

LAW OFFICES

**KLEINFELD, KAPLAN AND BECKER**

1140 NINETEENTH STREET, N.W.

WASHINGTON, D. C. 20036-6606

TELEPHONE (202) 223-5120

FACSIMILE (202) 223-5619

E-MAIL: kkb@kkblaw.com

WEST COAST OFFICE:  
ONE MARKET STREET  
STEWART TOWER, SUITE 1450  
SAN FRANCISCO, CA 94105-1313  
TELEPHONE (415) 538-0014  
FACSIMILE (415) 538-0016

VINCENT A. KLEINFELD  
1907-1993

ALAN H. KAPLAN  
1930-2001

THOMAS O. HENTELEFF  
RICHARD S. MOREY  
PETER O. SAFIR  
KINSEY S. REAGAN  
PETER R. MATHERS  
BONNIE A. BEAVERS  
DANIEL R. DWYER  
GLENN E. DAVIS  
PRESCOTT M. LASSMAN  
STACY L. EHRLICH  
JENNIFER A. DAVIDSON  
STACEY L. VALERIO  
ROBERT O. WINTERS

OF COUNSEL  
HARVEY A. SUSSMAN

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Dockets Management Branch  
Food and Drug Administration  
Department of Health and Human Services  
Room 1061  
5630 Fishers Lane  
Rockville, MD 20852

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**CITIZEN PETITION**

On behalf of Aventis Behring L.L.C. (Aventis Behring or Petitioner), the undersigned submits this petition under Section 527 of the Federal Food, Drug, and Cosmetic Act (Act) and Parts 10.30 and 316 of the Food and Drug Administration (FDA) regulations to request that the Commissioner of Food and Drugs (the Commissioner) refrain from granting effective approval of Alphanate® Antihemophilic Factor (Human) for the treatment of von Willebrand Disease (vWD) until the expiration of orphan drug exclusivity for Humate-P® on March 31, 2006.

**A. Actions Requested**

The Commissioner is requested to refrain from granting effective approval of Alphanate® for the treatment of vWD until the expiration of orphan drug exclusivity for Humate-P® on March 31, 2006.

**B. Statement of Grounds**

By letter dated October 16, 1992, FDA designated Humate-P® Antihemophilic Factor/von Willebrand Complex (Human), Dried, Pasteurized as an orphan product pursuant to Section 526 of the Act for the "treatment of patients with von Willebrand's disease."<sup>1</sup> The indication for Humate-P® was expanded on April 1, 1999, when FDA approved the drug for use "in adult and pediatric patients for treatment of spontaneous and trauma-induced bleeding episodes in severe von Willebrand disease, and in mild and

<sup>1</sup> In 1986, Humate-P was approved by FDA for treatment and prophylaxis of patients with classical hemophilia (hemophilia A) in whom there is a demonstrated deficiency of coagulation factor VIII.

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moderate von Willebrand disease where use of desmopressin is known or suspected to be inadequate.” On April 14, 1999, FDA issued a letter to Centeon LLC (now Aventis Behring) informing it that Humate-P® is entitled to seven years of exclusive marketing pursuant to Section 527 of the Act for use “(1) in adult patients for treatment and prevention of bleeding in hemophilia A (classic hemophilia) and (2) in adult and pediatric patients for treatment of spontaneous and trauma-induced bleeding episodes in severe vWD where use of desmopressin is known or suspected to be inadequate.” See Exhibit 1 hereto. The orphan drug exclusivity granted to Humate-P® expires March 31, 2006.

On January 5, 1996, FDA designated Alpha Therapeutic Corporation’s Alphanate® as an orphan drug for “treatment of von Willebrand’s disease.” Alphanate® is currently approved only for prevention and control of bleeding in patients with Factor VIII deficiency due to hemophilia A or acquired Factor VIII deficiency. Indeed, the current Alphanate® label specifically states: “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.” We understand that a clinical study of Alphanate® for treatment vWD has been completed and published. We further understand that Alpha Therapeutic is currently seeking approval of Alphanate® for treatment of vWD. Moreover, as you can see from the attached August 22, 2002 letter to the Advertising and Promotional Labeling Branch of the Center for Biologics Evaluation and Research (CBER) (Exhibit 2), Alpha Therapeutic has been disseminating an advertisement that falsely suggests that Alphanate® is indicated for the treatment of vWD. We therefore believe that approval of Alphanate® for treatment of vWD may be imminent.

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). There is no question that Humate-P® and Alphanate® are the same drug for orphan drug purposes. Both Humate-P® and Alphanate® are derived from the same raw material, i.e., human source plasma collected in U.S. plasma collection centers. The manufacturing processes for each product are also the same in that they are designed to extract the same molecules from the human source plasma – von Willebrand factor and Factor VIII proteins – with minimal disruption to the active moiety of the molecule.

In addition, the indication for which it appears Alphanate® may be imminently approved is the same as the indication for which Humate-P® was granted orphan drug exclusivity. The current indication of Humate-P® for which it was granted orphan drug exclusivity is 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.” The indication listed in the Alphanate® orphan drug designation (and the indication Alpha Therapeutic has been

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promoting in its advertisement), “treatment of von Willebrand’s disease,” clearly overlaps with the indication for which Humate-P® was granted orphan drug exclusivity. FDA may not, therefore, approve Alphanate® for treatment of vWD until the expiration of the orphan drug exclusivity for Humate-P®, i.e., March 31, 2006.

Even if the indication for Alphanate® were restricted to treatment of vWD in the surgical setting, this indication would still be encompassed within the indication for which Humate-P® was granted orphan drug exclusivity. The current Humate-P® label states 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 von Willebrand disease patients. Adequate data are not presently available on which to evaluate or to base dosing recommendations in either of these settings.” It should be noted that Aventis Behring’s commitment to FDA to conduct a Phase IV trial of Humate-P® in the surgical setting is being fulfilled. This study is proceeding under an FDA-approved protocol at more than 25 study sites, and patient recruitment has commenced.

It is also noteworthy that the statements in the labeling for Humate-P® and Alphanate® regarding what these drugs are not approved for are significantly different. The Alphanate® label specifically states that “the product is not approved for this use [vWD disease]”). In contrast to the limitation in the Alphanate® label, the Humate-P® label does not state that use of Humate-P® to prevent spontaneous bleeding and to prevent excessive bleeding related to surgery is contraindicated or that Humate-P® was specifically not approved for this use. Thus, the current approved indication of Humate-P® for which it was granted orphan drug exclusivity specifically encompasses treatment of vWD patients in the surgical setting.

Accordingly, Alphanate® may not be approved for treatment of vWD, even if limited to use in the surgical setting, until March 31, 2006, i.e., the date on which the orphan drug exclusivity for Humate-P® expires.

### **C. Environmental Impact**

According to 21 C.F.R. §25.25(a)(8), this petition qualifies for a categorical exclusion from the requirement for submission of an environmental assessment.

### **D. Economic Impact**

According to 21 C.F.R. § 10.30(b), information on economic impact is to be submitted only when requested by the Commissioner following review of the petition.

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**E. Certification**

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data known to the petitioner which are unfavorable to the petition. See also Exhibit 3.

Respectfully submitted,



Stacy L. Ehrlich  
Counsel for Aventis Behring L.L.C.

SLE/s