF, ¶ 99; *see* PTX-53 (Out of Specification Report, PR661354); Tr. 224:4-225:16 (Kirsch). Eagle subsequently made manufacturing changes, which involve continued mixing, in an attempt to better control the pH during manufacturing. Tr. 362:12-19; 364:2-5.

Despite tweaking its manufacturing process, however, Eagle did not change its release specification to decrease the upper-end of its acceptable pH range of 3.4 to 3.6. Instead, Eagle adjusted its in-process pH specification. There, however, "Eagle broadened the upper limit of its in-process pH specification, from 3.50 to 3.54, after manufacturing the optimization/confirmation batches (SVA007-009)." Par's FOF, ¶ 78; *see also* Eagle's FOF, ¶ 372.

2. "Optimized" Batches Demonstrate Post-Release Upward Drift of pH.

Eagle's "optimized" manufacturing process was performed on several batches, but the pH continued to drift upward with in-process testing and post-release stability testing. The "optimization" of the manufacturing process refers to extended stirring of the pH adjusted product for more uniformity, but does not affect the pH drift of the final product. The data revealed at trial and contextualized in the post-trial briefings reveal that the pH of Eagle's product will drift upward over time even when produced using the "optimized" method. *See* Par's FOF, ¶ 57; *see also* PTX-1435 (ANDA Module 3.2.P.8.1), 9-10.

"[T]he pH of SVA011 at the post-filtration in-process test was 3.50 yet had pH values upon release testing (reported as 'initial') as high as 3.56 and 3.57—a 0.06 and 0.07 pH unit increase," and "the post-filtration in-process pH test for SVA012 was 3.44, yet it had pH values on release as high as 3.50—a 0.06 pH unit increase." Par's FOF, ¶ 110; *see* DTX-993 (stability testing data for batches SVA007-9, 11-14, 16-17); Tr. 244:6-19 (Kirsch), 460:12-461:4 (Park). These were not abnormal findings and, in fact, were also categorized as "representative of"

commercial batches: "Eagle's expert Dr. Park agreed that 0.07 or 0.06 pH unit increases from post-filtration pH testing to release testing is 'representative of' and could be expected of commercial batches." Par's FOF, ¶ 111; *see* Tr. 461:8-12.

"Given that Eagle's current in process specification would allow commercial manufacture at pH 3.54, adding 0.06 or 0.07 pH units to the in-process specification would result in a pH at release of 3.60 or 3.61, within the upper end of the release specification." Par's FOF, ¶ 111; *see* Tr. 246:9-22 (Kirsch). Based on this upward drift, "future batches manufactured at the upper limit of Eagle's post-filtration in-process pH specification (3.54), would be expected to have release values as much as 0.07 pH units higher (i.e., at least as high as pH 3.61) by the time of release testing, which would place the batch within the upper-end of the release pH specification." Par's FOF, ¶ 115; *see* Tr. 245:9-246:22 (Kirsch), 461:8-12, 473:13-474:2, 474:7-18 (Park).

Although batches were allegedly "optimized," they still had "significant post-release drift, oftentimes within the very first month thereafter." Par's FOF, ¶ 112. Eagle's expert agreed:

> Q: We saw increases of .05, .04, .04, .06, .04, .05 in the data that you say is representative of the batch between release and shelf life; correct?
>
> A: Yes.

Tr. 474:7-11. These values indicate that the pH may increase by as much as 0.06 in representative commercial batches during the shelf life. *See id.* These representative batches demonstrate that the "optimization" process has not changed the upward drift of the pH for either in-process release testing or during the product's shelf life. Batches that are released at the upper end of the specification are likely to show an upward drift and have a pH greater than 3.6 during the shelf life of the product. *See* Par's FOF, ¶ 116.

B. FDA Should Not Approve Eagle's ANDA Until the Specifications Are Changed.

Eagle's current stability specification of 3.4 to 3.6 therefore may not encompass all batches that are released. This is impermissible and poses safety and efficacy concerns. In fact, Eagle admits that "a product that is released at pH 3.4 to 3.6, but that can later drift [outside of that range] . . . would be non-compliant with Eagle's stability specification, which requires a pH of 3.4 to 3.6 over the entire shelf life of the product." Eagle's FOF, ¶ 339.

Chief Judge Colm Connolly identified the precise issue with Eagle's release and stability specifications: "I can't believe the FDA would allow a product to go out on the market with the understanding that the release specification matches the stability specification unless . . . nothing was brought to its attention to form a belief that the product would degrade over the shelf life." Tr. 47:4-9. Judge Connolly later assumed the following about FDA's procedures in issuing his decision after trial:

> Eagle's ANDA product cannot lawfully be distributed for use and would not be approved for distribution by the FDA unless, at all periods during the product's shelf life, the product's pH is between 3.4 and 3.6 (i.e., before rounding between 3.35 and 3.64). Thus, to comply with its ANDA specifications, Eagle's generic version of Vasostrict® must have a pH of 3.4 and 3.6 at the time of its release for distribution and for its entire shelf life.

Par Pharm., Inc. et al. v. Eagle Pharm. Inc., No. 18-823-CFC-JLH, slip op. at 11 (D. Del. Aug. 31, 2021). Eagle should be required to amend the stability specification before its ANDA is approved and demonstrate that such amended stability specification does not pose any concerns with impurities or other safety issues. Alternatively, Eagle should be required to change its release specification and demonstrate that a lower upper limit for the pH range in the release specification will ensure that, even with an upward pH drift, Eagle's product will remain within the stability specification parameters during the entirety of its shelf-life.

1. Eagle's ANDA Product Must Be Within the Established Specifications.

For an ANDA product that is not yet approved, like Eagle's ANDA product, FDA should not approve the ANDA unless and until the product conforms to all final specifications. Among other requirements, an ANDA must contain a full description of the drug substance, the method of purification of the drug substance, and "the specifications necessary to ensure the identity, strength, quality, and purity of the drug substance."[6] Batches of an ANDA product must "meet each appropriate specification and appropriate statistical quality control criteria as a condition for their approval and release."[7] ANDA products that fail to meet release and stability specifications do not achieve "satisfactory conformance to final specifications for the drug product" and "shall be rejected."[8]

FDA's Good Manufacturing Practice ("GMP") standards further require that all manufacturers maintain "scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity."[9] In addition, there must be a "[d]etermination of conformance to written descriptions of . . . appropriate specifications for drug products."[10]

Ensuring that the product is within the specification is important because "[s]pecifications are chosen to confirm the quality of the drug substance and the drug product . . . and should focus on those characteristics found to be useful in ensuring the safety and efficacy of the drug substance and drug product."[11] Specifications established in the ANDA are needed for conformance with stability specifications to ensure that the product will maintain its safety and efficacy profile throughout its entire shelf life.[12]

2. Eagle's ANDA Product May Not Meet the Specifications Established in Eagle's ANDA.

As discussed more fully above, the evidence that came out during the patent trial demonstrated that product released by Eagle near the upper end of its release specification for pH is likely to drift above Eagle's stability specification for pH, which is improper. Par's FOF, ¶ 57; *see also* PTX-1435 (ANDA Module 3.2.P.8.1), 9-10. "[T]he evidence from Eagle's registration batches demonstrates that batches released at the upper end of the release pH

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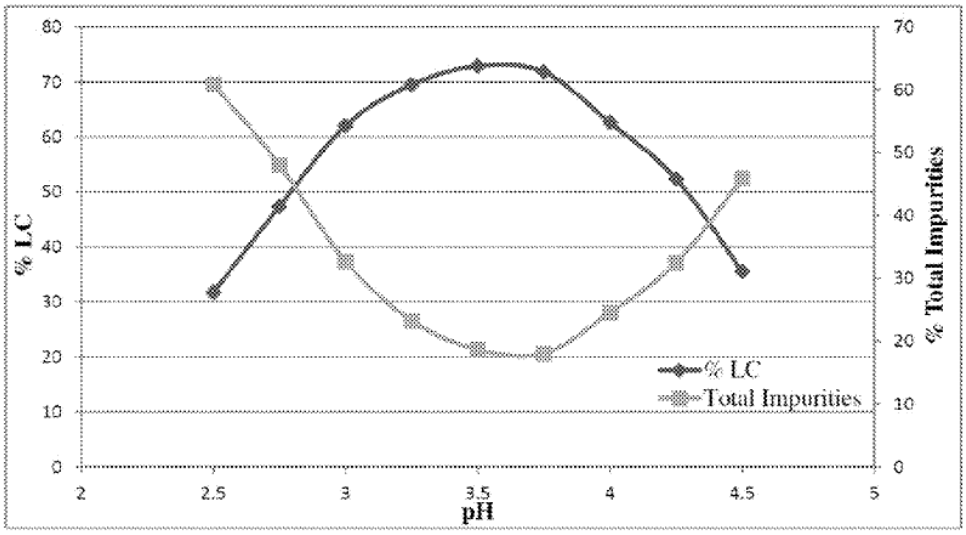
[6] 21 C.F.R. § 314.50(d)(1)(i).
[7] 21 C.F.R. § 211.165(d).
[8] 21 C.F.R. §§ 211.165(a), (f).
[9] 21 C.F.R. § 211.160(b).
[10] 21 C.F.R. § 211.160(b)(3).
[11] Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances, 65 Fed. Reg. 83,041, 83,042 (Dec. 29, 2000), https://www.govinfo.gov/content/pkg/FR-2000-12-29/pdf/00-33369.pdf.
[12] *See* Guidance for Industry: Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production, at 2 (Oct. 2006) ("Laboratory testing . . . is necessary to confirm that . . . finished products conform to . . . stability specifications."); *see also* 21 C.F.R. §§ 211.160, 211.165.

specification would be expected to have pH values between 3.7-3.9 during their shelf-lives." Par's FOF, ¶ 116. These batches would fall outside of the stability specification even though they met the release specification requirements.

In addition, after Eagle's OOS investigation, Eagle broadened its in-process specification by increasing the upper limit after the optimization batches. These broader in-process specifications were never subsequently tested to ensure that the products met the pH stability specifications. *See* Par's FOF at 24.

3. The ANDA Product's pH Must Be Within the Established Specifications to Ensure Safety and Efficacy.

Specifications in an ANDA are used to support a finding of safety and efficacy, and a product that is outside of the prescribed specifications can potentially pose a risk that the drug is not safe and efficacious.[13] For vasopressin in particular, researchers have determined that stability for a vasopressin formulation varies based on pH; likewise, impurities also increase with increasing pH:



U.S. Patent No. 9,744,209, Fig. 9; *see id.* at col. 57, ll. 40-55. Specifically, it is understood that a "pH outside the 3.4-3.6 range will accelerate the degradation of vasopressin," leading to the creation of additional impurities in the product.[14]

Stability and immunogenicity are critical for the safety and efficacy of a drug.[15] Further, impurities may cause immunogenicity issues and should be carefully controlled and

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[13] *See* 21 C.F.R. § 211.165(d).

[14] Medical Review (Vasostrict), 204485Orig1s000, Cross-Discipline Team Leader Review, at 5 (June 12, 2013), available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/204485Orig1s000MedR.pdf.

[15] *See, e.g.,* Yusuf A. Haggag et al.*, Peptides as Drug Candidates: Limitations and Recent Development Perspectives*, 8 BIOMEDICAL J. SCI. & TECH. RES. 1-4 (2018) ("Stability, biological efficacy, pharmacokinetic profile and immunogenicity are the most critical parameters to develop a peptide as a therapeutic agent."); Peize Wu et al., *Impurity identification and quantification for arginine vasopressin by liquid chromatography/high-resolution mass spectrometry*, 34 RAPID COMMC'NS IN MASS SPEC. e8799 (2020) ("For pharmaceutical quality control, impurities may have unexpected pharmacological or toxicological effects on quality, safety, and efficacy of drugs."); Nonclinical Safety Evaluation of the Immunotoxic Potential of Drugs and Biologics, Guidance for Industry, at 2 (Feb. 2020) ("The ability of drugs and

characterized.[16] As a result, FDA recommends that "[a] risk-based evaluation of potential immune responses to . . . process- and product-related impurities should be performed . . . ."[17]

Any increase of the pH of Eagle's product during its shelf life to a level outside of the pH specification range of 3.4 to 3.6 raises potential issues of increased impurities from degradation. If Eagle is not going to reduce its pH release specification in a manner that ensures that its product will remain within the pH stability specification, then Eagle should be required to both amend the upper range of its stability specification and specifically identify and characterize any further degradation and resulting impurities caused by the higher pH level. Without changes to its pH specifications, Eagle's ANDA product may not "meet each appropriate specification and appropriate statistical quality control criteria," may not be safe and efficacious, and should therefore not be approved.[18]

CONCLUSION

Evidence that was made public during the recent patent trial involving Eagle's vasopressin ANDA have demonstrated 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 (pH of 3.4 to 3.6). FDA should not approve an ANDA where the product is likely to fall outside of the ANDA's stability specification during its shelf life, particularly where, as here, the increased pH environment can lead to further degradation of the vasopressin and the creation of additional impurities and immunogenicity issues. FDA should thus refrain from approving Eagle's ANDA until either: (1) Eagle amends its stability specification and demonstrates that such amended stability specification does not pose any concerns with impurities or other safety issues; or (2) Eagle amends its release specification and demonstrates that a lower upper limit for the pH range in the release specification will ensure that, even with an upward pH drift, Eagle's product will stay within the stability specification parameters during the entirety of its shelf life.

Sincerely,

Chad A. Landmon

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biologic products to modify the activity of the immune system is an important part of evaluating the safety and efficacy of these products."); Immunogenicity Testing of Therapeutic Protein Products - Developing and Validating Assays for ADA Detection ("Immune responses to therapeutic protein products have the potential to affect product pharmacokinetics, pharmacodynamics, safety, and efficacy.").

[16] Immunogenicity Assessment for Therapeutic Protein Products, at 10 (Aug. 2014) ("Sensitization to the excipients or process/product-related impurities of a therapeutic protein product may also predispose a patient to an adverse clinical consequence.").

[17] Immunogenicity Assessment for Therapeutic Protein Products, at 14 (Aug. 2014); *see also* ANDA Submissions – Refuse to Receive for Lack of Justification of Impurity Limits, Guidance for Industry, at 3 (Aug. 2016) ("To ensure purity, [ANDA] applicants should propose and justify appropriate limits on the impurities in their drug substances and drug product.").

[18] 21 C.F.R. § 211.165(d).