PPTA
Plasma Protein Therapeutics Association

November 12, 2004
Reference No.: FDAA04020

Dockets Management Branch, HFA-305
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

VIA E-Mail & USPS

SUBJECT: Public Workshop, "Scientific Considerations Related to Developing Follow-On Protein Products." September, 2004.
Docket No. 2004N-0355.

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) Public Workshop entitled, "Scientific Considerations Related to Developing Follow-On Protein Products." [Hereinafter "Workshop"]. 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 would like to thank the Agency for holding this Workshop, and are pleased to understand that more workshops are being considered. We think that the complexity of this issue, ranging from scientific and technical inquiries, to broad questions of intellectual property protection and patient access, warrants a methodical approach in which the Agency collects as much informed public opinion as practicable. The open public process to be used for further policymaking on this important issue is a valuable forum for both the Agency and the regulated community to present ideas and hear other perspectives. We were pleased to participate in the September meeting and look forward to further meaningful participation in future discussions.

The comments contained in this letter attempt to track with the program organization used by the Agency in its Federal Register notice and the September workshop agenda. As PPTA represents Source Plasma collectors, fractionators who use recovered and Source Plasma, and manufacturers who make recombinant analog therapies, our

comments are general and meant to be inclusive of the plasma protein industry. There are instances where it is more appropriate to mention one therapy or another as an example and we have done so in this written submission. Where appropriate, we have expanded on PPTA's initial points made during its presentation and have added further concerns or points relevant to that section.

Biological products, and, within that term, plasma protein products and recombinant analog therapies, are life-saving therapies made by proprietary processes to exacting specifications. As such, the process is highly determinative of the final product. Biological therapies have unique aspects that lend any regulatory structure the necessity of particular safety and efficacy paradigms. Biological products require greater testing than chemical drugs, and, more specifically, plasma protein products are singularly unique with the specific patient populations served and special methods used for pathogen clearance. In specific terms of the plasma collection and fractionation industries, unique paradigms are necessary, including accounting for the inherent variability of the starting material for human-plasma derived therapies and vigilance for infectious pathogen activity throughout the product life cycle.

Though we certainly agree with many Workshop presenters that scientific progress will continue to foster innovation and greater knowledge, including practical outcomes with regard to therapeutic development, the current regulatory mechanism has been used for many decades and for many products. The Agency should be cognizant that changing such a long-term mechanism may have far-reaching and long-lasting effects –both positive and negative-- that currently cannot be predicted. Therefore, this public workshop was but the first step in a discussion that must be carefully heard and understood before any regulatory or statutory change.

Terminology

The FDA questions regarding terminology are important ones. In the PPTA presentation, we stated that the difficulty within the proposed follow-on protein product (FOPP) definition is that the definition itself is swallowed by a larger ambiguity than the solution it represents. The term "identical" connotes a subset of being "similar;" indeed, something that is "identical" holds the distinction of being the most similar. The question of "how similar is similar" resonated throughout the presentations among both innovators and follow-on manufacturers. As an industry, we do have reservations about the use of "generic" as a term, because of its connection to statutory passages involving the regulatory approval mechanism for approvals of abbreviated new drug applications and related phenomena. We are concerned that the statutory regime contained in the Federal Food, Drugs, and Cosmetics Act (FDCA) for generic chemical drugs would be emulated, and we agree with viewpoints given by other parties that forcing a biologic through an approach tailored for chemical drugs would be inappropriate. There are basic differences between the two in terms of its physical and legislative implications, and the current language used in the FDCA and its interpretive regulations, as used by

FDA staff at the Workshop, properly recognizes this. Though the Workshop ostensibly focused on general scientific inquiries surrounding FOPP manufacture, definitional issues related to statutory and regulatory interpretation do have an impact on the way these purely scientific questions can be considered.

PPTA and its member companies do not currently have an opinion on the term "second-generation protein product" in terms of its role within the FOPP debate. However, it is essential that stakeholders have a clear understanding regarding the definition as to the FDA's current thinking about what constitutes a generational change. We understand, in itself, the definition proposed by the Agency for the purposes of the Workshop, but participants and the public must receive greater clarification into the ramifications of this definition prior to another workshop. In other words, the next set of discussions could be clearer and better served if all parties better understood the role of the "second-generation protein product" definition, and how it would relate to any future regulatory action or changes to a product licensing mechanism for FOPP manufacturers and innovators alike.

We are encouraged by the FDA's use of its current regulatory definitions for terms such as bioequivalence, therapeutic equivalent, and other, well-understood terms at the Workshop. [Presentation by Dr. Keith Webber] While we understand that these definitions are subject to future revision, these definitions given by Dr. Keith Webber at the Workshop accurately reflect the intent of the current statutory framework. The vast majority of PPTA member companies have products licensed under the Public Health Service Act (PHSA) with approved Biologics License Applications (BLAs). We understand that because biologics fit the statutory definition of drug under the Food, Drug, and Cosmetics Act (§201(g)(1)), our member companies' therapies are encompassed by these regulations as well, although the marketing authorizations have been issued under a statute that has no mechanism for generic approvals. Other proposals at the workshop included terminology aimed at helping to resolve the important questions regarding similarity, sameness, and difference. Terms such as "statistically similar" or "sufficiently similar" were suggested. As rightly described by FDA, the terms currently used are statutorily based in the FDCA; the other terms suggested for insertion and use are not within the contemplation of the statute or the controlling regulations.

While it is understood that comments for this docket should be limited to discussion of the proceedings in the Workshop, the Agency and all stakeholders should be aware of the use of terminology not only within these specific and technical discussions, but on ramifications the terms have outside of the Workshop. Above, we mentioned the impact of terminology on the current statutory and regulatory mechanism. It should also be noted that terminology used could well have an impact on other regulatory mechanisms administered by FDA's sister agencies, such as the Centers for Medicare and Medicaid Services. It is of the utmost importance that government agencies use a common lexicon when developing and administering the pertinent regulatory mechanisms. If

definitions conflict or if regulatory schemes cannot be reconciled, a situation is created wherein not only slowdowns occur, but tangled areas of confusion wherein all progress is halted. This is, of course, the end result that neither the agency nor any stakeholders desire.

Terminology also plays an important role in other issues discussed at the Workshop, such as product labeling. Some organizations' representatives at the Workshop suggested that a product label for a FOPP be identical to the therapeutic protein being copied. This type of understanding is dependent upon the terminology that will be used for the regulatory regime governing FOPP development. If a manufacturer creates a true follow-on product, a true copy with the same exact indications, pharmacology and distribution, along with identical safety and immunogenicity profiles, then the labeling should most likely be identical. Difficulties may arise in terms of the dosage forms, and if the follow-on product has the same formulation. If not, the implication is that the products are not identical, and the same labeling cannot be used.

Overall, we tend to disagree with the assertion that all labeling can and should be the same. Many further reasons why we disagree in this context will be explored in greater detail below, but generally we believe that this assertion misconstrues the proper role of product labeling for a protein product. Innovator chemical drugs and copies of them are essentially interchangeable; the final molecular product is fixed and homogeneous. The labeling reflects this. However, for biological products, especially those with heterogeneous starting material, such as human plasma, the labeling must reflect the importance of the individual manufacturing process and the heterogeneous nature of the material. Because different manufacturing processes are by their very nature different, and naturally-derived proteins heterogeneous, identical labels do not accurately reflect this and are inappropriate. This is drawn out in greater detail below, as PPTA and its member companies firmly assert that the manufacturing process is determinative of the product and, as the current regulatory structure shows, the current Agency methodology is correct.

Biological manufacturers expend a large amount of resources for regulatory approval of particular labeling claims for particular indications for specific products made by an exact manufacturing process. Of course, a class of therapies designed for a particular disease or condition must, by its regulatory approval pathway, be safe and efficacious for this condition. But each product and process navigating this regulatory pathway is held to high standards by the regulatory authorities; stating simply that a given protein is a copy of this class and should have identical labeling to any member in a pharmaceutical class undermines not only the competitive nature of labeling claims, but the important safety and efficacy data upon which the claims are based.

Manufacturing

PPTA member companies are concerned by the assertion by some representatives at the Workshop, dismissing the importance of the manufacturing process. Claiming that processes are essentially interchangeable, especially for enormously complex therapies such as plasma therapeutics, is disingenuous and misleading. If there was a thread of commonality among all presenters at the Workshop, it is that the complexity of the molecule to be copied will be highly determinative of any question regarding the ability of a manufacturer to duplicate a different process. While the points made about the ability for different processes' ability to create a "similar" or "identical" product are well-taken and certainly deserving of further discussion, it is at least as likely that two different proprietary processes will result in two different products as two different proprietary processes resulting in the same product. Indeed, it is more probable that the products will be variants rather than copies.

The Agency posed a number of questions regarding manufacturing issues to the Workshop participants. These questions asked about specific parts of the manufacturing process that are determinative of a protein product and which are salient to determining similarity. PPTA stated in its presentation that all parts of the manufacturing process are determinative of the final product, and all are salient to assessing similarity. From the standpoint of a policymaker thinking in terms of changes to the current regulatory setting, these answers are not illuminative, but this draws attention to the importance of the process itself. The Agency has doubtless had experiences in reviewing instances of minor changes resulting in a significant difference in product outcome; we urge policymakers to consult these confidential records within the Agency regarding these instances and take them under advisement.

Differences in manufacturing processes can yield very different products, or, more insidiously, products that appear to be similar or analytically identical, but possessed of performance, structure, purity, glycosylation, or translational modifications that render the follow-on ineffective or unsafe, sometimes in ways that are difficult to detect and analyze. As discussed in greater detail below, PPTA member companies do not share the confidence of some other Workshop participants in the ability of analytical technology to disclose all relevant safety and efficacy information for a particular protein product. Our member companies have too many years of experience in using exacting technologies in areas such as pathogen clearance, process validation, clinical investigation, product manufacture, and other important arenas, to believe that analytical techniques represent a panacea that obviates the need for other methods of testing.

The manufacturing process must be considered in its totality, beginning generally with the type of product manufactured and moving to more specific areas of concern, given the specific product at issue in a given situation. Relevant considerations include portions of the manufacturing process that are likely to affect product performance,

which then focuses on the importance of critical control points. In essence, evaluation of a manufacturing process becomes a case-by-case assessment for the formulation, structural similarity, and pharmacodynamics of a particular product.

Important for products derived from human plasma, and which provides a distinction from other biotech and biological products, are proprietary and validated viral clearance methods. For each of these clearance methods, or change to a method, a manufacturer must study the impact on, for example, protein denaturation. Each change to a pathogen clearance method is investigated for impact on structural or molecular changes to the product. While PPTA member companies would prefer to see a larger role for comparability protocols for such changes, we find arguments by would-be FOPP manufacturers relating to the use of comparability protocols disingenuous.

A thematic concern we also share regarding the presentations of the follow-on manufacturers is that the follow-on premise seems to be: if a single representative of an entire product type can be copied, then any new entrant to the market for a particular product type can be copied. In short, the contention seems to be that if you copy one, you copy them all. Putative follow-on manufacturers repeatedly used the market for human growth hormone as an example of this, citing the fact that the FDA had identified all HGH market participants as being identical to the natural compound; therefore, the FOPP manufacturer argument states, all HGH is identical. Furthermore, stressing the point made above with regard to the labeling, a would-be FOPP manufacturer presentation used the identical, FDA-approved labeling of these products as leverage in arguing that the therapies are themselves interchangeable [Presentation by Ms. Suzanne Sensabaugh].

PPTA member companies strongly disagree with this assertion, noting that competition in a market with even a small number of participants, such as Factor VIII, is already quite robust and offers patients a wide variety of choices of product. Those in favor of interpreting the current regulatory structure as supportive of a FOPP approval process argue through other assertions made at the Workshop in reality dilute the FDA standards of safety and efficacy. This is argued by stating essentially that two products which have analytically equivalent safety and efficacy profiles are, therefore, follow-on therapeutic proteins. By definition, *any* product licensed by the FDA has some loose equivalence in terms of safety and efficacy, or the Agency would not license the product as meeting these basic requirements. Thus, the FOPP argument misstates not only the regulatory and statutory definition of equivalence, but the reasoning behind the use of those terms in the current licensing regime.

While even innovative manufacturers may disagree as to the abstract or theoretical possibilities of a framework for FOPPs, PPTA asserts that if the premise above –that all those entities conducting business in a pharmaceutical class are identical-- is granted, then the market is already genericized and the need for further discussion is obviated. If this approach is taken, however, ramifications throughout the Federal statutory and

regulatory framework will require careful consideration. These ramifications will have an impact not only on certain sections within the PHSA and FDCA, but also the Social Security Act, the newly-passed Medicare Modernization Act, the Orphan Drug Act, and any other number of regulations and statutes administered by FDA's sister agencies and other areas of government, including those governing research and government contracts.

Overall, there are aspects of the manufacturing process that should be considered in formulating a framework for follow-on proteins, regardless of the type of therapy. These aspects are key in terms of safety, potency, characterization and immunogenicity. The manufacturing process, starting from the derivation of the source material and carrying through to the final packaging, is determinative of the product itself.

Characterization

The workshop proceedings divulged a polemic involving the capabilities of current and future analytical methods for purposes of protein characterization. We observed with great interest the cutting-edge techniques expounded by various firms and will investigate those of relevance to our companies; however, we must also temper our enthusiasm with common sense and common knowledge. Some participants in the workshop stated that *current* analytical technology is sufficient to characterize *all* biologic products. We disagree strongly with this position, especially in terms of complex molecular products derived from naturally-sourced human plasma. Assertions relating to the preference for analytical technology surpassing the viability of clinical studies are stated in terms of clinical studies being the "least sensitive and least reliable measure of protein product equivalence." [FOPP Workshop Presentation by Dr. Charles DiLiberti, Barr Laboratories, Slide 6]. This argument misses the mark, however, because the purpose of clinical studies for biological products is *not* to demonstrate equivalence, but to demonstrate safety and efficacy, for which current analytical technology is inadequate by itself, without other methods of testing.

While PPTA views current assays as adequate in terms of the purposes for which they were originally designed, some assays and many processes are constantly evolving. Determinations of assay adequacy are naturally connected to the steps and controls in the manufacturing process. One cannot apply a blanket term to primary, secondary, and tertiary assays and assume that all assays at each of these levels are interchangeable and can take the place of a carefully constructed and monitored process. These questions become magnified when the process creates a product with many varying parameters, such as heterogeneous immunoglobulins manufactured from human plasma. Furthermore, questions abound regarding isoform characterization, and comparison of human-derived to recombinant product, such as Factor VIII. Human-derived plasma attributes simply cannot be characterized by current technology, and any look into the near future does not disclose any radical breakthroughs that would alter this current state of affairs.

Innovative manufacturers use analytical methods and characterization techniques to demonstrate safety and efficacy for a therapy after a change has been made to the manufacturing process. The utility of these methods are leveraged from a vast array of scientific knowledge and technological know-how possessed solely by the innovator. The publication of a particular use of a certain analytical tool should not be taken as a universal bellwether of the appropriateness of the technique in all processes by all companies. Comparability protocols, as described in greater detail below, are properly pathways for companies that have substantial knowledge of their own product and processes and are not blueprints for universal implementation. The database consisting of process and product knowledge shared by an innovator with the Agency with regards to a specific product is there for product improvement in safety and efficacy profiles in an innovator product. Using these proprietary data as a knowledge foundation for a company that claims "approximate" similarity is a gross mischaracterization of the purpose and utility of a comparability protocol. [See Presentations, Dr. Charles DiLiberti, Slides 4, 7, and Dr. Jacob Hartman, Slide 10].

We certainly agree that new analytical technology is promising. Advances are being made and will be made in the future that will allow for more rapid identification of molecular structure and associated activity, and our member companies look forward to applying these technologies to our products, when applicable. Current technologies, however, are inadequate when pressed to exceed the boundaries in which they are designed. Analytical studies should not be pushed into realms where they do not answer enough questions with sufficient veracity, such as many areas of safety and immunogenicity.

Safety and Immunogenicity

The plasma industry has led the field in research involving pathogen clearance; over the past two decades, improvements in the industry's capacity to ensure safety from pathogens has substantially increased. However, in the interests shared by industry and by the Agency –continuous improvement, safety, efficacy, and availability—the industry is constantly engaged in the process of product safety. These efforts, of course, include improvement in pathogen safety and also involve the study of any immunogenic responses to a therapeutic protein.

Certain analytical studies done routinely, such as acute toxicity and primary biological activity, are possible through analytical studies. However, as explained in some detail above, analytical and characterization technology for complex proteins is sufficient for their current purposes only. No truly robust model exists for analytical safety studies; in the absence of such a model, analytical studies alone are insufficient to answer questions regarding safety. Some of the opinions expressed by those favoring a liberal regulatory scheme for FOPP approval point out that the lack of ability to understand specific protein structures does not equate to increased risk. We can agree that a lack

of knowledge is not necessarily causative of increased risk, but we must point out that the two are frequently associated. Absence of evidence is not evidence of absence.

Questions regarding immunogenicity cannot be identified solely with current analytical technology. Much of the immunogenicity phenomenon is not well understood even in experimental laboratories; analytical technology fully capable of identifying and characterizing and immunogenic response is many years away. What we know of the immunogenic response is that it is highly dependent on the starting material used in the finished product and its method of derivation.

As in the discussion above of the questions posed by FDA regarding the manufacturing process, distinctions between types and families of therapeutic proteins exist and are keys to discussing safety and immunogenic profiles. These profiles may be dramatically different and trigger different concerns if a therapy is given as acute treatment, as opposed to chronic use over months, years, and decades; a sharp immunogenic response to an acute incident may not be as singularly important as mild immunogenic responses to repeated doses.

Some would-be FOPP manufacturers point out that the majority of immunogenic events are found through pharmacovigilance exercises. We certainly agree with this assessment; pharmacovigilance can be a prime component in a complete safety profile for a protein therapy, though the practice of pharmacovigilance, by its very nature, cannot be relied upon in all instances, due to the fact that its observations do not always protect users with a chronic need. Some arguments against the use of clinical investigation tools use pharmacovigilance as a sum-total substitute for such clinical investigations. While explored in greater detail below, PPTA member companies do not agree with the apparent assertion that clinical trials add no value to the safety or immunogenicity profile of a protein therapy. While we certainly do see the value in eliminating non-value added duplicative clinical trials, and favor the ongoing development of adaptive clinical trial design, we do not think that other technologies have yet surpassed the ability of clinical investigations in this area.

Our conclusion, based on our industry's long experience in pathogen clearance and product safety, is that there is no substitute for studying a molecule in the human system. For plasma-based products, there are no animal models or animal study methodologies with sufficient predictive value for application to humans. There are no shortcuts to patient safety.

As the Agency is well aware, while the Workshop program offers a framework for discussion and for comments submitted to the docket, many issues are crosscutting and do overlap. It is impossible to discuss important steps in manufacturing process without the understanding as to why certain steps are important. Likewise, the issues of safety and immunogenicity cut across many of the other areas of discussion, especially in terms of the utility of clinical and preclinical studies. The Agency's inquiry regarding

clinical and preclinical studies centered on the possibility of streamlining human and animal studies. Assuming that this initial focus is from the standpoint of a putative FOPP manufacturer, one must ask how the FOPP manufacturer acquired the baseline of information possessed by an innovator. The most-frequently cited response to such an inquiry is that the information was acquired through literature reviews of information published by an innovator company. At the Workshop, however, several compelling cases were made and examples used regarding the fact that not every innovator publishes all information related to the development of a complex therapeutic protein. Product information databases shared between the regulatory review team at the Agency and the product developers at an innovator company are of paramount proprietary importance; as such, innovators must continue to have complete assurance and confidence in the robust information protection regimes currently in place at the Agency.

Indeed, it is not inconceivable that reliance on published information may instead place a chilling effect on scientific publication by innovator companies. A company, having made a significant investment in research and development of a particular assay for a particular product, would have little incentive to either create new processes or publish its findings if its reward were that its investment and hard work be expropriated by a competitor lacking the ingenuity to create its own breakthrough. With ongoing publication of scientific discoveries more important than ever before, it would be extraordinarily unfortunate for such a chilling effect to occur and may undermine the same public policy purposes described for the creation of a follow-on approval mechanism.

On July 30, 2004, PPTA, on behalf of its member companies, submitted comments to the FDA docket regarding the White Paper "Innovation/Stagnation," outlining the FDA approach to the Critical Path. In those comments, we stated:

> [O]nerous 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….
>
> [T]he [pharmaceutical pipeline] 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.

In short, our companies' successes with regard to comparability protocols have been mixed. We find it remarkable that putative FOPP manufacturers would claim that a comparability protocol –with the innovator's concomitant proprietary databases—would be a tool by which all safety and efficacy studies could be circumvented by virtue of FOPP manufacture. A comparability exercise assumes that the company undertaking a comparison has substantial –even trade secret and proprietary knowledge—of the manufacturing process and finished product. To assume that published scientific literature discloses all necessary and relevant information and that a follow-on process is "close enough" to the innovator product to be equivalent or identical is to misconstrue a comparability exercise in its entirety.

In theory, an innovator company will use its proprietary knowledge and expertise to successfully undertake a comparability exercise. Because of the enhanced, internal knowledge of the innovator, a comparability exercise should allow that company to make a process change to scale back and/or reduce the necessity of ongoing clinical trials. As mentioned above, some FOPP manufacturers claim that pharmacovigilance studies are more than adequate for a clinical trial when testing for immunogenicity. We view this as a grave mischaracterization of the use of clinical trials, either in product development or in process changes; clinical trials should remain an important component in the safety and immunogenicity profiles of a product. While it may be possible to reduce or scale back human studies, especially with the development of an appropriate animal model or better assay technology, this possibility should be examined on a case-by-case basis, with a thorough evaluation protocol and robust innovator data protection.

Potency and Surrogates

Potency is the ability of the active ingredient in a therapeutic product to exert its intended activity. Surrogate markers for potency hinge upon the markers' own biological relevance to the intended activity and are dependent on clinically validated assays. As such, for the plasma industry, *in vitro* studies are no generally appropriate

for safety testing. Similarly, *in vivo* assays may be adequate for testing acute toxicity and general efficacy, but are insufficient for purposes of testing for immunogenicity.

Current regulatory requirements, as mentioned above in the context of comparability, already place heavy burdens of proof on innovator companies. Within a comparability protocol, companies with encyclopedic knowledge of their own products already undertake significant studies for process changes. This situation demands balance in a FOPP regulatory framework, in such a way that innovation is not stifled and the current abilities of innovator companies in using comparability protocols are not constrained.

International Comity

PPTA and its member companies consider international harmonization to be a strategic goal, with far-reaching importance for the plasma collection and plasma fractionation industries. We are very interested in the current European regime for approval of biogenerics, and were pleased that information on the European perspective was presented at the Workshop. PPTA staff has also had other, informal discussions with EMEA representatives on this issue, and have confidence in the current European requirements for innovator data protection.

As presented at the Workshop, a European marketing authorization considers a biological product to be a specific, independent product by studying a number of factors: the cell line used, the manufacturing process, scale of manufacture, and particular facilities. The European requirements also demonstrate the differences in consideration between comparability and that of copying. We also agree that, irrespective of the theoretical or practical aspects of FOPP manufacturing, any regulatory structure in the U.S. must take into consideration the European regulatory structure and that of the ICH as well.

Conclusion

We again would like to express our gratitude to the Agency for sponsoring an open public process that includes participation from all stakeholders. We would like to encourage the Agency to have further discussions on the scientific issues, for new questions, questions that need further exploration, and for questions left unresolved in the September workshop. We also encourage the Agency to not limit itself to resolution of the scientific issues; we firmly believe that these scientific issues cannot be resolved in a vacuum and that public participation in the policy, legal, and regulatory frameworks is as important as participation in the scientific debate.

We look forward to further discussions. PPTA and its member companies believe that the scientific challenges associated with creation of a follow-on therapeutic protein are great, especially in the context of the current regulatory mechanisms. In terms of scientific progress in the manufacturing process, the characterization context, adaptive

clinical trial design, and countless other ways, follow-on protein products may one day be a reality for both biotechnologically-derived and naturally-derived biological products. Any regulatory structure that allows for approval of follow-on protein products must include meaningful data protections for innovators, robust patient protections, and a streamlined regulatory process for both the innovator and the FOPP manufacturer. Use of comparability protocols in many of the ways suggested by those promoting FOPPs at the Workshop is not an appropriate path for licensure.

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,

Mary Gustafson
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VIA E-Mail & USPS

SUBJECT: Public Workshop, "Scientific Considerations Related to Developing Follow-On Protein Products." September 2004.
Docket No. 2004N-0355.
Addendum to Comments Submitted November 12, 2004
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Dear Sir or Madam:

The Plasma Protein Therapeutics Association (PPTA) is pleased to provide these additional comments on the Food and Drug Administration's (FDA's) Public Workshop entitled, "Scientific Considerations Related to Developing Follow-On Protein Products." [Hereinafter "Workshop"]. 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 mentioned in our original comments of November 12, 2004, that international harmonization is a strategic goal for the plasma products industry. Similarly, we asked the Agency to investigate other international regulatory regimes and policies regarding follow-on protein products. At the time of our comments, we had not yet analyzed the draft European Medicines Agency (EMEA) document entitled, "Guideline on Similar Biological Medicinal Products" with reference number CHMP/437/04, which is currently being considered for consultations and not in final form. In our previous comments, we stated:

> As presented at the [September FDA] Workshop, a European marketing authorization considers a biological product to be a specific, independent product by studying a number of factors: the cell line used, the manufacturing process, scale of manufacture, and particular facilities. The European requirements also demonstrate the differences in consideration between comparability and that of copying. We also agree

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> that, irrespective of the theoretical or practical aspects of FOPP manufacturing, any regulatory structure in the U.S. must take into consideration the European regulatory structure and that of the ICH as well.

We would like to use this opportunity to make the Agency aware of language contained in the EMEA document. For example, on page 7/8, Section 3.4:

> The [Biotechnology Working Party] and [Blood Product Working Group] guidelines listed below should be taken into consideration, in addition to the applicable CHMP guidelines (Section 3.1 and 3.2).
>
> In view of the complex and variable physico-chemical, biological and functional characteristics of the products listed in the BPWG guidelines mentioned below, it will not be acceptable to submit a reduced clinical dossier when claiming similarity to an original (reference) medicinal product. As a result, applications for such similar products will still need to satisfy the safety and efficacy requirements described in these BPWG guidelines for "new products".

In essence, the EMEA has, at this point, precluded the use of a comparability-like approach to the licensure of a "similar" plasma-derived product. This policy approach is used by the EMEA for naturally-derived plasma products and for recombinant analog therapies. We mentioned in our presentation at the Workshop that the complexity of our member companies' therapies may be prohibitive in terms of adequate characterization and other attributes that would allow for a follow-on framework. It is apparent that the EMEA shares our caution with regard to these and other issues, and we ask that the FDA take this into consideration prior to issuing any draft guidance document.

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,

Mary Gustafson
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