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March 31, 2003

VIA HAND DELIVERY & UPS

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

Re: Docket Number 02P-0435 (Citizen Petition) – Second Submission of Comments by Alpha Therapeutic Corporation

Dear Sir or Madam:

Please accept the attached second submission of comments (in four copies) on behalf of Alpha Therapeutic Corporation in response to the Citizen Petition filed by Aventis Behring L.L.C. on October 2, 2002.

Sincerely,

David G. Adams

02P-0435 C4

March 31, 2003

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

Re: Docket Number 02P-0435 (Citizen Petition) – Second Submission of Comments by Alpha Therapeutic Corporation

Dear Sir or Madam:

These comments are submitted on behalf of Alpha Therapeutic Corporation (Alpha) in response to the Citizen Petition filed by Aventis Behring L.L.C. (Aventis Behring) on October 2, 2002 (Aventis Petition). The petition requests that the Commissioner refrain from granting effective approval of Alphanate® Solvent Detergent/Heat-Treated Antihemophilic Factor (Human) (Alphanate or Alphanate SD/HT) for the treatment of von Willebrand Disease (vWD) until the expiration of orphan drug exclusivity for Humate-P® Antihemophilic Factor/von Willebrand Disease (Human) (Humate-P) on March 31, 2006.

Alpha's comments set forth below supplement comments submitted by Alpha on January 21, 2003, and respond to comments submitted by Aventis Behring dated March 14, 2003 (Aventis Comments). Although Alpha submitted comments rebutting the Aventis Petition in January 2003, Aventis Behring seeks to raise last-minute questions based on comments filed this month that are in part misleading and in part demonstrably erroneous.

1. Alphanate is New and is Supported by Prospective Clinical Studies.

Aventis Behring asserts in its comments: "Alphanate is not a new drug. It has been marketed for nearly 30 years, having been licensed in 1974 for the treatment of Hemophilia A. . . ."[1] This statement is erroneous. The initial Alphanate formulation was

[1] Aventis Comments, at 1 (Mar. 14, 2003).

approved on July 13, 1994.[2] Prior Factor VIII products manufactured by Alpha were different because they were of intermediate purity and were marketed under different names. The current Alphanate formulation (Alphanate SD/HT) was approved on February 14, 1997.[3] This is the product that is the subject of the Aventis Petition. Humate-P was first approved in the United States on May 1, 1986.[4]

Alphanate has been studied in a prospective, multicenter clinical trial in patients with vWD in whom desmopressin was ineffective or contraindicated. The data from this prospective trial indicate that Alphanate is effective in the treatment of bleeding episodes and in surgical prophylaxis in these patients.[5] The Humate-P approval for the vWD indication is based on reports from a retrospective collection of information from patient files.[6] This method of data collection increases the likelihood of error and of omitting critical efficacy and safety information. In the case of Humate-P, efficacy was evaluated post hoc based on subjective assessments. Although the prospective data provided in the Alphanate trial are more compelling than the retrospective data provided for Humate-P, there has been no comparative study to assess the relative efficacy of Alphanate and Humate-P. Accordingly, the clinical superiority of either product relative to efficacy cannot be demonstrated. Nevertheless, as described below, Alphanate is clinically superior to Humate-P in terms of the safety of the product.

2. Alphanate is Clinically Superior to Humate-P in Terms of Safety.

Aventis Behring's comments argue that Alphanate SD/HT is not clinically superior to Humate-P because Humate-P (a) has a better method of viral inactivation, (b) has a better ratio of vWF:RCof to FVIII, (c) has higher quality multimers, (d) has a better half-life, and (e) has data related to prion removal. Each of these assertions is either misleading or erroneous.

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2 *See* Letter from Jay S. Epstein, M.D., Acting Director, Office of Blood Research and Review, Center for Biologics Evaluation and Research, FDA, to M. Sue Preston, Alpha Therapeutic Corp. (July 13, 1994).

3 *See* Letter from Jay S. Epstein, M.D., Director, Office of Blood Research and Review, Center for Biologics Evaluation and Research, FDA, to Sue Preston, Alpha Therapeutic Corp. (Feb. 14, 1997).

4 *See* FDA, SUMMARY BASIS FOR APPROVAL FOR HUMATE-P, Ref. No. sPLA 96-1099, at 1, *in* Comments by Alpha Therapeutic Corp., at Tab M (Jan. 21, 2003).

5 *See* P.M. Mannucci et al., *Treatment of von Willebrand Disease with a High-Purity Factor VIII/von Willebrand Factor Concentrate: A Prospective, Multi-center Study*, 99 BLOOD 450 (2002), *in* Comments by Alpha Therapeutic Corp., at Tab J (Jan. 21, 2003).

6 *See id.*

a. Alphanate's Method of Viral Inactivation is Demonstrably Superior to that of Humate-P

Viral inactivation steps are the patient's primary protection against infection by known and unknown viral agents since these steps have been specifically introduced with the intent of destroying the virus. As explained in Alpha's prior comments, the manufacturing process for Alphanate SD/HT includes two viral inactivation steps, a solvent-detergent treatment step and a heat treatment step. In contrast, the Humate- P manufacturing process employs only a single viral inactivation step, pasteurization. It is reasonable to expect that two different viral inactivation process steps, each using a different and accepted method for inactivating virus particles, would naturally provide greater protection than a single step process.

This expectation cannot be challenged logically and, indeed, is borne out by the current evidence on viral transmissions. As discussed more fully in Alpha's prior comments submitted on January 21, 2003, there are no literature reports of hepatitis transmission for the current Alphanate formulation, whereas there are multiple instances reported in the literature for Humate-P. Indeed, experts have noted such transmissions. In one instance, following a brief literature review presented as part of a discussion identifying a case of hepatitis C, in a patient with hemophilia A treated exclusively with Humate-P, who had never received any other blood or plasma product, experts concluded:

> Based on our data and previous trials from other investigators . . . we conclude that there is now doubt that the pasteurised [sic] FVIII and IX concentrates (Behringwerke Marburg) carry a very low hepatitis C risk but the few single case reports of HCV indicate that the risk is not completely absent.[7]

Aventis Behring's response to the relative inadequacy of its single viral inactivation step is to present a chart purporting to compare log kill results for Alphanate and Humate-P.[8] This chart is misleading because Aventis Behring's adds purported viral

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[7] D. Klarmann et al., *Hepatitis C and Pasteurised Factor VIII and IX Concentrates*, 73 THROMB. HAEMOST 736 (1995) (Tab A).

[8] Aventis Behring also advances the feeble assertion that the reports are not "confirmed." Aventis Behring fails to explain, however, who must "confirm" the reports or why any such confirmation is required. Indeed, these reports have been published in peer-reviewed journals and have been accepted by experts in the field. Aventis Behring's call for confirmed reports of viral transmission on Humate-P is cynical given FDA's treatment of Aventis Behring's Mononine® Coagulation Factor IX (Human) (Mononine). FDA licensed Mononine despite Alpha's orphan exclusivity on AlphaNine® Coagulation Factor IX (Human) (AlphaNine). FDA found Mononine to be "probably a safer drug" even though there were *no reported cases of viral transmission whatsoever* with regard to AlphaNine. FDA, SUMMARY BASIS FOR APPROVAL FOR MONONINE, Ref. No. 90-0030, at 6 (1992) [hereinafter Mononine SBA], *in*

removal data for manufacturing process steps to its single viral inactivation step and compares these inflated numbers with the data from the labeling of Alphanate.[9] Aventis Behring's reliance on "data on file" is particularly inappropriate. The Aventis Behring "data on file" are unsubstantiated and cannot properly be evaluated against the limited but validated data from Alphanate's approved labeling. Moreover, Aventis Behring's "data on file" cannot even be considered because Aventis Behring fails to provide the data for full assessment as is required under FDA's regulations.[10] Finally, as Aventis Behring must know, neither the Humate-P package insert nor Alphanate's package insert contains log kill data from all of the types of additional manufacturing steps relied upon by Aventis Behring for its chart. The comparison of Aventis Behring's "data on file" with Alpha's approved package insert is specious.

Aventis Behring appears bent on a campaign to mislead both the agency and the public about the relative effectiveness and robustness of pasteurization, its single viral inactivation step. On January 23, 2003, FDA issued a letter regarding misleading promotional claims by Aventis Behring related to its pasteurization process for the product, Gammar-P I.V.[11] The agency's letter provides in relevant part:

> The following statements . . . represent comparative safety claims that mislead the reader to believe that pasteurized IGIV products are safer than non-pasteurized IGIV products.
>
> - You state that, "Pasteurization is more effective than solvent/detergent in reducing the risk of viral transmission" and "Pasteurization inactivates certain non-lipid enveloped viruses that can be resistant to the solvent/detergent method." It is not sufficient to declare pasteurization to be more effective simply because it may inactivate certain non-enveloped viruses. Solvent/detergent viral inactivation has its own unique advantages. For example, it is more effective than pasteurization in the inactivation of hepatitis C and related model viruses and it is more robust than heat treatment.
>
> . . .

Comments by Alpha Therapeutic Corp., at Tab B (Jan. 21, 2003). FDA's determination was based on reports of viral breakthroughs on different products with the same method of viral inactivation as AlphaNine. *Id.* Aventis Behring's assertion that FDA's determination was based on "documented cases of viral transmission with Alphanine" is demonstrably false. Aventis Comments, at 6 (Mar. 14, 2003).

[9] Aventis comments, at 6.

[10] 21 C.F.R. 10.20(c)(1).

[11] *See* Letter from Mary A. Malarkey to Leonard M. Baum, R.Ph. of 1/23/03, *available at* http://www.fda.gov/cber/adpromo/igivave012303.htm.

- Your ad prominently displays the statement, "Pasteurized. For safety's sake." This statement misleadingly implies that if a product is not pasteurized, it is not safe. You should immediately cease any further dissemination of all advertising and promotional materials that contain these claims and similar presentations.[12]

b. Differences in vWF:RCof to FVIII Ratios Have No Demonstrated Clinical Relevance.

Aventis Behring provides a misleading analysis of the clinical effect of the ratio of vWF:RCof to FVIII. Aventis Behring notes that Humate-P has a higher ratio of RCof/vWF to Factor VIII than Alphanate and argues that this difference establishes that Humate-P is safer.[13] This is demonstrably incorrect. Aventis Behring bases its argument on the assertion that ". . . high levels of FVIII have been implicated in reports of venous thrombosis in patients with VWD."[14] An examination of the reference cited by Aventis Behring in support of this proposition, however, reveals that Aventis Behring relies on a study that was performed in patients with no specific underlying disease state who were enrolled following an initial episode of venous thromboembolism and in whom oral anticoagulants were subsequently discontinued.[15] There is no mention whatsoever of a diagnosis of underlying vWD in this patient population. Accordingly, Aventis Behring misrelies on the study.

There are, of course, reports of venous thrombosis in patients with vWD. Alpha identified and reported three instances of venous thromboembolism, including one instance of superficial thrombosis, in patients participating in its clinical trial in vWD patients.[16] On the other hand, four instances of venous thrombosis following the use of Humate-P have recently been reported in the United Kingdom in a publication from U.K. treatment centers.[17] Additionally, a recent survey of 160 treatment centers reported three

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12 *Id.*

13 *See* Aventis Comments, at 4. Aventis Behring notes that an Alpha employee stated at a prior presentation that Alphanate had a lower ratio of vWF:RCof to FVIII. *See id.* This statement was based on the best available data at the time. Alpha believes its current assessment of this ratio is more reliable.

14 *Id.*

15 *See* P. Kyrlie et al., *High Plasma Levels of Factor VIII and the Risk of Recurrent Venous Thromboembolism*, 343 NEW ENG. J. MED. 457-58 (2000) (Tab B).

16 *See* P.M. Mannucci et al., *Treatment of von Willebrand Disease with a High-Purity Factor VIII/von Willebrand Factor Concentrate: A Prospective, Multi-center Study*, 99 BLOOD 450-56 (2002), *in* Comments by Alpha Therapeutic Corp., at Tab J (Jan. 21, 2003); P.M. Mannucci, *Venous Thromboembolism in Von Willebrand Disease*, 88 THROMB. HAEMOST 378-79 (2002) (Tab C).

cases of venous thromboembolism in vWD patients associated with Humate-P that had not been identified in other publications.[18] The single instance reported for Alphanate was previously well-documented in Alpha's prospective clinical trial.[19] These data are clearly contrary to Aventis Behring's suggestion that Humate-P is safer than Alphanate.

c. Differences in Molecular Weight of Multimers Have No Demonstrated Clinical Relevance.

Aventis Behring notes that Humate-P contains more high-molecular-weight multimers than Alphanate and asserts that this difference results in greater efficacy.[20] In fact, there are no data demonstrating greater efficacy on the part of Humate-P, based on molecular weight of multimers or otherwise.

d. Differences in Half-Lives Have No Demonstrated Clinical Relevance.

Aventis Behring notes that the half-life of Humate-P is longer than that of Alphanate-SD/HT in von Willebrand's disease and argues that this difference results in greater efficacy.[21] The difference in half-lives between the two products is small and has not been demonstrated to have any clinical relevance.

e. Removal of Prions Has No Demonstrated Clinical Significance.

Aventis Behring suggests that the partitioning of prions during the manufacture of Humate-P results in greater safety by reducing the risk of transmissible spongiform encephalopathies.[22] In fact, as Aventis Behring has recently stated at the Plasma Protein Therapeutics Association Consensus Conference on the Blood Product Safety, in Tokyo, there is currently no scientific evidence to substantiate that persons with pre-clinical or clinical Creutzfeldt-Jacob disease (CJD), including new variant Creutzfeldt-Jacob disease (vCJD), carry infectious prions in their blood or have transmitted them through blood or

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17 *See* M. Makris et al., *Venous Thrombosis Following the Use of Intermediate Purity FVIII Concentrate to Treat Patients with Von Willebrand's Disease*, 88 THROMB. HAEMOST 387-88 (2002) (Tab D).

18 *See* P.M. Mannucci, *Venous Thromboembolism in Von Willebrand Disease*, 88 THROMB. HAEMOST, at 378-79 (Tab C).

19 *See id.*

20 *See* Aventis Comments, at 4.

21 *See id.* at 5.

22 *See id.* at 6.

plasma products.[23] In fact, no cases of CJD or vCJD have been noted among identified recipients of blood or plasma products from known vCJD donors to date.[24] Prions have never been detected in human plasma or plasma derivatives[25] and there is no evidence that any prion-linked disease has been transmitted by therapeutic administration of plasma or a plasma product.[26]

3. Continuous Inventory of Humate-P Remains a Concern.

Past shortages of Humate-P are a fact. Aventis Behring's promises that there will be no future shortages cannot overcome this fact and cannot ensure that patients will always have access to this critical drug.

4. The *Bracco* Decision Supports Alpha's Position

The court's decision in *Bracco Diagnostics, Inc. v. FDA*[27] squarely supports Alpha's position. In *Bracco,* FDA was enjoined from regulating similar products according to inconsistent standards and procedures.[28] As Alpha described in its earlier comments submitted on January 21, 2003, Aventis Behring's claim of orphan protection raises the same issues that were presented in the approval of Aventis Behring's Mononine product.

FDA approved Aventis Behring's Mononine product despite Alphas orphan exclusivity on AlphaNine. Both AlphaNine and Mononine were derived from the same raw material (human source plasma collected in U.S.-based plasma collection centers) and contained the same active moiety after manufacturing. Mononine was found to be a different drug based on FDA's determination that Mononine was "probably a safer

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23 *See* Presentation by H. Baron at the Plasma Protein Therapeutics Association Consensus Conference on the Blood Product Safety in Tokyo (Mar. 2003).

24 *See id.*

25 *See* THE NAT'L CJD SURVEILLANCE UNIT, W. GEN. HOSP. & DEP'T OF INFECTIOUS AND TROPICAL DISEASES, LONDON SCHOOL OF HYGIENE AND TROPICAL MEDICINE, TENTH ANNUAL REPORT 2001: CREUTZFELDT-JAKOB DISEASE SURVEILLANCE IN THE UK, *available at* http://www.cjd.cd.ac.uk/ rep2001.html (Tab E).

26 *See* EMEA, CPMP POSITION STATEMENT ON CREUTZFELDT-JAKOB DISEASE AND PLASMA-DERIVED AND URINE-DERIVED MEDICINAL PRODUCTS (2003), *available at* http://www.emeaeu.int/pdfs/human/press/ pos/ 287902en.pdf (Tab F).

27 963 F. Supp. 20 (D. D.C. 1997).

28 *Id.* at 20.

drug."[29] This determination was based on the agency's finding that AlphaNine was manufactured using a single viral inactivation step that was deemed to present a risk of viral breakthrough whereas no viral breakthrough had been observed for Mononine.[30] It is important to note that FDA found a risk of viral breakthrough for AlphaNine even though there were no reported viral breakthroughs associated with AlphaNine itself.[31] Aventis Behring's statement that "there were documented cases of viral transmissions with Alphanine"[32] is flatly incorrect and is clearly contradicted by the SBA for Mononine,[33] which Aventis Behring quotes in its comments.[34]

Here, Humate-P is manufactured under a single viral inactivation step that has resulted in reports of viral breakthrough on Humate-P itself whereas no viral breakthrough had been reported for Alphanate SD/HT, which has two viral inactivation steps. As in the case of Mononine, Alphanate SD/HT "is probably a safer drug" than Humate-P.

5. Humate-P Is Not Approved for Surgery.

Aventis Behring again asserts that Humate-P is approved for use in surgical bleeding. As noted in its Package Insert, Humate-P has been approved by the FDA for the ". . . treatment of spontaneous and trauma-induced bleeding episodes in severe von Willebrand disease and in mild and moderate von Willebrand disease where use of desmopressin is known or suspected to be inadequate."[35] It is not approved for use in surgical prophylaxis. The Summary Basis of Approval for Humate-P in vWD and the Humate-P Package Insert state that "Controlled clinical trials to evaluate the safety and efficacy of prophylactic dosing with Humate-P to prevent spontaneous bleeding and to prevent excessive bleeding related to surgery have not been evaluated in vWD patients."[36] Indeed, FDA has required Aventis Behring to conduct Phase IV studies to provide data on the use of Humate-P in a surgical setting.

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29 Mononine SBA, at 6, *in* Comments by Alpha Therapeutic Corp., at Tab B (Jan. 21, 2003).

30 *See id.*

31 *See id.*

32 Aventis Comments, at 6.

33 *See* Mononine SBA, at 6, *in* Comments by Alpha Therapeutic Corp., at Tab B (Jan. 21, 2003).

34 *See* Aventis Comments, at 6.

35 FDA, SUMMARY BASIS FOR APPROVAL FOR HUMATE-P, Ref. No. sPLA 96-1099, at 1, *in* Comments by Alpha Therapeutic Corp., at Tab M (Jan. 21, 2003).

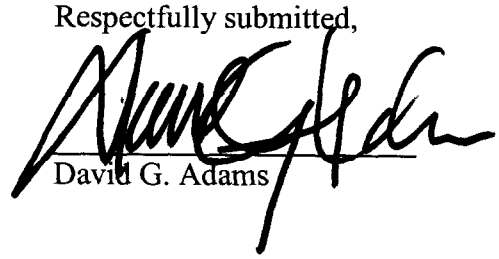
36 *Id.*

Aventis Behring attempts to argue that the approval of Humate-P for "treatment of . . . trauma-induced bleeding" constitutes an approval for prevention of surgical bleeding because, according to Aventis Behring, surgery "is a form of trauma."[37] Contrary to Aventis Behring's claim, treatment of trauma-induced bleeding is different from treatment of surgical bleeding. As Aventis Behring must know, in the surgical setting coagulation products are administered as prophylaxis, which involves a different treatment protocol from that of follow-on treatment for excessive bleeding from trauma.

CONCLUSION

For all of the foregoing reasons, the relief requested in Aventis Behring's Citizen Petition must be denied or, in the alternative, the petition must be removed from the docket and returned to Aventis Behring as facially inadequate.

Respectfully submitted,



David G. Adams

[37] Aventis Comments, at 7.