Plasma Protein Therapeutics Association

14 December 2012 **BY Courier**
Reference: RASC12042 E

Dirceu Brás Aparecido Barbano
Diretor-Presidente

Agência Nacional de Vigilância Sanitária - ANVISA
Coordenação de Biológicos - CPBIH/GESEF/GGMED
SIA, trecho 5, área especial 57
CEP 71.205-050

Brasília-DF

Brazil

Subject: Resolution RDC No. 55, from December 16, 2010

Dear Dr. Barbano,

The Plasma Protein Therapeutics Association (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 plasma protein therapies. These include clotting therapies for individuals with bleeding disorders, immunoglobulins to treat a complex of diseases in patients 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 widely in emergency room settings to treat individuals with shock, trauma, and burns, among other therapies. PPTA members are committed to assuring the safety and availability of these medically needed life-sustaining therapies for the people who depend on them.

On behalf of PPTA member companies, we are seeking clarification of the current clinical trial requirements for registration and renewal of registration of plasma protein therapies and their recombinant analogs in Brazil. We have been notified by our members that registration requirements have changed based on the implementation of regulation RDC 55 from 16. of December 2010 (Registration of Biological Products). We would like to better understand the implication of this regulation on the new registration of products that have been approved for marketing in other regions of the world, e.g., European Union and the United States, and the renewal of registration of products that have been successfully marketed in Brazil for a number of years.

It is our understanding that under the new legislation Anvisa is requiring the submission of clinical trial data. Specifically, we would like clarification on the impact of Resolution RDC No. 55 on the following categories:

1. New products that are to be marketed in Brazil without approvals in other regions;
2. Products that are being introduced in Brazil for the first time that have been approved (sometimes for years) in other regions (.e.g. EU, USA);

and

3. Renewal of products that are marketed in other regions and have been successfully marketed in Brazil for several years.

We have received varying messages about the requirements on clinical trial data for the latter two categories. While Anvisa now demands submission of clinical data it is unclear why the studies that supported the approval in the original region (e.g. EU, USA) for the pursued indications are considered insufficient for Brazil. Plasma protein therapies, including their recombinant analogues are well-established products supplied by a number of different manufacturers. Proof of approval, i.e. the original approval and submission of the data that supported that approval should be adequate for marketing in Brazil.

Plasma protein therapies are among the most highly regulated medicinal products. In the US and in the European Union, where most manufacturers are based there is a tight network of legislation and regulation beginning at the collection of the starting material through manufacture and during the life-cycle of plasma protein therapies, including clinical trials. The European provisions also cover plasma protein therapies not intended for patients in the European Union (see The Rules Governing Medicinal Products in the European Union, Volume 4, EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use, Annex 14: Manufacture of Medicinal Products Derived from Human Blood or Plasma). Until recently, Anvisa has accepted plasma protein therapies which were manufactured under these regulations. To our knowledge, there are no reasons to question their validity.

The number of patients depending on plasma protein therapies is small and when clinical studies are performed they are often lengthy multicenter trials located in different countries to enroll the number of patients required by regulatory provisions. If manufacturers are forced by a country to perform additional clinical trials with products that have already been approved the number of available patients will be very limited. Furthermore, patients are often reluctant to participate in clinical trials particularly when the benefit of these trials is highly questionable. In view of these constraints, it may be expected that registration of plasma protein therapies will either be significantly delayed or even abandoned, which would result in product shortages and hence limitation of supply and choice to patients in Brazil.

We are most interested in receiving clarification of the current regulatory requirements for registration of plasma protein therapies in Brazil and hope that you will find our arguments convincing and remain at your disposal for further discussion. Please be so kind to answer to the address below.

Sincerely Yours,

Dr. Ilka von Hoegen
Senior Director, Quality and Safety

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