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January 21, 2003

VIA HAND DELIVERY & FEDERAL EXPRESS

Dockets Management Branch
Food and Drug Administration
Room 1-23
12420 Parklawn Drive
Rockville, MD 20857

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

Dear Sir or Madam:

Please accept the attached 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

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02P-0435

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12420 Parklawn Drive
Rockville, MD 20857

Re: Docket Number 02P-0435 (Citizen Petition) - 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® Antihemophilic Factor (Human) (Alphanate) 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.

As set forth below, petition must be denied based on the following grounds:

1. The petition reflects an effort by Aventis Behring to deny vWD Patients a new and clinically superior therapy.

2. Aventis Behring's exclusivity cannot block approval of a clinically superior product.

3. Alphanate is safer than Humate-P.

4. Humate-P is not approved for prophylaxis of surgical bleeding;

5. The *Bracco* decision precludes Aventis Behring's requested relief;

6. Aventis Behring has been unable to ensure adequate supplies of Humate-P;

7. The petition's Statement of Grounds omits material information that is unfavorable to the petitioner's position.

DISCUSSION

I. Aventis Behring Seeks to Deny vWD Patients A New and Superior Therapy.

Von Willebrand disease (vWD) is a hereditary bleeding disorder caused by the deficiency or dysfunction of von Willebrand Factor resulting from mutations in the gene encoding of this multimeric glycoprotein. The symptoms of the disease can be mild or serious and can occur after injury or without any cause at all. Symptoms include frequent nosebleeds, easy bruising, and in women, long/heavy menstrual periods. More serious symptoms include bleeding into joints or internal organs. It can lead to serious complications during surgery and/or childbirth.

The needs of vWD patients have not been adequately served by the pharmaceutical industry. Currently there is only one drug, Aventis Behring's Humate-P, approved for vWD patients, and it has a limited safety and effectiveness profile. The product is purified under a single-step pasteurization process that has resulted in three reported instances of viral transmission. The product is approved only for use in "in adult and pediatric patients for *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,"[1] and Aventis Behring has failed to complete any studies supporting the use of the product as prophylaxis of surgical bleeding in vWD patients, leaving vWD patients with no approved therapy for this important indication.

As Aventis Behring notes in its petition, Alpha has completed a clinical investigation on Alphanate in vWD patients. This study, along with other data, demonstrates Alphanate to be clinically superior to Humate-P in terms of safety and purity. The study has also addressed the indication of prophylaxis of surgical bleeding. Aventis Behring clearly fears that the approval of Alphanate for vWD patients will suppress Aventis Behring's profits on Humate-P.

Although Aventis Behring has failed to provide vWD patients with a product for prophylaxis of surgical bleeding, it seeks to prevent Alpha from providing vWD patients with such a product, claiming that FDA should not approve Alphanate for *any possible use* in vWD, including prophylaxis of surgical bleeding. This stance is remarkable. Aventis Behring would deny vWD patients a second source for treatment of spontaneous and trauma-induced bleeding episodes, even though vWD patients have faced shortages of Humate-P for this use, and even though Alphanate has been demonstrated to be safer than Humate-P. Aventis Behring would also deny Alphanate to vWD patients for

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[1] Humate-P approved package insert (Tab A).

prophylaxis of surgical bleeding, even though this will leave vWD patients with *no approved therapy* for this use.

Aventis Behring raises no safety or efficacy concerns with regard to Alphanate. Indeed, there are no such concerns. Instead, Aventis Behring seeks to deny Alphanate to vWD patients based on a purported marketing exclusivity. As Aventis Behring well knows, however, it has no entitlement to such a marketing exclusivity because Alphanate is clinically superior to Humate-P and because Humate-P is not approved for prophylaxis of surgical bleeding.

II. Aventis Behring's Exclusivity Cannot Block Approval of a Clinically Superior Product.

Aventis Behring correctly states in its petition: "Under the Orphan Drug Amendments, where a drug has been granted orphan drug exclusive approval, FDA may grant no approval to a subsequent sponsor of the *same drug* product for the same indication for seven years. 21 C.F.R. § 316.3(b)(12)."[2] The statement is correct. Aventis Behring fails to note, however, that the cited regulation provides in the very next subsection that, "if the subsequent drug can be shown to be clinically superior to the first drug, it will *not be considered to be the same drug*."[3]

As FDA states in the preamble to the regulation, "[a]ssuming that a subsequent drug's marketing application is otherwise approvable, FDA will not interpret the Orphan Drug Act to block approval of any drug proved to be clinically superior to a drug with currently effective exclusive marketing rights."[4] The regulation further provides that a drug is deemed clinically superior if it provides "a significant therapeutic advantage over and above that provided by an approved orphan drug" in terms of safety, effectiveness, or a major contribution to patient care.[5]

Aventis Behring ignores these provisions and asserts that "[t]here is no question that Humate-P and Alphanate are the same drug for orphan drug purposes" since "[b]oth Humate-P and Alphanate are derived from the same raw material, i.e., human source plasma collected at U.S. plasma collection centers" and "[t] manufacturing processes for each product are...the same in that they are designed to extract the same molecules from

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2 Aventis Petition at 2 (emphasis added).

3 21 C.F.R. 316.3(b)(13)(i) (small molecules) and (ii) (large molecules) (emphasis added).

4 57 Fed. Reg. 62076, 62078 (December 29, 1992).

5 21 C.F.R. 316.3(b)(3).

the human source plasma – von Willebrand factor and Factor VIII proteins – with minimal disruption to the active moiety of the molecule."[6]

The statement is quite remarkable. Ten years ago Alpha held orphan exclusivity on an earlier version of a related blood derivative product, AlphaNine® Coagulation Factor IX (Human) (AlphaNine).[7] Armour Pharmaceutical Company (now Aventis Behring)[8] sought to bring a similar product, Mononine™ Coagulation Factor IX (Human) (Mononine), onto the market. Mononine and AlphaNine 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.[9] The agency nevertheless found the Aventis Behring drug to be different for purposes of orphan exclusivity based on a determination that Mononine was "probably safer." The agency stated as follows:

> Coagulation Factor IX (Human), Mononine™, has been determined to contain the same active moiety as the Orphan-designated Coagulation Factor IX (Human), AlphaNine® for the treatment of hemophilia B. Therefore, if the FDA is to license Mononine™, it must find that it is a different drug from AlphaNine® by virtue of safety or effectiveness.
>
> . . .
>
> In view of the evidence for improved viral safety of Mononine™, CBER concludes that Mononine™ is probably a safer drug. Hence, it is a different drug within the meaning of the Orphan Drug Act and is licensable, AlphaNine®'s orphan-drug exclusivity notwithstanding.[10]

As in the case of Aventis Behring's Mononine product, Alphanate is clinically superior to Humate-P in terms of safety.

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6 Aventis Petition at 2.

7 The earlier version of AlphaNine was prepared under an older process that did not include the additional purification step (affinity column), the solvent detergent, and the nanofiltration step for viral safety that are now employed in the production of the current AlphaNine® SD product.

8 In 1996 Armour Pharmaceutical Company was consolidated in to Centeon, which changed its name to Aventis Behring in 2000.

9 FDA Summary Basis for Approval for Mononine, Ref. No. 90-0030 at 2, 6 (1992) (Tab B).

10 *Id.* at 6.

III. Alphanate Is Safer than Humate-P.

A. Lower Risk of Infection

Alphanate is less likely to transmit infection than Humate-P. This is because Alphanate is manufactured under a process that employs two specific viral inactivation steps rather than the single-step process used for Humate-P. The process for Alphanate involves (1) a mixture of tri (n-butyl) phosphate (TNBP) and polysorbate 80, commonly referred to as a solvent detergent (SD) step,[11] followed by (2) a heat treatment step at 80°C for 72 hours (following filling and lyophilization of the product). In contrast, the process for Humate-P involves only a single heat-treatment step, and that treatment step is limited to 60°C for 10 hours.[12]

This heat-treatment process, commonly referred to as pasteurization, has had a history of viral breakthroughs where it is employed as a single-step process. There have been three reports of viral transmission with Humate-P, two of which have been for hepatitis B and one for hepatitis C.[13] There have been no reports of any breakthrough with Alphanate during the four years in which the product has been manufactured under Alpha's two-step process.[14]

This may be explained by *in vitro* data of surrogate virus reduction. It is particularly significant to note the impact of the Alphanate dual viral inactivation method on one of the common hepatitis C surrogate viruses (Bovine Viral Diarrhea) tested by both manufacturers. For Alphanate, a ≥ 4.5 log reduction was achieved following the SD step, and an additional ≥ 4.9 log reduction was reached after the heat treatment step,

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[11] B. Horowitz, *et al.*, "Viral Safety of Solvent Detergent Treated Blood Products," 81 *Dev. Biol. Stand.* 147 (1993) (Tab C). *See also* M.P. Smith, *et al.*, "Successful Clinical Use of a Plasma-derived, Dual Virus In a titrated Factor VIII Concentrate Incorporating Solvent-detergent and Dry Heat Treatment," 77 *Thrombosis and Haemostasis* 406, 407 (Feb. 1997) ("The combination of solvent-detergent inactivation and a terminal heat treatment step in Alphanate™ production is unique amongst commercially available plasma-derived factor VIII concentrates in the UK, further widening the safety margin of this concentrate against potential transmissible viral infection") (Tab D).

[12] C.K. Kasper & M. Coata e Silva, *Registry of Clotting Factor Concentrates*, Table 2 (2d ed. 2000) (Tab E).

[13] *See* Tabs F and G.

[14] Alpha reports that, since Alphanate was first licensed in 1996, over 400,000,000 units have been sold, with no reports of viral transmission and or material adverse effects to patients.

combining for a ≥ 9.4 log reduction by those two steps.[15] With Humate-P, the pasteurization step's best reported result was a ≥ 5.4 log reduction.[16]

As FDA concluded in the case of Aventis Behring's Mononine product, this superior measure of protection from potential transmission of infectious diseases such as hepatitis B and C constitutes greater safety.[17] Moreover, FDA regulations provide as an example of "greater safety" the elimination of "an ingredient or contaminant that is associated with relatively frequent adverse effects."[18]

B. Greater Purity

Alphanate is manufactured under a superior purification process pioneered by Alpha, which provides an improved purity profile and superior recovery. Alphanate is purified by use of a heparin-coupled, cross-linked agarose affinity column, which binds to the heparin binding domain of the vWF/FVIII:C complex. The vWF/FVIII:C complex

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[15] *See* Table 1 of Alphanate approved package insert (Tab H).

[16] *See* "Viral Reduction Capacity," Humate-P approved package insert (Tab A).

[17] The agency's approval of Aventis Behring's Mononine product provides the template for this determination. The agency explained the Mononine approval as follows:

> With respect to safety, the Center for Biologics Evaluation and Research (CBER) has determined that there is a reasonable basis for concluding that the manufacture of Mononine™ may result in a Coagulation Factor IX (Human) product that is less likely to transmit hepatitis C infection than the current Orphan-designated, license material, AlphaNine®. The AlphaNine® production process uses heating at 60° C for 20 hours in n-heptane suspension for virus inactivation. No prospective clinical study of hepatitis C in previously untreated recipients of AlphaNine® has been performed; however, in other coagulation factor concentrates, this viral inactivation method has been shown to allow breakthrough transmission of hepatitis C. Thus, the use of these products poses some level of risk. In a study of previously untreated hemophilia B patients, no apparent case of hepatitis has been observed with the use of Mononine™...In light of this study, which gives no evidence of transmission of hepatitis by Mononine™, and in the absence of a parallel clinical study with AlphaNine®, CBER concludes that Mononine™ is less likely to transmit hepatitis C than is AlphaNine®.
>
> In view of the evidence for improved viral safety of Mononine™, CBER concludes that Mononine™ is probably a safer drug. Hence, it is a different drug within the meaning of the Orphan Drug Act and is licensable, AlphaNine®'s orphan-drug exclusivity notwithstanding.

Mononine Summary Basis for Approval, *supra* n. 9, at 6 (Tab B).

[18] 21 C.F.R. 316.3(b)(3)(ii). FDA states in the preamble to the regulations that even "a small demonstrated...diminution in adverse reactions may be sufficient to allow a finding of clinical superiority." 57 Fed. Reg. at 62078. *See also Berlex Laboratories, Inc. v. FDA*, 942 F. Supp. 19 (D.D.C. 1996) (drug provided greater safety than a previously approved orphan drug because there were less frequent occurrences of injection site necrosis associated with the newer drug).

is then eluted from the column and subjected to a selective salt precipitation step that yields an enriched concentration of vWF/FVIII:C complex, Alphanate.[19]

Humate-P is purified from pooled human plasma through multiple precipitation steps.[20] This results in an intermediate purified mixture of vWF, FVIII:C, and other proteins.[21]

Thus the uniquely different manufacturing processes result in two products of differing composition of proteins in the final container (excluding albumin added after purification),[22] differing vWF:RCof to FVIII:C ratios,[23] and different mean recoveries *in vivo,*[24] as summarized in the table below:

	Alphanate	**Humate-P**
Purification steps	1. PEG fractionation 2. Heparin Affinity Chromatography 3. Selective precipitation	Multiple Precipitation
Other proteins (non-FVIII, non-vWF, non-Albumin)	Not measurable	1-7mg/mL
vWF:RCof to FVIII:C ratio	0.83	2.2
Mean vWF:RCof *in vivo* recovery	3.10 (IU/mL)	1.89 (IU/mL)

The higher purity of Alphanate provides potential clinical benefits. For example, an *in vitro* study of Alphanate compared to Humate-P demonstrated that Alphanate

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19 *See* P. Bhattacharya, *et al.*, "Characteristics and Viral Safety of Alphanate™ [sic] and Its Heat-Treated Version" (abstract printed for the XVth Congress of the International Society on Thrombosis and Haemostasis, Jerusalem, Israel, June 1995) (Tab I).

20 Kasper, *supra* n.12 (Tab E).

21 *Id., compare* Table 2 (Humate-P specific activity (S.A.s. Alb. IU/mg) = 38) *with* Table 3 (Alphanate specific activity (S.A.s. Alb. IU/mg) = 140).

22 *Id.*, *compare* Table 2 *with* Table 3.

23 *Id* ; Alphanate BLA.

24 Regarding Alphanate, *see* P. Mannucci, *et al.*, "Treatment of von Willebrand disease with a high-purity factor VIII/von Willebrand factor concentrate: a prospective, multicenter study," 99 *Blood* at 450 (Jan. 2002) (Tab J). Regarding Humate-P, *see* Package Insert (Tab A). The figure of 1.89 IU/ML is based on the pharmacokinetic study discussed in the Humate-P package insert. The actual dosing suggested by the package insert is 1.50 IU/mL. *Id.*

exerted virtually no inhibitory effects on PHA-induced lymphocyte proliferation whereas Humate-P exerted substantial inhibitory effect.[25] In contrast to Humate-P, Alphanate showed no immune system modulation in this sensitive test system. The higher purity of Alphanate should also result in significantly lower dosing schedules.

IV. The *Bracco* Decision Precludes Aventis Behring's Requested Relief.

In *Bracco Diagnostics, Inc. v. FDA*,[26] FDA was enjoined from regulating similar products according to inconsistent standards and procedures. The court noted that, as the United States Court of Appeals for the District of Columbia has repeatedly held, "an agency must treat similar cases in a similar manner unless it can provide a legitimate reason for failing to do so."[27]

Aventis Behring's claim of orphan protection here raises the same issues as were presented in the approval of Aventis Behring's Mononine product, and requires the same result. As described above, Alpha held orphan exclusivity on its blood derivative product, AlphaNine. FDA approved Aventis Behring's Mononine even though 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 a potentially lower level of risk. The agency noted that the earlier AlphaNine formulation was manufactured under a simple pasteurization process that had allowed for viral breakthrough.[28] No viral breakthrough had been observed for Mononine and the agency found that Mononine presented a lower likelihood of viral transfer, even though no reported breakthrough for AlphaNine was noted.[29]

Thus, under *Bracco*, the agency cannot grant Aventis Behring's petition and treat Alphanate differently than the agency treated Mononine under the same circumstances.

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[25] W. Harel, "Lack of Inhibitory Effects on Cell Proliferation by High-Purity Coagulation Factor VIII Concentrates" 77 *Thrombasis and Haemostasis* at 406-07 *(1997)* (Tab K).

[26] 963 F. Supp. 20 (D. D.C. 1997).

[27] *Id.* at 20, *quoting Independent Petroleum Association of America v. Babbitt*, 92 F.3d 1248, 1258 (D.C. Cir. 1996).

[28] *See supra* note 17.

[29] *Id*

V. Humate-P Is Not Approved for Prophylaxis of Surgical Bleeding.

Aventis Behring correctly states in its petition that orphan exclusivity bars approval "of the same drug product for *the same indication*."[30] Accordingly, Humate-P's orphan exclusivity is limited to the indication for which it was granted orphan exclusivity.

The approved labeling for Humate-P states that the product "is indicated . . . in adult and pediatric patients for *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."[31] Despite this clear limitation, Aventis Behring asserts that Humate-P's orphan exclusivity extends to surgical bleeding prophylaxis.

Treatment of spontaneous and trauma-induced bleeding episodes is clearly different from prophylaxis of surgical bleeding. As Aventis Behring well knows, *treatment* is not the same as *prophylaxis*.[32] As Aventis Behring also knows, *spontaneous* bleeding and *trauma-induced* bleeding are not the same as *surgical* bleeding.[33] Aventis Behring's admission that it is currently conducting a study on surgical bleeding prophylaxis[34] proves the point. There would be no need for such a study if the product were approved for that use.

Aventis Behring's statement that "the current approved indication of Humate-P for which it was granted orphan drug exclusivity specifically encompasses treatment of vWD in the surgical setting" challenges credulity. Aventis Behring claims that Humate-P is approved for prophylaxis of surgical bleeding because Humate-P's labeling does *not* include a broad statement that the product is *not approved* for use in

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30 Aventis Petition at 2 (emphasis added).

31 Humate-P Package Insert (Tab A) (emphasis added).

32 *See, e.g.*, package insert for Aventis' product LOVENOX® (enoxaparin sodium) Injection, which provides separate indications for "prophylaxis" of thrombosis and for "treatment" of thrombosis. (Tab L). *See also* 21 U.S.C. § 321 (g)(1)(B) (defining the term "drug" to mean an article intended for the "treatment *or* prevention of disease . . .").

33 The labeling for Humate-P distinguishes the different types of bleeding in the "Indications and Usage" where the labeling notes that Humate-P has not been evaluated for prophylactic use in "spontaneous bleeding *and* . . . bleeding due to surgery." (Emphasis added.)

34 Aventis Petition at 3.

vWD disease.[35] Such a statement would, of course, be inappropriate because Humate-P is, in fact, approved for certain uses in vWD.[36]

More fundamentally, however, Aventis Behring must realize that FDA's approval of a product without a statement in labeling that the product is *not* approved for a particular use does not mean that the product *is* approved for that use. The approved use[s] of a product are set forth in the labeling as the product's "indication[s]." The Humate-P label states that that the product is indicated for treatment of spontaneous and trauma-induced bleeding.

Oddly, Aventis Behring focuses on the statement in Humate-P labeling that the product has "not been evaluated" for prophylactic use of spontaneous bleeding and surgical bleeding.[37] A statement that a product has not been evaluated for prophylactic use does not mean that the product is approved for that use. It means the opposite. FDA reiterated this in its Talk Paper announcing the Humate-P approval, stating: "Currently not enough evidence exists from clinical trials to evaluate the efficacy of Humate-P in preventing spontaneous or excessive bleeding related to surgery in vWD patients."[38] The agency also noted in the Summary Basis for Approval for Humate-P that, although the original orphan designation for Humate-P was for the broad indication of vWD, Centeon (Aventis Behring) sought orphan exclusivity only for the "vWD spontaneous and trauma-induced bleeding indication."[39]

VI. Aventis Behring Has Been Unable to Ensure Adequate Supplies of Humate-P.

Aventis Behring's Petition masks a fatal flaw in its position, *i.e.*, a clear pattern of product shortfalls for Humate-P dating back to 1998. In a letter dated June 5, 1998, Centeon (now Aventis Behring) refers to projected shortfalls of Humate-P,[40] which were

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35 Aventis Petition at 3.

36 Although Aventis notes that Alphanate's labeling carries this broad statement, Aventis fails to appreciate that Alphanate is, in fact, not approved for any vWD indication.

37 Tab A ("Indications and Usage").

38 "First Biologic Approved for Clotting Disorder," FDA Talk Paper (April 1, 1999).

39 The last page of the Humate-P Summary Basis for Approval (Tab M, unpaginated set) provides as follows:

> Humate-P® was granted Orphan Drug Status for the indication of vWD (Ref. No. 92-679) on October 16, 1992. Centeon seeks to exercise marketing exclusivity for the vWD spontaneous and trauma-induced bleeding indication

later realized. In September 1999 the National Hemophilia Foundation notified the community of the out-of-stock status of Humate-P.[41] In the January 2001 issue of *Transfusion*, two physicians from Massachusetts General Hospital stated in a letter to the editor that, [b]ecause the supply of Humate-P is limited, it is occasionally necessary to use other FVIII preparations, such as Alpha-nate [sic]."[42] Because the products were not labeled for such use, the physicians provided a list of available FVIII preparations and their vWF activity.[43] These shortfalls require an assessment under the orphan drug regulations of whether Aventis Behring can adequately supply the market.[44]

V. The Aventis Petition Omits Material Information.

FDA's regulations governing citizen petitions require that each such petition contain a "Statement of Grounds" that includes "representative information . . . which is unfavorable to the petitioner's position."[45] Failure to include this information requires that the agency FDA "not file the submission" and return it to the petitioner.[46]

The Aventis Petition fails to provide important information that is unfavorable to its position. Among the information Aventis Behring neglects to provide is the following:

1. Aventis Behring asserts that Alphanate and Humate-P must be deemed the same drug because the drugs are derived from the same source and are manufactured to

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40 Tab N.

41 Tab O.

42 Y.P. Agrawal & W. Dzik, 41 *Transfusion* at 153 (2001) (citations omitted) (Tab P).

43 *Id.*

44 Under the regulations, FDA must notify Aventis of the "*possible* insufficiency," and offer Aventis one of the following options:

> (1) Provide . . . views and data as to how the holder can assure the availability of sufficient quantities of the orphan drug within a reasonable time to meet the needs of patients with the disease or condition for which the drug was designated; or
> (2) Provide . . . consent for the approval of other marketing applications for the same drug before the expiration of the 7-year period of exclusive approval.

21 C.F.R. 316.36(a)(1)-(2).

45 21 C.F.R. 10.30(b).

46 21 C.F.R. 10.20(c)(6).

produce the same active moiety. Aventis Behring fails to inform the agency that its product Mononine, a similar blood derivative product, was deemed to be not the same drug as Alpha's AlphaNine even though the two products were derived from the same source and manufactured to produce the same active moiety.

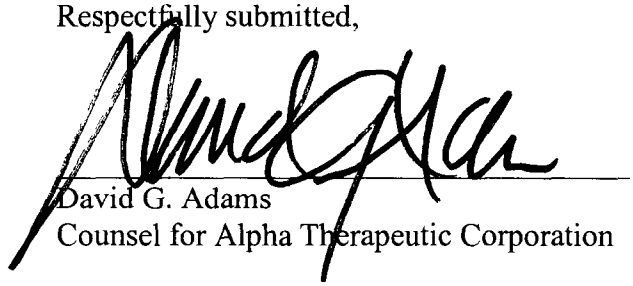
2. While asserting that Alphanate and Humate-P must be deemed the same, Aventis Behring fails to reveal that Humate-P, unlike Alphanate, depends on a single-step pasteurization process and has been the subject of reported viral breakthroughs.

3. Aventis Behring also fails to reveal that the study on Alphanate that Aventis Behring describes in its petition (but does not identify or provide the agency)[47] demonstrates that Alphanate has a superior mean vWF:RCof recovery *in vivo*.[48]

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
Counsel for Alpha Therapeutic Corporation

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47 Aventis Petition at 2.

48 *See supra* n.24.