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Food and Drug Administration  
5630 Fishers Lane, Room 1061  
Rockville, MD 20852

**VIA E-Mail & USPS**

**SUBJECT: Whitepaper, "Innovation/Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products." March, 2004  
Docket No. 2004N-0181**

Dear Sir or Madam:

The Plasma Protein Therapeutics Association (PPTA) is pleased to provide these comments on the Food and Drug Administration's (FDA's) Whitepaper entitled, "Innovation/Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products" [hereinafter "Whitepaper"]. PPTA is the international trade association and standards-setting organization for the world's major producers of plasma-derived and recombinant analog therapies. Our members provide 60 percent of the world's needs for Source Plasma and protein therapies. These include clotting therapies for individuals with bleeding disorders, immunoglobulins to treat a complex of diseases in persons with immune deficiencies, therapies for individuals who have alpha-1 anti-trypsin deficiency which typically manifests as adult onset emphysema and substantially limits life expectancy, and albumin which is used in emergency room settings to treat individuals with shock, trauma, burns, and other conditions. PPTA members are committed to assuring the safety and availability of these medically needed life-sustaining therapies.

We appreciate the opportunity to comment on this project and are enthusiastic about the possibilities presented in the Whitepaper. We appreciate the FDA's engaging in this strategic initiative, which we believe demonstrate the Agency's foresight in addressing cutting-edge public health issues. We have reviewed the Whitepaper and the accompanying Federal Register notice ("Notice") and the specific areas in which the FDA has asked for comment. While we appreciate the specific issues with which FDA has asked for comment in the Notice, we mention in advance that we have been unable to appreciate all of the nuances involved in the Whitepaper and the Notice requests for specific areas of comment. Similarly, the plasma collection and fractionation industry also has areas ripe for renewed focus that are not easily placed within the Notice requests.

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For example, one of the difficulties faced by the plasma industry as a whole is that market and cost dynamics are markedly different from that of the chemical-entity pharmaceutical industry. The market for plasma therapies, including plasma-derived antihemophilic factor and its recombinant analogs, immune globulins, and others, is relatively small compared to new chemical entities or other products with indications applicable to a larger proportion of the population. Yet, while markets are small, plasma therapies are biological products with the high costs associated with massive physical plants, long development times, and considerable development outlay (which the Critical Path, as we understand it, is designed to aid.)

While the antihemophilic factor market for replacement of the coagulation factor is relatively defined, immune globulins represent an area of the plasma industry that could have varied indications for use and an expanded market. However, onerous FDA requirements that compel industry to engage in clinical trials for the smallest of process or product changes not only increases costs, but discourages research for new indications, new markets, and, ultimately, new patient populations that may be in desperate need of new therapies. Some of our member companies report experiencing inflexible regulatory burden, in terms of immunogenicity testing and clinical trials demands, without regard to the product type or the relevance of a clinical trial associated with expanded use. Therefore, product indication expansion is certainly one area in which we can present a plasma-industry response to the Notice pertaining to new evaluation tools.

1. The hurdle identified in this context is the repeated use of clinical trials when existing data would suffice or, in the alternative, a more permissive approach with regard to clinical evaluation.
2. Reworking of the requirement would significantly shorten the time needed to expand life-saving and life-improving therapeutics to patient populations.
3. The relevant product is primarily immune globulins, but other possibilities do exist.
4. A solution would be a protocol for examination of data acquired in earlier clinical trials, deriving safety and efficacy benchmarks from expensive research that need not be repeated.
5. The solution for this problem already exists in the form of completed clinical trial data.
6. This could be accomplished within 24 months, as the data already exist.
7. The FDA's role would be major, in terms of evaluation of existing data sets submitted for approval and a new decision protocol to determine the viability of the existing data for the new indication.

As inviting as it may conceptually seem to counter any innovation slowdown with new analytical tools or assays, the slowdown is due in large part to a regulatory approval process that is itself inimical to rapid product development. Defining regulatory requirements for product licensure within the regulatory process is vastly more

important than compounding the complexity with new analytical tools or assays. Some of our member companies have reported to us that the slightest process or product change results in overwhelming regulatory review burdens. For example, a manufacturer may have an immune globulin product on the market for the better part of twenty-five years; when slight changes were introduced into the purification process, the company was assumed by CBER to have no knowledge regarding its own product and was forced to begin at the earliest stages to validate this process. This resulted in significant delays to a product that had already been licensed and marketed for more than twenty years.

Part of the difficulties lay, as mentioned above, in defining regulatory licensing criteria. In part, FDA Guidance Documents purportedly serve this function. What our industry has found is that, instead, the Agency process for issuing guidance documents has grown as cumbersome as the process for formal rulemaking. The Good Guidance Practices (GGPs) were targeted toward more interaction between regulator and regulated, and for greater flexibility in criteria that the Agency would deem suitable for licensure. The flexibility has been lost, along with a sizeable portion of the interaction. The result is that product approval criteria are announced under the guise of agency "current thinking" on an ad hoc basis at Advisory Committee meetings. Without any opportunity for industry comment, this defeats the purpose of GGPs and results in "podium policymaking."

We are encouraged by Dr. Jesse Goodman's presentation, "CBER 2004: Innovation Advancing Public Health," given at the Biotechnology Industry Organization's annual meeting in June, 2004. Dr. Goodman pointed out that Critical Path investment opportunities exist for the plasma industry in areas of pathogen detection and inactivation. We would like to explore these ideas in greater detail, and look forward to the opportunity to do so. PPTA would note that its member companies have made great progress in the use of model virus validation data and employment of it; and indeed, PPTA member companies have led the effort in several areas of research conducted on transmissible spongiform encephalopathies.

Other areas for potential improvement in streamlining approval are examples of current practices which may be diverting valuable resources away from innovation. Many of the regulations pertinent to the plasma industry, along with associated Guidance Documents and elements of the Guide to Inspections, Compliance Policy Guides, and the like, have layers of requirements and recommendations that no longer appreciably add to safety and instead create inefficiencies and slow-downs. Plasma donor recruitment and retention continue to be of concern; the plasma industry's submission for a Uniform Donor History Questionnaire (UDHQ) is a step in the right direction to improve this particular facet, as plasma therapies start with quality donors. While the review period for the UDHQ submission was nearly seventeen months, PPTA and its member companies are taking Agency comments under advisement and are continuing to improve the plasma UDHQ, noting also that the FDA has issued a Draft Guidance

with a DHQ approved for the blood industry. Other areas for improvement in the plasma donor center could be the elimination of outmoded requirements that have no public health benefit. One such outmoded requirement is the mandate to track for a ten-pound donor weight loss in two months. Another advancement would be broader acceptance of Nucleic Acid Testing (NAT) to reduce the window of potential infectivity, and incorporation of robust viral clearance processes in product manufacture when evaluating the need to continue deferring donors for secondary behavioral risks, such as tattoos and piercings, and conducting lookbacks. Lookbacks are high in labor and financial costs with no commensurate benefit when source material has already been processed in final product manufacture. And while lookbacks are costly and add no measurable safety, resources allotted to conducting lookbacks represent a portion of money that could be turned inward for product development for both fractionators and plasma collectors. In addition, the current collection of guidance documents applicable to plasma collection is voluminous and difficult to use. The industry would benefit from the Agency's organization and compilation of relevant guidance documents into an easy-to-use compendium.

PPTA appreciates the opportunity to comment on the Critical Path Initiative. Should you have any questions regarding these comments or would like additional information, please contact PPTA. Thank you for your consideration, and we look forward to working on the exciting possibilities that the Initiative may present.

Respectfully submitted,



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