



**AMPHASTAR PHARMACEUTICALS, INC.**

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May 31, 2005

Dockets Management Branch  
Food and Drug Administration  
5630 Fishers Lane  
Room 1061 (HFA-305)  
Rockville, Maryland 20852

**RE: Docket No. 05P-0134 – Comments in Opposition to ISTA  
Pharmaceuticals, Inc. (“ISTA”) Citizen Petition Concerning Marketing  
Exclusivity for Vitrase® (hyaluronidase injection).**

Dear Sir or Madam,

The above-referenced citizen petition (the “Petition”) requests that the agency revert to its earlier determination that three- rather than five-year exclusivity be granted to Vitrase. FDA should deny the request because the agency took appropriate action when it corrected what it deemed to be a mistake in its earlier determination of the period of exclusivity to assign to the product.

If FDA nonetheless grants ISTA’s request and reverts to its earlier determination that Vitrase is entitled to only three years exclusivity, this change should have no bearing whatsoever on the regulatory status of Amphastar’s hyaluronidase product, Amphadase®. Vitrase’s three-year exclusivity would not have blocked approval of the Amphadase application. Moreover, even if FDA disagrees with regard to the scope of Vitrase’s three-year exclusivity, it would be fundamentally unfair for FDA to retrospectively determine that Amphadase’s approval should have been blocked.<sup>1</sup>

<sup>1</sup> We note that ISTA’s Petition does not request such action. Indeed, the Petition mentions Amphadase only in a footnote, and does not propose what practical effect, if any, its request should have on the product. Petition at 8, note 9.

2005P-0134

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## **Background**

FDA has apparently had difficulty determining the appropriate period of exclusivity due Vitrase, ISTA's ovine-source hyaluronidase product, which was submitted to FDA on August 4, 2003 and approved on May 4, 2004. Immediately after approval of the product, FDA included Vitrase in the "CDER New Molecular Entity ("NME") Drug and New Biologic Approvals" list, presumably signaling that it would be assigned five-year new chemical entity ("NCE") exclusivity. Soon thereafter, however, FDA removed the product from that list, and apparently informed ISTA that the product was entitled to three years of exclusivity.

On October 26, 2004, the agency informed ISTA that it had determined that Vitrase was entitled to five-year NCE exclusivity after all pursuant to sections 505(c)(3)(D) and 505(j)(5)(D) of the Federal Food, Drug, and Cosmetic Act ("FDCA") and 21 C.F.R. § 314.108(b). That letter recognizes that FDA had earlier told ISTA that Vitrase had three-year "new clinical investigation exclusivity," but that after "reviewing information and data regarding hyaluronidase products" FDA decided that five-year exclusivity was appropriate. Letter from Jonca C. Bull, M.D., FDA, to Marvin J. Garrett, ISTA, Oct. 26, 2004.

Amphastar's new drug application for Amphadase (hyaluronidase injection, USP), a bovine-source hyaluronidase product, was submitted to FDA on June 6, 2003. Amphadase was approved by FDA on October 26, 2004, the same day that ISTA was informed of FDA's decision to assign five-year exclusivity to Vitrase. Amphadase was also assigned five-year NCE exclusivity.

Both ISTA and Amphastar submitted 505(b)(2) applications for their hyaluronidase products, relying in part on FDA's DESI review of hyaluronidase to demonstrate safety and effectiveness.

On March 1, 2005, ISTA met with FDA's Office of Chief Counsel to discuss FDA's decision to assign five-year NCE exclusivity to Vitrase. ISTA's Petition followed. Petition at 2.

## **Discussion**

### **I. Regardless which period of exclusivity is assigned to Vitrase, approval of Amphadase was appropriate.**

Petitioner's request should be denied because FDA took appropriate action when it corrected what it deemed to be a mistake in its earlier determination of the period of exclusivity to assign to Vitrase. Agencies are entitled, sua sponte, to correct prior actions they determine to be inconsistent with the governing statute. See, e.g., Gun South, Inc. v. Brady, 877 F.2d 858, 862 (11th Cir. 1989) ("courts have recognized an implied authority [of agencies] to reconsider and rectify errors . . .") (citations omitted).

If FDA nonetheless grants ISTA's request, approval of Amphadase was appropriate because Vitrase's three-year new clinical investigations exclusivity would not have blocked Amphadase. The Amphadase application did not rely on any studies conducted by ISTA.

#### **A. Based on the plain meaning of the statute, approval of the Amphadase application was appropriate because it did not rely on any clinical studies conducted by ISTA.**

The applicable statutory language prevents FDA from making effective the approval of another 505(b)(2) application for the same drug, but only where the subsequent applicant relies on studies conducted by the holder of the exclusivity:

If an application submitted under subsection (b) of this section for a drug, which includes an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application approved under subsection (b) of this section is approved after September 24, 1984, and if such application contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant, the Secretary may not make the approval of an application submitted under subsection (b) of this section for the conditions of approval of such drug in the approved subsection (b) application effective before the expiration of three years . . . if the investigations described in clause (A) of subsection (b)(1) of this section **and relied upon by the applicant** for approval of the application were not conducted by or for the applicant and if the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted.

21 U.S.C. § 355(c)(3)(E)(iii) (emphasis added).

A 505(b)(2) application may be submitted where an applicant seeks approval of a drug product that represents modifications to a listed drug for which submission of an abbreviated new drug application (“ANDA”) would not be permitted, e.g., a new indication or a new dosage form. 21 C.F.R. § 314.54(a). The FDCA does not permit ANDAs for changes to a listed drug if investigations (other than bioavailability or bioequivalence studies) are essential to approval. *Id.* A 505(b)(2) application need only include the information that is necessary to support the modification from the listed drug. *Id.* For hyaluronidase products, if human safety data on the specific product is not available, FDA requires clinical studies to assess allergic potential. See FDA Denial of Citizen Petition 2003P-0494, at 6 (May 5, 2004).

Both Amphastar and ISTA relied on publicly-available scientific findings (i.e., FDA's DESI review of Wydase) to establish the safety and effectiveness of its product, and each company conducted its own hypersensitivity clinical study to confirm the safety of its own product. Neither company relied on the other's clinical investigations for approval. Therefore, one's exclusivity cannot block the other.

1. FDA took this position with regard to levothyroxine products.

Concluding that Vitrase's three-year exclusivity should have blocked approval of Amphadase would be inconsistent with FDA's position on levothyroxine products, which was affirmed by the D.C. District Court. Memorandum and Opinion, King Pharmaceuticals, Inc v. FDA, C.A. No. 04-cv-1058 (D.D.C. July 8, 2004). King challenged FDA's decision to approve competitors' supplements to 505(b)(2) applications that did not contain certifications to King's formulation patent for its levothyroxine product. FDA determined, and the court agreed, that patent certifications were not necessary in part because the applications at issue did not rely on studies conducted by King. Memorandum in Opposition to Plaintiffs' Motion for a Temporary Restraining Order and a Preliminary Injunction, King Pharmaceuticals, Inc v. FDA, C.A. No. 04-cv-1058, at 2-3 (D.D.C. July 1, 2004) ("FDA Memo") (emphasis added).

The patent certification provision at issue in King – like the three-year exclusivity at issue here – is a benefit that Congress gave manufacturers to encourage research and development.<sup>2</sup> FDA has taken the position before the court that a manufacturer that has not conducted the “expensive and time-consuming clinical trials” required to establish the safety and effectiveness of its product deserves no such benefit. FDA Memo at 3. In

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<sup>2</sup> FDA Memo at 3 (“The patent certification provision to which King refers is one of several benefits Congress gave to manufacturers of innovator drugs to encourage research and development . . .”).

King, each company relied on publicly-available scientific literature to establish the safety and effectiveness of its products, and each company conducted its own bioequivalence study. Id. Amphastar and ISTA stand in the same position as the applicants in the levothyroxine case. In the levothyroxine case none of the applicants relied on the safety and efficacy data on King's drug. Here, both Amphastar and ISTA relied on publicly-available scientific findings (i.e., FDA's DESI review of Wydase) to establish the safety and effectiveness of its product, and each company conducted its own hypersensitivity study to confirm the safety of its own product. Similar to the intervenors in King, Amphastar did not rely on ISTA's proprietary data, and ISTA's exclusivity cannot bar Amphastar from the marketplace.

The court also agreed with FDA's interpretation of statutory language, which, in relevant part, tracks the language at issue here.<sup>3</sup> The patent certification provision at issue in the levothyroxine states:

(2) An application submitted under paragraph (1) for a drug for which the investigations described in clause (A) of such paragraph **and relied upon by the applicant for approval** of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted shall also include –

(A) a certification, in the opinion of the applicant and to the best of his knowledge, with respect to each patent which claims the drug for which such investigations were conducted or which claims a use for such drug for which the applicant is seeking approval under this subsection . . . .

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<sup>3</sup> Memorandum and Opinion, King Pharmaceuticals, Inc v. FDA, C.A. No. 04-cv-1058, at 9 (D.D.C. July 8, 2004) (noting agreement with FDA's construction of the statute even though the court found that Congress had spoken directly to the issue).

21 U.S.C. § 355(b)(2) (emphasis added).

In the levothyroxine case, FDA explained that section 355(b)(2)'s reference to "clause (A)" in the phrase "for a drug for which the investigations described in clause (A)" is a reference to section 355(b)(1)(A), which indicates that NDAs must contain full reports of the safety and effectiveness of the drug. FDA Memo at 15. Specifically, section 355(b)(1)(A) states that NDAs must include "full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use . . . ." 21 U.S.C. § 355(b)(1)(A). In its argument to the court, FDA then linked this description of safety and effectiveness studies to the next phrase in section 355(b)(2): "and relied upon by the applicant for approval of the application." Id. FDA concluded that the words "and relied upon by the applicant for approval of the application" mean that "the applicant is relying on findings of safety and efficacy that were made for another drug to fill in gaps and obtain approval of its own application." Id.

Based on its analysis of the words of the statute, FDA concluded that patent certifications are only necessary where safety and effectiveness studies were conducted on the drug which the patent claims, and when the applicant relies on those studies to obtain approval of its application. FDA Memo, at 16. The same words that FDA analyzed for the levothyroxine case appear in the section of the statute at issue here:

If an application submitted under subsection (b) of this section for a drug, which includes an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application approved under subsection (b) of this section is approved after September 24, 1984, and if such application contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and

conducted or sponsored by the applicant, the Secretary may not make the approval of an application submitted under subsection (b) of this section for the conditions of approval of such drug in the approved subsection (b) application effective before the expiration of three years . . . **if the investigations described in clause (A) of subsection (b)(1) of this section and relied upon by the applicant for approval of the application** were not conducted by or for the applicant and if the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted.

21 U.S.C. § 355(c)(3)(E)(iii) (emphasis added).

The three-year exclusivity at issue here is analogous to the patent certification provision in the levothyroxine case. In the levothyroxine case, the applicants did not rely on the patent holder's studies to obtain approval of their applications, therefore no patent certification was required. In our case, Amphastar never relied on any study conducted by the holder of the exclusivity (if three-year exclusivity is granted to Vitrase), therefore approval of Amphastar's application was appropriate.

Tying reliance on studies to exclusivity is also consistent with FDA's reasoning as stated in the 1989 preamble to FDA's proposed rule on 505(b)(2) applications and abbreviated new drug applications. There FDA explained that three-year exclusivity would be available for 505(b)(2) applications that contained clinical investigations that were new, essential to approval, and conducted or sponsored by the applicant. FDA said that if these requirements were met, 505(b)(2) applications for similar products would be delayed for three years, but only where the subsequent application "*relies on the information supporting the new conditions of approval of the first-approved application.*"

54 Fed. Reg. at 28,899 (emphasis added).<sup>4</sup> Amphastar's 505(b)(2) application relied in no way on any information supporting approval of ISTA's formulation. Rather, each company relied on publicly-available data to establish safety and effectiveness of hyaluronidase. And each company relied on its own clinical study data to confirm the safety of its own product formulation.

B. The scope of Vitrase's three-year exclusivity would not have blocked approval of Amphadase.

1. The reason for the new clinical study should determine the scope of the exclusivity.

Three year exclusivity is a reward for the time and expense required to complete necessary clinical studies.<sup>5</sup> Therefore the scope of the exclusivity should be related to the work done to achieve the innovation. With regard to ISTA's Vitrase, FDA required a hypersensitivity clinical study to ensure the safety of the particular formulation. See

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<sup>4</sup> Later in the same preamble FDA makes an apparent inconsistent statement:

If two 505(b)(2) applications are under review at the same time and one is approved before the other, the effective date of approval of the second application to be approved will be delayed, regardless of the date of submission, if the first contained new clinical investigations essential for approval and thereby qualified for exclusivity.

54 Fed. Reg. at 28,901. However, as FDA stated at 54 Fed. Reg. 28,899, the scope of the exclusivity prevents a subsequent (or simultaneous) applicant from relying on the new clinical investigations "supporting the new conditions of approval." Where two 505(b)(2) applications are under review at the same time, it would appear to be impossible for one application to rely on information supporting approval of the other. Moreover, as discussed in section I.B.2 of this document, in this instance not only was there no reliance by Amphastar on ISTA's data, the conditions of approval are different.

<sup>5</sup> See Amendment of Senator Hatch, Cong. Rec. August 10, 1984, at S10505.

FDA Denial of Citizen Petition 2003P-0494, at 6 (May 5, 2004). Likewise, FDA required the identical study be conducted on Amphastar's bovine-source hyaluronidase. It would be illogical to conclude that ISTA's hypersensitivity study should result in Amphastar's exclusion from the marketplace when Amphastar was subject to the same exact requirement.

Indeed, fairness and logic suggest that the purpose of the clinical study that justifies the three-year exclusivity should define the scope of that exclusivity. Tying the scope of the exclusivity to the scope of the required clinical investigation is also consistent with the nomenclature used by FDA to describe the three-year exclusivity previously assigned to Vitrase: "ISTA was informed earlier that it had received three years of new clinical investigation exclusivity." Letter from Jonca C. Bull, M.D., FDA, to Marvin J. Garrett, ISTA, Oct. 26, 2004 (emphasis added).

ISTA's hypersensitivity clinical study was conducted to demonstrate that ISTA's product was safe. The scope of ISTA's exclusivity is therefore limited to ISTA's formulation.<sup>6</sup> FDA has indicated that it intends to require clinical hypersensitivity testing for any "hyaluronidase product for which there is no product-specific data on human exposure," as well as for changes in the source or manufacturing process. *Id.* That said, it would not make sense to allow one hyaluronidase product to block approval of another hyaluronidase product, particularly one that is derived from a different species.

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<sup>6</sup> This is consistent with the court's finding with regard to the Zeneca's market exclusivity for Diprivan (propofol) containing EDTA. FDA approved an ANDA for a propofol product that contained a different preservative. The court agreed with FDA that the clinical investigations that were essential to approval of Zeneca's product were necessary due to specific concerns related to EDTA. Therefore the court concluded that Zeneca's "exclusivity applies to propofol products including EDTA, not to propofol products with other preservatives." Zeneca, Inc. v. Shalala, No. 99-307, 1999 U.S. Dist. LEXIS 12327, at \*38 (D. MD. Aug. 11, 1999), aff'd on other grounds, 213 F.3d 161 (4th Cir. 2000).

FDA has stressed the importance of demonstrating the safety of each hyaluronidase product. In addition to requiring clinical safety studies for new formulations, FDA noted:

Because we do not know which specific protein contaminants in any current or future products might have an allergic potential, adequate standards for manufacturing are necessary to ensure consistency with the product used in the tests for allergenic potential. For all new drug applications for these products, we require careful review of the manufacturing of the drug substance and the drug product. This includes review of the hyaluronidase source material, its handling, and its processing.

FDA Denial of Citizen Petition 2003-P 0494, at 6-7 (May 5, 2004).

Thus, even if FDA maintains that there are no specific safety problems that can be attributed to any particular mammalian source, see id., our reasoning remains sound. The basis for requiring that ISTA (and Amphastar) conduct new clinical studies was that each and every version of the drug may have different allergic potential. Apparently, the allergenicity of the product may be wholly unrelated to the active ingredient or any other generalizable property of the drug. If FDA grants ISTA's request, Vitrase's three-year exclusivity should be equally specific.

2. The "conditions of approval" of Amphadase and Vitrase are different.

If Vitrase had been assigned three-year new clinical investigation exclusivity, the applicable statutory language would prevent FDA from making effective the approval of another 505(b)(2) application, but only if that application seeks approval of the same drug and the same "conditions of approval" apply:

If an application submitted under subsection (b) of this section for a drug, which includes an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application approved under subsection (b) of this section is approved after September 24, 1984, and if such application contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant, the Secretary may not make the approval of an application submitted under subsection (b) of this section **for the conditions of approval of such drug** in the approved subsection (b) application effective before the expiration of three years . . . if the investigations described in clause (A) of subsection (b)(1) of this section and relied upon by the applicant for approval of the application were not conducted by or for the applicant and if the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted.

21 U.S.C. § 355(c)(3)(E)(iii) (emphasis added).

The ISTA Petition cites FDA's response to a comment regarding the phrase "conditions of approval" in the preamble to FDA's final rules on market exclusivity, and concludes that only a full 505(b)(1) NDA would not be blocked by another applicant's three-year exclusivity. Petition at 8-9. A closer reading of the comment and FDA's response shows that it is unclear that FDA reached any such interpretation. While FDA noted in response to the comment that a "full" 505(b)(1) NDA would not be blocked by another applicant's three-year exclusivity, it does not necessarily follow that a 505(b)(2) applicant that conducts its own clinical studies and relies in no manner whatsoever on data contained in the application submitted by the holder of the three-year exclusivity would be blocked.

The comment asked FDA to “interpret the phrase ‘conditions of approval’ to limit exclusivity to studies conducted by the original applicant.” 59 Fed. Reg. 50,338, 50359 (Oct. 3, 1994) (emphasis added). FDA’s response appears to be focused on clarifying that applicants may conduct their own studies or fund the conduct of those studies in order to obtain exclusivity. *Id.* (“[T]he statute does not require that the original applicant ‘conduct’ the study to obtain exclusivity. FDA interprets the act to allow for exclusivity where the applicant has supported the study by providing more than 50 percent of the funding or by purchasing exclusive rights to the study.”).

Claiming that this exchange supports its interpretation of the phrase “conditions of approval,” Petitioner makes a huge leap and concludes that “conditions of approval” means the “indications” for which the product is approved. Petition at 8 (“Therefore, if Vitrase is granted three-year exclusivity, Vitrase is protected for three years against the approval of any ANDA or 505(b)(2) for the same ‘conditions of approval’ – that is, against any application that purports to contain the same active ingredient (hyaluronidase) and that seeks approval for the same indications as Vitrase.”).

FDA’s response to the comment regarding the phrase “conditions of approval” provides no support whatsoever for this interpretation, and Petitioner offers no other explanation for its conclusion that “conditions of approval” means indications for use. If FDA had meant to say that three-year exclusivity would block a 505(b)(2) application for the product that sought approval for the same indications, it would have used that term as it does in other sections of the regulations. *See, e.g.*, 21 C.F.R. § 201.57(c) (describing the Indications and Usage section of prescription drug labeling). Indeed, Congress itself has used the term “indications” when that is what it means. 21 U.S.C. § 379g(1)(B)(ii) (defining the term “human drug application” for purposes of user fees to include a 505(b)(2) application that requests approval of a new molecular entity or a new indication).

We are not aware of any explicit statutory or regulatory definition of the phrase “conditions of approval.” However, a common sense reading of the plain meaning of the words supports our position: A significant change to the drug that would require approval by FDA prior to its implementation is, on its face, a “condition of approval.” For example, if ISTA changed from ovine-source material to bovine-source material, a preapproval supplement to its NDA would be required. See 21 C.F.R. § 314.70(b)(2004) (describing “major changes”). Stated another way, continuing to use ovine-source material is a condition of ISTA’s current approval, and use of bovine-source material in Amphastar’s application is a different condition of approval. Because Amphastar’s application did not seek approval of the same product with the same conditions of approval, ISTA’s three-year exclusivity is meaningless as to Amphastar’s product.

We recognize that not every “major change” to an application can be said to equate to a new “condition of approval.” For example, certain changes to the production process, equipment, or facilities require FDA approval prior to implementation. Significant changes to the drug substance, drug product, or labeling would equate to different “conditions of approval.”

This interpretation of the term “conditions of approval” fits with FDA’s explanation of the type of change that ought to be granted three-year exclusivity and the scope of that exclusivity. In the 1989 preamble to FDA’s proposed rule on 505(b)(2) applications and abbreviated new drug applications, the agency indicated: “FDA expects that only those changes in an approved drug product that affect its active ingredient(s), strength, dosage form, route of administration, or conditions of use would be granted exclusivity.” 54 Fed. Reg. 28,872, 28,899 (Jul. 10, 1989). FDA explained that these changes are “the types of changes in a drug product that require prior approval by FDA before the change may be made.” Id. (citing 21 C.F.R. § 314.70) (emphasis added).

In addition, FDA explained the scope of three-year exclusivity in the preamble as follows:

Exclusivity would be provided only if the clinical studies were “new,” “essential to approval,” and “conducted or sponsored by the applicant.” If these requirements are met, approval of an ANDA or of a 505(b)(2) application . . . **that relies on the information supporting the new conditions of approval of the first-approved application**, may not be made effective before the expiration of 3 years from the date of approval of the original new drug application.

54 Fed. Reg. at 28,899. Because the “conditions of approval” of the Vitrase application differed from that of the Amphadase application, approval of Amphadase was appropriate. The information that supported the “conditions of approval” of the Vitrase application was the data gathered from ISTA’s hypersensitivity clinical study of its product. The information that supported the “conditions of approval” of the Amphadase application was the data gathered from Amphastar’s own hypersensitivity clinical study of its own product. The “conditions of approval” therefore must have differed between the two products, otherwise a new clinical study would not have been required.

**III. Whatever FDA’s decision, any impact on approval of Amphadase would be unfair.**

Even if FDA grants ISTA’s request, and determines, despite the arguments set forth herein, that the scope of Vitrase’s three-year exclusivity should have blocked approval of Amphadase, it would be fundamentally unfair to apply that new policy retrospectively.

Amphastar relied in good faith on FDA's October 26, 2004 approval of Amphadase and immediately launched the product. Indeed, Amphastar responded to a public health need in so doing. Removal of hyaluronidase from FDA's drug shortages list upon approval of ISTA's product was premature because ISTA delayed the commercial launch of Vitrase until January 2005.<sup>7</sup> Amphastar, on the other hand, launched its product immediately upon approval.

Regardless of FDA's conclusions as to the appropriate basis for and scope of marketing exclusivity for Vitrase, there should be no impact on the regulatory status of Amphadase. Applying such a change in policy retrospectively would be unfair and inconsistent with FDA precedent. There are numerous examples of FDA applying changes in policy, regulation, or law, prospectively only, particularly where otherwise the change would unfairly disadvantage applicants. See, e.g., FDA Guidance, Court Decisions, ANDA Approvals, and 180-Day Exclusivity Under the Hatch-Waxman Amendments, 4-5 (March 2000) ("The Agency believes that an implementation plan for the new definition of court that recognizes the industry's reliance on the previous definition and establishes a bright line for ANDAs affected by the new definition will minimize the disruption to the ANDA approval and 180-day exclusivity programs. Moreover, the Agency believes that this approach will lessen the likelihood that ANDA applicants will sue the Agency alleging that they . . . would be irreparably injured by application of the new interpretation to pending ANDAs."); 56 Fed. Reg. 3338, 3340 (Jan. 29, 1991) (proposing that FDA's orphan drug regulations when final would apply prospectively, noting that FDA would not "reconsider any prior actions under the Orphan Drug Act, or change any orphan-drug status, to conform to the final regulations.").

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<sup>7</sup> Remarks of Vincente Anido, Jr., Ph.D., President & CEO, ISTA, Healthcare Tailwinds 2004 (Sept. 8, 2004), available at <http://www.istavision.com>.

**Conclusion**

FDA took appropriate action when it assigned five- rather than three-year exclusivity to Vitrase. Even if FDA grants ISTA's request, however, for all the reasons set forth herein the decision should have no bearing on Amphastar's bovine-source hyaluronidase product, Amphadase.

Sincerely,

A handwritten signature in black ink, appearing to read "Stephen A. Campbell". The signature is written in a cursive, flowing style with some loops and flourishes.

Stephen A. Campbell, Esq.

Senior Vice President, Regulatory Affairs