Aventis Behring
Worldwide Regulatory Affairs

Aventis

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May 7, 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 March 31, 2003

Dear Sir or Madam:

This is in response to the comments submitted under cover of letter dated March 31, 2003 on behalf of Alpha Therapeutic Corporation (Alpha) in respect of the above-referenced Citizen Petition.

Consistent with its prior submissions, Alpha once again fails to provide any compelling reason to justify its attempt to undermine the Orphan Drug process. Rather, Alpha restates the same arguments that Aventis Behring has already effectively addressed and then relies upon unfounded claims that Aventis Behring's submissions are misleading and erroneous. Aventis Behring reaffirms everything that it has stated in its prior submissions. The statements and arguments presented by Aventis Behring are based upon facts and data, and are accurate.

Aventis Behring would like to use this opportunity to discuss in greater detail the Orphan Drug Act (the "Act") and the Alpha-orchestrated letter writing campaign through which Alpha seeks to obfuscate the true issues under consideration.

Aventis Behring's Commitment to the Orphan Drug Act

As a global leader in the therapeutic protein industry, Aventis Behring is committed to developing high quality therapies and services for a wide range of disorders and chronic diseases. Many of the conditions for which our products are indicated and used affect small patient populations for whom the Act was designed to benefit.

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The Act provides pharmaceutical companies with incentives to develop treatments for rare disorders. Included among these incentives is market exclusivity for a period of seven years from the date of approval. This period of exclusivity is granted in recognition by the United States Congress of the significant amount of time, effort and capital expended in the research and development of treatments for these rare disorders. In fact, as FDA stated to Aventis Behring upon granting it orphan exclusivity for Humate-P, "[t]he whole premise of the Orphan Drug Act and program is based on the realization that the resources and commitment devoted to the development of products for 'orphan' populations may not provide financial returns to their sponsors. It is with genuine gratitude that we recognize your efforts." (See Attachment 1).

Clearly, the Act has had the desired effect because in the decade before its passage, only 10 new treatments for orphan diseases were developed. In the 20 years since it was enacted, more than 200 new treatments for orphan conditions have been approved by FDA and an additional 900 are in various stages of development.

It is also clear that pharmaceutical companies must remain confident in the integrity of the orphan drug process so as to continue to invest the resources necessary to treat rare diseases. FDA must not permit the exclusivity afforded by the Act to be vitiated by opportunists such as Alpha who seek to take advantage of loopholes in the process rather than abiding by the letter and spirit of the Act.

Von Willebrand's disease (VWD) is a rare disorder that affects an orphan population of less than 200,000 persons in the United States. In 1999, Humate-P® was granted Orphan Drug status by the U.S. Food and Drug Administration for the treatment of VWD. As part of its initiative to bring this therapy to this patient community, Aventis Behring (i) invested approximately $80 million dollars in the expansion of our Humate-P production capacity; (ii) supplied $10 million worth of free Humate-P to patients during the product registration process, and (iii) spent $5 million dollars for clinical trials leading to the licensure of Humate –P for its VWD indications. Additionally, we are currently enrolling patients in a surgical study. It is the market exclusivity provisions of the Orphan Drug Act that make these investments feasible.

There are two circumstances where a company can lose its right to exclusively market a product under the Orphan Drug Act: the inability to adequately supply the marketplace or the availability of a clinically superior therapy. Because of our substantial investment in manufacturing capacity, Aventis Behring has provided uninterrupted supply to the marketplace, and just as importantly we have the capability to continue to do so. In this regard, it should be noted that at no time since Humate-P was granted orphan exclusivity has the Director of FDA's Office of Orphan Products Development notified Aventis Behring of any concern over Aventis Behring's ability to assure the availability of sufficient quantities of Humate-P to meet the needs of patients with VWD. See: 21 C.F.R. § 316.36(a). Furthermore, in accordance with 21 C.F.R. § 316.36(a)(1), this is to confirm that Aventis Behring has more than adequate inventory to supply Humate-P to the patients who need this drug. Therefore, supply cannot serve as a basis to withdraw the orphan exclusivity of Humate-P.

In addition, as Aventis Behring has demonstrated in it prior submissions in respect of this Citizen Petition, although Alphanate has been used off-label for the treatment for VWD, it is not a clinically superior therapy to Humate-P. In fact, clinicians have shown a distinct preference for using Humate-P for the last two decades, and it is widely recognized by clinicians as the treatment of choice for VWD. Both Humate-P and Alphanate have been marketed for a substantial number of years. Both drugs have demonstrated a good safety and efficacy. While differences in the drugs, including the method of manufacture, exist, these differences do not translate into any clinical data that would warrant a conclusion that Alphanate is clinically superior to Humate-P. As noted in many of the letters submitted by doctors on behalf of Alpha, "both Humate-P and Alphanate are excellent products." Thus, there is no clinical superiority that would justify withdrawing the orphan exclusivity of Humate-P.

Aventis Behring would also like to use this opportunity to supplement the record with the information below.

Product Supply

Alpha persists in challenging the capability of Aventis Behring to supply the market for patients with von Willebrand Disease (VWD) and raises the specter of product shortages. As discussed above, it is incontrovertible that Aventis Behring has adequate inventory to supply the VWD market. Thus, Alpha has failed to demonstrate that Aventis Behring cannot assure the availability of sufficient quantities of Humate-P to meet the needs of patients with VWD for which Humate-P was duly granted orphan exclusivity. Accordingly, there is no basis for the Agency to issue a license or certification to Alpha to market Alphanate for patients with VWD.

Product Safety

As Aventis Behring demonstrated in its submission dated March 14, 2003, Alphanate is neither safer nor more effective than Humate-P. The robust viral inactivation data that Aventis Behring has provided to FDA proves this fact. Moreover, Alpha cannot substantiate its claim that Alphanate is "probably safer" than Humate-P. There are no data to support this contention. Accordingly, for the reasons stated by Aventis Behring in our prior submissions, the Mononine versus Alphanine situation is inapposite to this matter.

Overlapping Indications

The indication(s) sought by Alpha for Alphanate clearly overlaps with the indications for Humate-P. Terry Clyburn, M.D., Assistant Professor of Orhopaedics at the University of Texas, is an experienced orthopedic surgeon and who has performed surgical procedures on a number of patients with bleeding disorders. In his submission to the record of this matter, which is enclosed as Attachment 2, Dr. Clyburn states that surgery is a refined form of trauma and that the treatment of bleeding induced by general trauma and the treatment of bleeding induced by the trauma of surgery are the same. Given Dr. Clyburn's expert opinion, it is clear that surgery falls within the therapeutic areas for which Humate-P is already indicated.

Accordingly, 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.

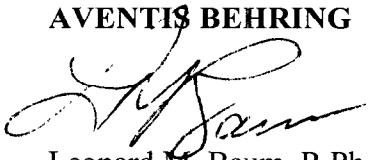
Conclusion

Once again, Alpha has failed to present any arguments that would justify withdrawing the orphan exclusivity of Humate-P. There is nothing to support Alpha's contention that Alphanate is "probably safer" than Humate-P. In addition, Aventis Behring is fully capable of meeting market demand for Humate-P. Finally, the indication(s) sought by Alpha for Alphanate overlaps with the existing indications for Humate-P.

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. Accordingly, Aventis Behring requests that FDA grant this Citizen Petition thereby preserving the integrity of the Orphan Drug Act and program.

Respectfully submit,

AVENTIS BEHRING



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

Cc: P. Safir, Esq.
Covington & Burling