PPTA Statement on
Clinical and Surrogate Endpoints for Evaluating Efficacy of Alpha 1-Proteinase Inhibitor (Human) Augmentation Therapy

FDA Blood Products Advisory Committee
July 20, 2009

The Plasma Protein Therapeutics Association (PPTA) is pleased to provide comments to the Blood Products Advisory Committee (BPAC) on the issue of clinical and surrogate endpoints for evaluating efficacy of Alpha 1-Proteinase Inhibitor (A1-PI) therapies.

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 member companies are committed to providing safe and efficacious augmentation therapy to people who have inheritable A1-PI deficiency. A1-PI therapies have been available since 1987 when Prolastin was licensed by FDA using biochemical surrogate endpoints consistent with criteria proposed at a 1985 FDA-NHLBI workshop. Recently, interest has shifted to the use of clinically meaningful endpoints. FDA has requested that sponsors of currently licensed A1-PI therapies perform post-marketing studies using clinically meaningful endpoints, for example, High Resolution Computerized Tomography (HRCT), pulmonary function tests, pulmonary exacerbations, and mortality.

HRCT is a good endpoint for clinical trials.
PPTA views HRCT as a validated and operationally feasible primary clinical endpoint for the evaluation of A1-PI products. HRCT has been utilized in studies outlined in CBER's briefing document and has demonstrated consistent performance and better discrimination than pulmonary function tests, rate/severity of pulmonary exacerbations, or other clinical endpoints. HRCT studies can be accomplished with a reasonable number of study participants, which is an essential consideration when studying a rare disease with a very small patient population.

The current methodology for licensing A1-PI therapies works well.
For systemically administered A1-PI therapy, PPTA views that the effect of these products should continue to be studied using currently accepted biochemical surrogate endpoints [i.e., alpha1-antitrypsin (AAT) serum trough levels]. Demonstration of pharmacokinetic equivalence to marketed products should suffice as a surrogate of clinical effectiveness of augmentation therapy. Introducing additional licensing criteria pre- or post-market may have an inhibitory effect on introducing new or improved systemic A1-PI therapies to provide better patient care. For inhalation A1-PI therapy, PPTA agrees that serum A1-PI levels cannot be used as a surrogate marker of efficacy due to the local mode of administration. PPTA views the current knowledge of HRCT provides assurance of obtaining a clinically meaningful endpoint for pivotal efficacy studies for approval of inhalation therapy products.

The current dose is effective. Additional dose ranging studies are not practical.

Data from retrospective and observational studies as well as exploratory clinical trials support that a therapeutic benefit is obtained with a dose of 60 mg/kg. It has become a recent topic of discussion as to whether higher doses provide additional benefit. Conventional dose ranging or dose comparison studies to address this issue would be difficult to conduct in this rare disorder, as fully powered dose comparison studies require a large number of study subjects to discriminate a modest treatment difference between the approved dose and higher dose level(s). For practical reasons, randomized controlled clinical studies in A1-PI deficiency are limited to 100 to 200 patients. As an example, one PPTA member company is currently running a post-licensure study as required by the FDA. The study opened for enrollment in March, 2006. It has taken over three years to reach its current enrollment of 130 patients, despite significant efforts to enroll subjects. To get to this high number of patients, 120 sites were screened around the world, and 32 sites are currently participating. Such recent efforts to investigate efficacy using clinically meaningful endpoints make it clear that large conventional dose ranging studies are impractical.

There are not adequate surrogate endpoints to base clinical studies to change the dose.

The total number of patients required to participate in studies and the length of time to enroll an adequate number of patients should be considered before recommending dose comparison studies for this small patient population. The slow progression of disease and lack of good biochemical markers currently make conventional dose ranging trials impossible in this rare disease. While PPTA believes that alternatives to conventional dosing studies should be considered, PPTA is concerned about the potential utilization of biomarkers in dose ranging or dose comparison studies. To date, biomarkers specific to severe A1-PI deficiency disease progression and treatment effect in patients have not been established, let alone validated as meaningful surrogate markers. These may present future potential but at this time are in early exploratory phase and are not currently applicable to therapeutic product development.

PPTA member companies would like to reiterate their commitment to providing safe and efficacious A1-PI therapies for augmentation therapy in people with A1-PI deficiency and look forward to working with the FDA to establish the most practical and feasible way to improve the therapies for A1-PI deficiency.