Aventis Behring

Aventis

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Worldwide Regulatory Affairs

14 March 2003

Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
Room 1061
5360 Fishers Lane
Rockville, Maryland 20852

Re: Docket Number 02P-0435 (Citizen Petition) – Comments of Aventis Behring L.L.C. in Response to Submission by Alpha Therapeutic Corporation dated January 21, 2003

Dear Sir or Madam:

This is in response to the comments submitted on January 21, 2003, on behalf of Alpha Therapeutic Corporation (Alpha) in respect of the above-referenced Citizen Petition. As shall be discussed below, Alpha offers no compelling reasons that would justify its attempt to vitiate the Orphan Drug process. Therefore, Aventis Behring's Citizen Petition should be granted.

Alpha raises a number of arguments that are irrelevant and designed to obfuscate the only issue for consideration, i.e., the orphan status of Humate-P®. Conversely, Aventis Behring has demonstrated that for orphan drug purposes, Humate-P® and Alphanate are the same drug because they contain the same active moiety. Alpha is unable to dispute this fact. Thus, in order to obtain the approval it seeks, Alpha must demonstrate that Alphanate is clinically superior to Humate-P®. Alpha has failed to do so. Accordingly, there is no basis to support the approval of Alphanate for the treatment of von Willebrand Disease (VWD).

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 (see Attachment II, lines 1-3). Although it is not approved for the treatment of VWD, Aventis Behring acknowledges that as is their prerogative, physicians use Alphanate for the treatment of VWD. Although Alpha's improper attempts to promote Alphanate off-label for the treatment of VWD were recently halted by FDA (see Attachment I), physicians can continue to use Alphanate as they deem appropriate in their medical judgment. Alphanate is available today and the granting of this Citizen Petition by FDA will not curtail its availability nor in any way limit physician or patient access to this product. However, the granting of Aventis Behring's Citizen Petition by FDA will serve to reinforce the very purpose of the Orphan Drug process.

Aventis Behring
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Telephone 610-878-4000
King of Prussia, PA 19406-0901

02P-0435

RC1

In an attempt to overcome the orphan drug exclusivity of Humate-P®, Alpha seeks to invoke the case of Mononine® and Alphanine as precedent. There, FDA's determination that Mononine® was "probably safer" than Alphanine was made at the time of first approval of Mononine® in August 1992. The facts clearly supported FDA's decision because there were confirmed reports of viral transmissions with Alphanine. There were no such viral transmissions with Mononine® because of its robust viral inactivation methods. Thus, the FDA deemed that Mononine® was "probably safer" than Alphanine thereby justifying the approval of Mononine®. Those facts simply do not exist in this case.

In addition, had FDA denied the application for approval of Mononine®, it would have kept the drug off the market and therefore unavailable to patients. Here, Alphanate already has FDA approval (1974) for the treatment of Hemophilia A. But unlike the case of Mononine®, FDA did not make the determination at the time of first approval of Alphanate that it was safer than Humate-P®. Despite its protestations to the contrary, Alpha has presented nothing that would suggest that anything has changed in the interim that makes Alphanate safer than or clinically superior to Humate-P®.

In its comments, Alpha raises seven grounds that purportedly support a denial of this Citizen Petition. Aventis Behring shall address these grounds in the order presented by Alpha and shall demonstrate that each is without merit and that Aventis Behring's Citizen Petition should be granted.

Aventis Behring's responses are summarized below:

(1) Aventis Behring is operating in a manner that is completely consistent with the letter and spirit of the Orphan Drug Amendments and is in no manner denying VWD patients access to a "new and clinically superior therapy." Alphanate is neither new nor clinically superior to Humate-P®.

(2) There are no data to support that Alphanate is clinically superior to Humate-P®.

(3) There are no data to support that Alphanate is safer than Humate-P®.

(4) Alpha's violative pre-approval promotion of Alphanate for treatment of VWD, its orphan drug designation for the "treatment of VWD" (granted on January 5, 1996, as per the List of Orphan Designations and Approvals posted on FDA's Office of Orphan Products Development website), and the breadth of the indications for Humate-P® demonstrate that Alphanate's proposed indication overlaps the indication for Humate-P®.

(5) The *Bracco* decision does not support Alpha's position.

(6) Aventis Behring has ample inventory of Humate-P® and can supply the market to meet the demands of VWD patients.

(7) Aventis Behring has not omitted any material information unfavorable to its Citizen Petition.

1. Alphanate is Neither New nor a Superior Therapy

Aventis Behring takes great exception to Alpha's contention that this Citizen Petition is motivated by concerns over profit. Quite to the contrary, Aventis Behring's Citizen Petition is motivated by the desire to ensure compliance with the letter and spirit of the Orphan Drug Amendments. The legislative history of the Orphan Drug Act and Amendments demonstrates Congress's intent to reward the innovation and initiative of those companies that commit the significant amount of time and resources necessary to research and develop drugs for orphan populations with a defined period of market exclusivity. FDA designated Humate-P® as an orphan product for the treatment and prevention of bleeding in hemophilia A (classical hemophilia) in adult patients; and 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 in adult and pediatric patients. Aventis Behring then proceeded to expend the resources necessary to obtain FDA's approval of Humate-P® for the treatment of VWD. All that Aventis Behring now seeks is that the intent of the Orphan Drug Act and Amendments be upheld.

As noted above, Alphanate is not a new drug and it is not superior to Humate-P®. In fact, it is generally recognized by the medical community that Humate-P® is the treatment of choice for patients with VWD.[1] Alpha cannot claim clinical superiority either in scientific presentations or in product promotion because there are no data generated from adequate and well-controlled clinical studies of Alphanate versus Humate-P® that would support such a claim.

Aventis Behring's Citizen Petition is not designed to prevent physicians from obtaining and using Alphanate for VWD. It cannot and will not do so. However, there are no data to substantiate Alpha's claims of clinical superiority and as will be discussed below, Alphanate's proposed indication does indeed overlap with the indication for Humate-P® for which orphan exclusivity takes precedence.

2. Alphanate is Not Clinically Superior to Humate-P®

Although Alpha correctly quotes from the regulations in respect of the Orphan Drug Amendments, Aventis Behring's current Citizen Petition, and FDA's summary Basis of Approval for Mononine®, it simply concludes that Alphanate is "clinically superior to Humate-P in terms of safety" without any data in support of that conclusion. Alpha's conclusion is incorrect because Humate-P® has (i) a better ratio of VWF:RCoF[2] to F VIII; (ii) higher quality multimers, and (iii) a better half-life.

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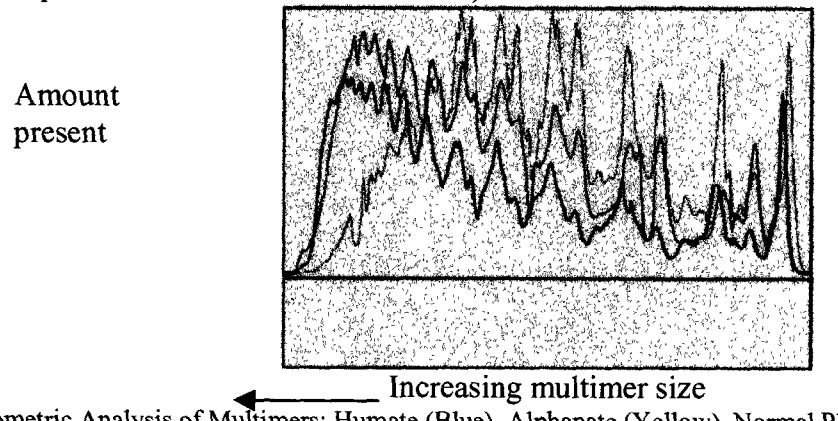
[1] The Plasma Fractions Market in the United States 2000, Marketing Research Bureau, Orange Conn. June 2001.

[2] RCoF is the abbreviation for Ristocetin Cofactor, a functional measure of von Willebrand Factor activity.

On page 7 of its submission Alpha asserts that Alphanate has a VWF: RCoF to F VIII ratio of 0.83. This claim contradicts data previously published regarding Alphanate. In testimony given by Alpha to the FDA at a September 1997 workshop on Factor VIII concentrates in the treatment of VWD, Alpha claimed a VWF: RCoF to F VIII ratio of 0.5. (See Attachment II, lines 15-17). The RCoF to F VIII ratio for Humate-P® is 2.5 which clearly favors Humate-P®. This ratio is clinically significant because high levels of F VIII have been implicated in reports of venous thrombosis in patients with VWD.[3] The higher the FVIII content of the concentrate, the greater the chance that a venous thrombosis might develop. Alphanate has more than three times the amount of FVIII per unit of vWF than Humate-P®.

Another critical difference between Humate-P® and Alphanate is the quality of the multimers of the von Willebrand Factor. Von Willebrand Factor is assembled into very large multimeric structures within endothelial cells. The larger the multimer, the more effective it is in aggregating platelets, i.e., it is more effective in stopping bleeding.[4, 5, 6] The multimers of the von Willebrand Factor of Humate-P® are significantly larger than the multimers of the von Willebrand Factor of Alphanate. Below is a densitometric scan of gels that separate the various sizes of vWF multimers. This scan reveals that the multimer structure of Humate-P® is very similar to that of normal human plasma, while Alphanate is missing a substantial proportion of the larger multimers. [Larger multimers are on the left in this figure]. Similar data have been published by Metzner, et al. (See Attachment VII - Hemophilia, 1998, proceedings of the FDA Workshop on FVIII concentrates in VWD.)



Densitometric Analysis of Multimers: Humate (Blue), Alphanate (Yellow), Normal Plasma (Black). [Larger multimers are on the left in this figure].[7]

[3] Kyrle, et al., "High Plasma Levels of Factor VIII and the Risk of Recurrent Venous Thromboembolism," *New England Journal of Medicine,* 2000; 343:457 (See Attachment III).

[4] Fukui H, Nishino M, Terada S, et al., "Hemostatic Effect of a Heat-Treated FVIII Concentrate (Haemate-P) in von Willebrand's Disease," *Blood,* 1988;56:171-178 (See Attachment IV).

[5] Furlan M, on Willebrand factor: Molecular Size and Functional Activity," *Ann Hematol,* 1996; 72:341 (See Attachment V).

[6] Federici A.B., et al., "Binding of von Willebrand factor to glycoproteins Ib and Iib/IIIa Complex: Affinity is Related to Multimeric Size, " *British Journal of Haematology*; 1989; 73:93 (See Attachment VI).

[7] Data on File, Aventis Behring L.L.C.

Also relevant to the discussion of clinical effect is product half-life. In the paper by Mannucci, et. al, that is referenced by Alpha, the authors state that the half-life of RCoF after administration of Alphanate is 6.5 hours. As noted in the Humate-P® product package insert that was approved by FDA, the RCoF half-life of Humate-P® is 10.3 hours. Humate-P® has a longer half-life.

Based upon all of the foregoing, it is clear that Alphanate is not clinically superior to Humate-P®

3. Alphanate is Not Safer than Humate-P®

Alpha claims that Alphanate has a lower risk of infection and a greater degree of purity than Humate-P®. It attempts to substantiate these claims through a disingenuous and misleading portrayal of the viral safety profile of Humate-P®. In addition, Alpha argues that the determination made by FDA more than 10 years ago to determine that Mononine® is "probably safer" than Alphanine (thereby justifying the approval of Mononine® despite the orphan status of Alphanine) serves as precedent for this Citizen Petition. Both arguments are without merit. Humate-P® has an excellent viral safety profile, and as discussed above, the decision in the case of Mononine® versus Alphanine was based on a completely different set of facts thereby making that case inapposite to the current Citizen Petition.

Viral Safety

To be absolutely clear, there have been no confirmed reports of viral transmissions with Humate-P®. While there were several isolated reports of viral transmissions purportedly associated with the use of Humate-P® in the early 1990s, they were unconfirmed reports.

In addition, it is expected that there will be reports of suspected viral transmission in patients with bleeding disorders that use plasma-derived products. However, to reiterate, there has never been a confirmed report of a viral transmission with Humate-P®.

In this regard, it is noteworthy that nearly one million units of Humate-P® have been used in clinical trials that have had a particular focus on the viral safety profile of the product. Not one of the study subjects who received Humate-P® during these trials showed a clinically relevant seroconversion for Hepatitis C, Hepatitis B or HIV. In addition, it should be noted that since its commercial launch, more than 500 million units of Humate-P® have been sold with no confirmed reports of viral transmission associated with its use.

The excellent viral safety record of Humate-P® is due in large part to the patented pasteurization process utilized by Aventis Behring. This viral inactivation/elimination step is designed specifically to inactivate viruses and involves heat treatment in an aqueous solution at 60°C for 10 hours. This process, which is referred to as denaturation, physically destroys the protein structure of the virus while preserving the efficacy of the drug. Pasteurization has been shown to inactivate both lipid-enveloped viruses and some non-lipid-enveloped viruses, including Hepatitis A. By contrast, the solvent-detergent viral inactivation method used by Alpha has no effect on Hepatitis A and other non-lipid enveloped viruses.

In addition to pasteurization, Aventis Behring utilizes other steps to further reduce or inactivate viruses. The cumulative effect of these multiple viral inactivation steps demonstrates the robust nature of Aventis Behring's viral inactivation procedures.

The viral inactivation method utilized by Alpha is a dry heat process. The table below demonstrates the log kill results for Humate-P® and Alphanate manufacturing processes.

Comparison of Viral Inactivation/Removal of Humate-P® to Alphanate SD/HT**

	Humate-P®			Alphanate		
	Pasteurization	**Manufacturing[1]**	**Total**	**SD/HT**	**Manufacturing**	**Total**
Virus						
HIV	≥ 6.2	≥ 10.8	≥ 17.0	≥ 11.1	≥ 2	≥ 13.1
Hepatitis C[2]	≥ 8.8	≥ 5.3	≥14.1	≥ 9.4	< 1	≥ 9.4
Hepatitis B[3]	≥ 6.8	≥ 7.9	≥14.7	≥ 10.1	≥ 8.9	≥ 19.0
Hepatitis A	4.2	5.0	9.2	≥ 5.8	2.1	≥ 7.9
Parvo B-19[4]	1.0	5.4	6.3	4.1	1.2	5.3

**Sources include Aventis Behring data on file and Alphanate SD/HT prescribing information

[1]Manufacturing steps that assist in viral reduction include aluminum hydroxide adsorption, glycine precipitation, sodium chloride precipitation, and others.
[2]Bovine viral diarrhea virus used as viral marker
[3]Herpes simplex virus used as a viral marker for Aventis Behring and Bovine Herpes virus used by Alpha Therapeutic
[4]Canine parvo virus used as a viral market

Mononine® versus Alphanine

Alpha advances the argument that this Citizen Petition presents the same situation that confronted FDA more than 10 years ago when it considered the request by Armour Pharmaceutical Company that Mononine® be licensed despite the orphan status of Alphanine. As FDA correctly noted, the improved viral safety of Mononine® made it "probably safer" than Alphanine, thereby correctly justifying its licensure. This is because there were documented cases of viral transmissions with Alphanine. That case is entirely different from that currently under consideration. As demonstrated by the viral log kill data set forth above, Alphanate does not have a "lower risk of infection" than Humate-P®.

Prion Removal

Another reason that Alphanate is not clinically superior to Humate-P® is due to the leading role that Aventis Behring is playing in the increasingly important areas of prion removal and research into Creutzfeld-Jakob Disease (CJD). Aventis Behring has presented prion removal data for Humate-P® at numerous meetings with FDA and other public fora, and most recently at the February 20, 2003, meeting of the Transmissible Spongiform Encephalopathies Advisory Committee (TSEAC). Alpha, to the best of Aventis Behring's knowledge, has not presented any such data.

In its Citizen Petition, Aventis Behring demonstrated that for orphan drug purposes, Humate-P® and Alphanate are the same drug because they contain the same active moiety. Since it is clear that Alphanate is not clinically superior to Humate-P®, either in terms of safety or efficacy, there is no basis to support the approval of Alphanate for the treatment of VWD.

4. The *Bracco* Decision Does Not Support Alpha's Position

As discussed above, there are significant differences between the current Citizen Petition and the case of Mononine® versus Alphanine. Given the distinctions between these competing cases, the ruling in *Bracco* must either be deemed inapposite to this Citizen Petition, or considered as providing no support to Alpha's position.

5. Alphanate's Orphan Drug Designation Overlaps with the Indication for Humate-P®

The indication listed in Alphanate's orphan drug designation is the same indication as that for Humate-P®, i.e., treatment of VWD. Alpha seeks approval for treatment of VWD during surgery. Humate-P® is indicated for, among other things, trauma-induced bleeding episodes in severe von Willebrand disease patients. Surgery is a form of trauma. Thus, Alpha seeks approval for an indication that is a narrow subset of trauma, one of the therapeutic areas for which Humate-P® is indicated. For purposes of orphan drug status, Alpha's proposed indication is not different from that of Humate-P®.

In this regard, as part of the approval of Humate-P® for VWD, Aventis Behring agreed with FDA that it would do a post-marketing Phase IV study of Humate-P® in the surgical setting to obtain additional information in respect of product safety and efficacy. This Phase IV study is ongoing, and this should not be used as the basis for undermining the orphan drug process. Since Alphanate's proposed indication so clearly overlaps with that of Humate-P®, FDA should not approve Alphanate for use in VWD until the expiration of the orphan drug exclusivity for Humate-P®, i.e., March 31, 2006.

6. Aventis Behring has Adequate Inventory of Humate-P®

Alpha persists in presenting FDA with misleading information. It is true that five years ago, in 1998, Aventis Behring did project shortfalls for Humate-P®, and that those shortfalls did indeed occur. However, in the intervening time period, Aventis Behring expended more than $77 million in plant and manufacturing enhancements designed to ensure, among other things, that such shortfalls do not recur. These enhancements have indeed been effective because what Alpha neglects to inform FDA is that since 2001, the inventory situation for Humate-P® has been more than adequate to supply the VWD market.

7. Aventis Behring's Citizen Petition Omits No Material Information

Aventis Behring again takes great exception to Alpha's position that the pending Citizen Petition is designed to mislead FDA. Aventis Behring did not omit material information in its Citizen Petition. As noted in detail above, the case of Mononine® versus Alphanine is irrelevant to the

current case. Given that it is irrelevant, it is not material and therefore of no moment to this matter.

Similarly, since Humate-P® has an impeccable viral safety record with no confirmed reports of viral transmissions, Alphanate is not safer than Humate-P®. As detailed above, the viral reduction and inactivation methods utilized in the manufacture of Humate-P® are robust and therefore, no material information in respect of safety has been omitted.

Conclusion

Alpha has presented no compelling arguments that would justify undermining the well established orphan drug process. If granted, Aventis Behring's Citizen Petition will pose no harm to the patient or medical community. Alphanate will continue to be available even if this Citizen Petition is granted. However, if FDA grants this Citizen Petition, it will have preserved the integrity of the orphan drug process.

Based upon all of the foregoing, it is clear that Alphanate may not be approved for the treatment of VWD in any setting until the date on which the duly granted orphan drug exclusivity for Humate-P® expires, March 31, 2006.

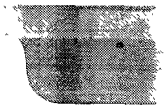
Respectfully submitted,

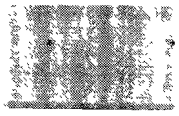
AVENTIS BEHRING

Leonard M. Baum, R.Ph.
Vice President
Worldwide Regulatory Affairs

Cc: P. Safir, Esq.
Covington & Burling

ATTACHMENT I





Violative Advertising and Promotional Labeling Letter

Antihemophilic Factor (Human), Alphanate (Alpha Therapeutic Corp)

November 27, 2002

Ms. Amy Feliciano
Associate Director of Regulatory Affairs
Alpha Therapeutic Corporation
5555 Valley Boulevard
Los Angeles, California 90032

Dear Ms. Feliciano:

Through routine monitoring and surveillance, the Advertising and Promotional Labeling Branch (APLB) in the Food and Drug Administration's Center for Biologics Evaluation and Research (CBER) has identified promotional material for your product, Alphanate (Antihemophilic Factor (Human)), that violates the Federal Food, Drug, and Cosmetic Act and its implementing regulations. APLB has reviewed a journal advertisement (ad) that has been published in at least two recent issues of *HemAware* and believes that this ad contains false claims about Alphanate. A copy of the referenced ad is enclosed.

False and Misleading

21 CFR 202.1(e)(6)(i) states that an advertisement is false...or otherwise misleading, if it contains a representation or suggestion, not approved or permitted for use in the labeling that a drug, ..., is more effective, useful in a broader range of conditions or patients, than has been demonstrated by substantial evidence or substantial clinical experience.... CBER is unaware of any evidence or clinical experience that Alphanate is effective or useful in treating von Willebrand disease.

Your ad, published in the July/August and September/October 2002 issues of *HemAware*, presents, on a single page:

- the name of your product, Alphanate;
- a line of text that states, in its entirety: "Factor VIII/von Willebrand Factor;" and
- a line of text that states, in its entirety: "A New Horizon. A New Direction."

However, Alphanate is "indicated for the prevention and control of bleeding in patients with Factor VIII deficiency due to hemophilia A or acquired Factor VIII deficiency." The approved package insert further states that, "No clinical trials have as yet been conducted using Alphanate for treatment of von Willebrand's disease, therefore the product is not approved for this use."

Your ad specifically suggests an unapproved indication for use for your product by the inclusion and

juxtaposition of the text "von Willebrand Factor" and "A New Horizon. A New Direction." There is no other reason for the reference, "von Willebrand Factor." You should immediately cease any further dissemination of all advertising and promotional materials that contain these claims and similar presentations.

This letter is not intended to be an all-inclusive list of deficiencies associated with your promotion of the above product. It is your responsibility to ensure that all materials distributed within the United States are in conformance with each requirement of the Act and applicable regulations.

You should respond within ten (10) days of the date of this letter. Your response should include a statement of your intent to comply with each of the above, a list of all promotional materials with the same or similar issues, and your methods for discontinuing these promotional materials.

Your response should be directed to Mr. Glenn N. Byrd, Chief, APLB, at the address listed below. Should you have any questions or concerns involving this matter, please contact Mr. Glenn N. Byrd at 301-827-3028.

Center for Biologics Evaluation and Research
Office of Compliance and Biologics Quality
Division of Case Management
Advertising and Promotional Labeling Branch, HFM-602
1401 Rockville Pike, 200S
Rockville, MD 20852-1448

Sincerely,

----- *signature* -----

Mary A. Malarkey
Director
Division of Case Management
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research

Enclosures

Last Updated: 11/29/2002

ATTACHMENT II

TRANSCRIPT OF PROCEEDINGS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE

FOOD AND DRUG ADMINISTRATION

WORKSHOP ON POTENCY AND DOSAGE
OF von WILLEBRAND FACTOR CONCENTRATES

Pages 1 thru 265

Bethesda, Maryland
September 26, 1997

MILLER REPORTING COMPANY, INC.
507 C Street, N.E.
Washington, D.C. 20002
(202) 546-6666

Alphanate is a high purity von Willebrand factor concentrate that was originally licensed for use in hemophilia A in the summer of 1974.

(Slide)

The original Alphanate included a single viricidal step in its purification methodology. The purification was provided by PG precipitation, chromatography through a capillary micorose column and salt precipitation.

(Slide)

The resulting concentrate has a specific activity of approximately 150 Factor VIII U/mg protein. The usual intermediate purity concentrates are present in low level or non-detectable amounts.

The major contaminant, if the word can be used in this context, is von Willebrand factor. Here, Alphanate contains 1 unit of ristocetin cofactor activity for every 2 units of Factor VIII. The ratio of ristocetin cofactor activity to von Willebrand factor antigen is approximately 0.72.

(Slide)

Here is a gel that shows the multimeric distribution of von Willebrand factor in a number of Alphanate lots, as well as in 2 commercially available concentrates from other manufacturers.

As one can see, there is substantial lot-to-lot