Plasma Protein Therapeutics Association

Date: October 16, 2015
Reference No.: FDAA15008 **VIA EMAIL**

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, MD 20852

SUBJECT: Rare Diseases: Common Issues in Drug Development; Draft Guidance for Industry [Docket No. FDA–2015–D–2818]

Dear Sir or Madam:

The Plasma Protein Therapeutics Association (PPTA) thanks FDA for the opportunity to participate in the guidance development process and is pleased to provide these comments on the draft guidance entitled "Rare Diseases: Common Issues in Drug Development."[1] PPTA understands that the purpose of this draft guidance is to advance and facilitate the development of drugs and biologics to treat rare diseases. PPTA agrees with FDA that drug development for rare diseases has many challenges related to the nature of these diseases. PPTA appreciates that this draft guidance is intended to assist sponsors of drug and biological products for treating rare diseases in conducting more efficient and successful development programs.[2]

About PPTA

PPTA is the international trade association and standards-setting organization for the world's major producers of plasma-derived and recombinant analog therapies, collectively referred to as plasma protein therapies. Plasma protein therapies are used in the treatment of a number of rare diseases. These diseases are often genetic, chronic, life-threatening conditions that require patients to receive regular infusions or injections of plasma protein therapies for the duration of their lives. These therapies 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.

[1] *See* FR Notice, 80 Fed. Reg. 49246 (August 17, 2015)
[2] *See id*. at 49246

PPTA
Plasma Protein Therapeutics Association

Comments

Consistency is needed

The draft guidance notes the flexibility provided by FDA regulations in applying regulatory standards because of the many types and intended uses of drugs:

> FDA "exercise[s] its scientific judgment" in determining the kind and quantity of data a sponsor is required to provide for individual drug development programs. This flexibility extends from early phases of development to design of adequate and well controlled clinical studies required to demonstrate safety and effectiveness to support marketing approval.[3]

The draft guidance also mentions potential areas of FDA flexibility in determining the nonclinical data necessary to support an evolving clinical development program described in internationally accepted, general guidance documents available for the timing and nature of nonclinical safety studies relative to clinical trials in drug development. The draft guidance notes that additional flexibility may be applied in evaluating development programs for drugs to treat serious and life-threatening disorders per regulation.[4] The draft guidance adds that

> [t]he number of patients to establish effectiveness and safety is determined on a case-by-case basis, taking into consideration the persuasiveness of the data (e.g., comprehensiveness and quality), the nature of the benefit provided (or expected in the case of surrogate endpoints), the length of treatment or exposure, the patient population that would be treated after marketing approval, and the concern for potential of harm from the treatment.[5]

While PPTA appreciates FDA's efforts to provide "flexibility" and "case-by-case" assessments, the Agency should balance these approaches with industry's need for consistency. Although such concepts frequently are requested by industry itself, their use by FDA can translate into a lack of consistency fueled by inter-reviewer variability. Concrete principles and numbers as requested by EMA are less ambiguous.

Statistical descriptions of alternative designs are needed

This guidance lacks resonance to statistical descriptions of alternative designs, such as described in the ICH E9 (Statistical Principles for Clinical Trials, September 1992) and the EMA Guideline (Clinical Trials in Small Populations, CHMP/EWP/83561/2005). The CFR, which in the end is the ultimate legal authority, over and above guidance, specifies, for example, the consideration of sequential designs. All these concepts are greatly advantageous to rare disorders.[6]

---

[3] Draft guidance at 2 (citation omitted)
[4] *See id.* at 7
[5] *Id.* at 12-13
[6] Farrugia A. Trialing plasma protein therapies for rare disorders: thinking outside the box. Pharmaceuticals Policy and Law 2009; 11:345-52 (attached)

Conclusion

PPTA appreciates the opportunity to comment on the draft guidance and looks forward to continued work with FDA on advancing and facilitating the development of drugs and biologics to treat rare diseases. PPTA welcomes from FDA any questions regarding these comments.

Thank you for your consideration.

Respectfully submitted,

Mary Gustafson
Vice President, Global Medical & Regulatory Policy
Plasma Protein Therapeutics Association

Attachment

Pharmaceuticals Policy and Law 11 (2009) 345–352
DOI 10.3233/PPL-2009-0230
IOS Press

Trialing plasma protein therapies for rare disorders: Thinking outside the box

Albert Farrugia
Plasma Protein Therapeutics Association, 147 Old Solomon's Island Road, Annapolis MD 21401, USA
Centre for Orthopaedic Research/Department of Surgery, Faculty of Medicine and Surgery, University of Western Australia WA, Australia
E-mail: afarrugia@pptaglobal.org

The application of evidence-based medicine to the indications addressed by plasma protein therapies is problematic. So-called Level 1 evidence in the form of randomized clinical trials using classical designs to demonstrate efficacy is seldom possible, because the small numbers of patients denies the appropriate level of power from being built in the trial design. In addition, patient accrual is difficult because of understandable patient resistance and "fatigue" at the number of trials. Efforts to address this by regulating agencies over the past years have yielded promising policies in some areas, which recognize the inherent problems and outline practical solutions. The use of patient registries to accrue safety and efficacy data, while rapidly becoming accepting an accepted component as a basis for pre-market review and approval, is also promising as a basis for the incorporation of post-market data, through Phase 4 surveys, of approved therapies. As such, innovative thinking to address the problem of rare disorders may also lead to desirable reform in all aspects of regulation, with a shift from pre- to post-market review.

1. Introduction

Many plasma protein disorders have such a low prevalence that a doctor in a typical general practice would not expect to see more than one case a year. These include the congenital deficiencies of most of the haemostatic proteins treatable by substitution therapy, the various immunodeficiency disorders ensuing from a low or absent synthesis of immunoglobulin and the auto-immune conditions treatable by high doses of immunoglobulin (Table 1).

These disorders are part of the spectrum of rare diseases, 7000 of which affect about 25 million people in the USA, extrapolated to about 500 million people globally. A legal definition of a rare disease relates to the concept of "orphan diseases", [6] which is not universal; both the specified disease rate which is used to define orphan drugs as well as the range and nature of the provisions offered by orphan drug legislation vary significantly between countries. The recognition of orphan diseases allows the establishment of an orphan drug/disease framework in a number of countries, characterized by incentives such as taxation credits, market exclusivity and exemptions from regulatory fees [7]. The pharmaceutical and clinical development of the products used to treat these conditions presents a particular set of challenges. The factors impacting on the plasma protein therapeutics industry's capacity to bring biotherapeutics to the market have been eloquently described by Walton [8] who has

1389-2827/09/$17.00 © 2009 – Network of Centres for Study of Pharmaceutical Law. All rights reserved

Table 1
Prevalence of some diseases treated by plasma protein therapies

Disease	Prevalence	Plasma protein therapy
Haemophilia A	10 – 20/105 males	Factor VIII concentrate
Primary immunodeficiency diseases	1/1200 (USA) [1]	Immunoglobulin
Common Variable Immune Deficiency	1/50,000 [2]	Immunoglobulin
Factor XI deficiency	1/105 [3] 10^5	Factor XI concentrate, FVIIa concentrate
Alpha one antitrypsin deficiency	1/4000 [4]	Alpha one antitrypsin concentrate
Guilliam Guillain-Barré Syndrome	1/105 [5] 10^5	Immunoglobulin

specified the particular challenge posed by the potential development of a product for a small patient population. However, the economic viability of a therapy is not necessarily a function of the patient population size. In advanced economies, a societal consensus to treat rare diseases such as haemophilia results in economically viable therapies for this disease, such as recombinant products, despite the patient numbers falling within the scope of an orphan definition [9]. Similarly, concern that rigid cost-effectiveness ceilings threaten to declare most orphan drugs as non-cost effective has led to the suggestion that rare diseases could be defined as those which are not cost-effective under traditional criteria [10]. All individuals affected by rare diseases are entitled to healthcare in accordance with Article 25 of the Universal Declaration of Human Rights of 1948, a fact which seems to escape the notice of the cost-effectiveness ideologues. The current approach to orphan disease designation needs to be more nuanced in that economic/viability considerations should be detached, when necessary, from the regulatory considerations. It makes little sense to moderate the economic landscape for revenue generating drugs like recombinant haemophilia products, but the limitations of clinical trials, patient populations, etc. still mandate consideration, irrespective of the economic/market features of the drugs. Consideration of patient access needs to assess whether market exclusivity for profitable orphan drugs is either necessary or, indeed desirable, although it may be expected to facilitate development for less common or economically supported diseases. It seems incongruous to adopt universal criteria for market exclusivity under the orphan definition, when the development costs for a drug directed for a population of 10,000 patients will be similar to that for a drug directed for a population of 150,000. A more nuanced approach, affording a longer period for less viable drugs, may be preferable. The purpose of this paper is to comment on the provisions which regulatory agencies have made to accommodate orphan diseases and to offer approaches to the primary regulatory hurdle of clinical trials.

2. Facilitating regulatory process for orphan therapies

Regulatory oversight of therapeutic goods in the developed economy is heavily influenced by the United States Food and Drug Administration (US FDA) and the

Table 2
Orphan drug provisions and outcomes in the FDA and the EMEA

FDA	EMEA	
Definition of orphan drug	$< 200,000$ in the USA population	Prevalence $\leqslant$ 5/10,000 population
Year of inception of scheme	1983	2000
Submissions approved for orphan drug designation	1793 (as of 2007) [11]	569 (as of end of 2008) [10]
Approved for marketing	322 (18%)	50 (8.8%) [12]
Market exclusivity	Yes (7 years)	Yes (10 years)
Regulatory fee exemption	Yes	Yes
Assistance in preparation for marketing application	Yes	Yes
Grants-in-aid	Yes	No
Taxation credits	Yes	No (at the discretion of individual member states)
Interval – Designation to approval	4 ± 3.3 years	2 ± 1 years [7]

European Medicines Agency (EMEA) in the European Union (EU). Orphan drug provisions exist in both jurisdictions, with indications that the regulatory process is generating some significantly different outcomes (Table 2).

The two programs thus appear to have significantly different levels of success. Joppi et al. [7] ascribe the lower uptake as well as the lower rate of approvals in the EU to the lack of economic incentives such as detaxation and grants-in-aid. They report on features of the marketing application of designated orphan drugs which they consider to be deficient. These include lack of controlled studies, use of surrogate endpoints and comparison to placebo rather than active comparators. It is noteworthy that review times in the EMEA averaged half of those in the FDA, despite these apparent deficiencies which led to over half the dossiers being considered incomplete and requiring additional studies to maintain the marketing authorization. While FDA review times for orphan drugs were shorter than those for other new chemical entities, this difference was not statistically significant when analysed for priority review and standard review subsets, and was more due to the relatively higher proportion of orphan drugs accorded priority and fast track procedures.

Therefore it appears that regulatory review of orphan drug medicines still requires further optimization of process and, indeed, principles. Although review times are (relatively) shorter in the EU, many applications are being granted approval on the basis of dossiers judged inferior by the agency's current criteria. The FDA is approving more applications, which are possibly being submitted due to enhanced economic incentives in the USA which are beyond the scope of this review. However, any enhanced review times are apparently due to more orphan drugs fulfilling the criteria for fast track and priority procedures, as well they should, given that these are preferentially accorded to drugs for life-threatening diseases, for which many orphan drugs are directed. When compared to other new chemical entities accorded a similar status, whether this was an accelerated or standard review process, orphan drug review times were not shorter. It appears that both these major agencies are

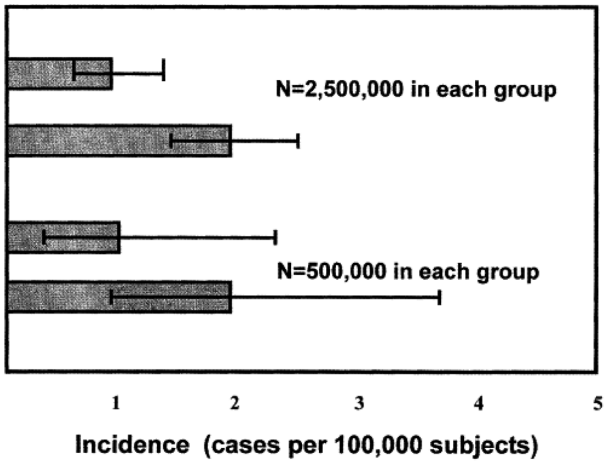

Fig. 1. Effect of sample size on power. In a disorder with a frequency of 1:50 000, demonstration of a 50% reduction in the occurrence of an end-point with 95% confidence would require 2 500 000 subjects in each arm of a study. With 'only' 500 000 in each arm, there is an overlap in the confidence intervals.

using similar review processes to the ones used for mainstream new drugs, with the result that applications are found deficient and review times are not abbreviated. It is, of course, unacceptable that dossier quality, and hence evidence of safety, quality and efficacy, is compromised. Companies submitting orphan drug applications must mount a maximum effort to optimize clinical trial size and the other parameters needed for compliance. For example, the recruitment of a trial population of 50 to treat a population size of 10,000 [7] is not indicative of such an effort.

Nevertheless, if agencies are still applying conventional paradigms to address efficacy, some candidates for alternative approaches bear examining. Randomized clinical trials (RCTs) are rightly considered to be the highest level of evidence possible for efficacy. But the statistical demands are formidable; Wilcken's [13] demonstration of the effect of sample size on power (Fig. 1) illustrates the difficulties for rare diseases. Hence, alternative approaches are required; thankfully, they are available.

3. Alternative approaches for efficacy assessment

3.1. Sequential analysis

In sequential analysis [14], data are analysed as they accrue, and the trial is stopped as soon as an effect assumes statistical significance. The data are analysed as the results for each patient are obtained. In sequential analysis, the final sample size is not fixed at the outset of the study, unlike the standard frequentist method. On

average, sequential analysis will lead to a smaller sample size than a fixed sample size design, while retaining the equivalent statistical power. In addition, the stoppage of the trial once an effect – or an adverse event – is confirmed, rather than at the end, permits a quicker benefit for the patients. Clearly, trials for small patient populations receiving plasma protein therapies are good candidates for sequential analysis. An example in [14, p. 67] shows how a study powered to detect a response rate to a drug could be performed with 25 patients using sequential analysis compared to the 150 patients needed with a standard design.

3.2. Bayesian analysis

A Bayesian [15] statistical approach to clinical trials for small patient populations accepts that a clinically useful effect is unlikely to be observed at the level of statistical precision by the standard – frequentist – clinical trial design [1]. Rather than treating the ideal – frequentist – approach as the enemy of the desirable, the level of certainty possible is changed through the Bayesian analysis by seeking a probability that the sought clinical effect lies in a particular range. A prior probability distribution is generated at the design stage and combined with trial data to give a posterior distribution, from which outcomes may be extracted. Information available before the trial from other studies eg single arm observations is used to construct the prior distribution; scores for these inputs are assigned as probabilities relative to the sought outcome [16]. Speighehalter et al. [17] demonstrate the use of this approach in a small trial of early thombolytic therapy, in which other studies are used to construct a prior distribution, which, combined with the results of the trial itself, leads to a posterior distribution specifying the treatment outcome. Bayesian analysis allowed incorporation of adult data into a pediatric trial of intravenous immunoglobulin in Guillain-Barré Syndrome [18]. Use of a Bayesian approach to analyze inhibitor formation in hemophilia associated with use of Factor VIII concentrate allowed the generation of acceptance criteria for product safety in relation to inhibitor risk [19]. An FDA approach based on the ITT paradigm generated limits which, if applied, would have resulted in the withdrawal of most approved products from the market.

3.3. N of 1 (trial of therapy) trials

The N of 1 trial is a randomized clinical trial used in just one patient. The patient undergoes pairs of treatment periods where one period is the experimental treatment and the other period is the comparator (placebo or alternative treatment). The treatment periods are randomly allocated within each pair. N of 1 trials are considered to provide the strongest level of evidence about the existence of a causal relationship between a treatment and an outcome [20]. They do not permit any

[1] Also known as the "Intent To Treat" (ITT) paradigm.

generalization of the findings on the individual patient to any patient population. However, N of 1 trials may be combined through meta-analysis [14, p. 83] and through a Bayesian random effects model [21] to provide a population estimate for treatment effectiveness while retaining the capacity to provide a distinct effectiveness estimate for each individual patient. The attractions of this approach to rare disease treatments are obvious.

4. Conclusions

Traditionally, medicines regulation has focused heavily on pre-market assessment to assure safety, quality and efficacy. The current mood in regulatory agencies [2] is to shift the emphasis to post-market measures to enable systematic examination of medicines on the market. This is highly appropriate. Phase 4 clinical studies, monitoring patients after approval of a medicine, are an integral part of post-market regulation. Such studies are an essential component of assuring and confirming the safety and efficacy of medicines, including plasma protein therapies, used to treat patients with rare disorders. The generation of patient registries incorporating treatment histories is another important mechanism for building up confidence in the use of a therapy, and such registries have been used to generate regulatory outcomes.

For patients with rare disorders, conventional regulatory provisions for efficacy assessment are necessarily "incomplete" relative to the current regulatory paradigm including its gold standard, the RCT. While industry needs to do its utmost to conform to appropriate practices, including performing trials, regulatory agencies need to reciprocate through being receptive to alternative approaches. It is commendable that the US FDA has included the use of sequential analysis in its Code of Federal Regulations (cited in [22]). It is sobering that, as of 2004, the FDA had approved only one drug using a Bayesian platform for clinical trials (cited in [23]).

It is the belief of this author that therapies for rare disorders can be assured of the same level of safety, quality and efficacy as any other medicine:

> "What can be imagined, will be done"
> ..... with hope
> ..... humility
> ..... patience
> ..... compassion
>
> P Noguchi, FDA, 2002 [24]

[2] The author was a senior manager in the Australian Therapeutic Goods Administration between 1994 and 2008.

Acknowledgement

The opinions voiced in this paper are solely those of the author, and do not reflect the position of any other entity.

References

[1] J.M. Boyle and R.H. Buckley, Population prevalence of diagnosed primary immunodeficiency diseases in the United States, *J Clin Immunol* **27**(5) (Sep 2007), 497–502.
[2] R.A. Schwartz, R.M. Modak and P. Modak, Common. Variable Immunodeficiency. On http://emedicine.medscape.com/article/1051103-overview. Accessed on 1 March 2009.
[3] P.H.B. Bolton-Maggs, Factor XI deficiency. Treatment of hemophilia June 2004 NO 16. On www.wfh.org Accessed on 1 March 2009.
[4] M.P. Kaczor, M. Sanak, M. Libura-Twardowska and A. Szczeklik, The prevalence of alpha(1)-antitrypsin deficiency in a representative population sample from Poland, *Respir Med* **101**(12) (Dec 2007), 2520–2525.
[5] B.S. Schoenberg, Epidemiology of Guillain-Barŕe syndrome, *Adv Neurol* **19** (1978), 249–260.
[6] A. Lavandeira, Orphan drugs: legal aspects, current situation, *Haemophilia* **8** (2002), 194–198.
[7] R. Joppi, V. Bertele and S. Garattini, Orphan drug development is progressing too slowly, *Br J Clin Pharmacol* **61**(3), 355–360.
[8] P. Walton, Factors Impacting Industry's Ability to Bring New (Rare Diseases) Biotherapies to Patients. Presented to the Food and Drug Administration Workshop on Rare Disorders. On http://www.fda.gov/cber/minutes/biother061305t.htm. Accessed on 1 March 2009.
[9] A. Gibbons, Billion-dollar orphans: prescription for trouble, *Science* (1990).
[10] J.K. Aronson, Rare diseases and orphan drugs, *Br J Clin Pharmacol* **61**(3), 243–245.
[11] E. Seoane-Vazquez, R. Rodriguez-Monguio, S.L. Szeinbach and J. Visaria, Incentives for orphan drug research and development in the United, *States Orphanet Journal of Rare Diseases* **3**(33) (2008), doi:10.1186/1750-1172-3-33.
[12] EMEA. List of orphan-designated authorised medicines. On www.emea.europa.eupdfshumancomp 56357508en.pdf. Accessed on 1 March 2009.
[13] B. Wilcken, Rare diseases and the assessment of intervention: What sorts of clinical trials can we use? *J Inherit Metab Dis* **24** (2001), 291–298.
[14] J.H. Evans and S.T. Ildstad, eds, Small Clinical Trials: Issues and Challenges. National Academy of Sciences 2001. On http://www.nap.edu/catalog/10078.html. Accessed on 1 March 2009.
[15] R.J. Lilford, J.G. Thornton and D. Braunholtz, Clinical trials and rare diseases: a way out of a conundrum, *BMJ* **311** (1995), 1621–1625.
[16] S.-B. Tan, K.B.G. Dear, P. Bruzzi and D. Machin, Strategy for randomised clinical trials in rare cancers, *BMJ* **327** (2003), 47–49.
[17] S. Pocock and D.J. Spiegelhalter, Domiciliary thrombolysis by general practitioners, *BMJ* **305** (1992), 1015.
[18] S. Goodman, Incorporating information from adults into pediatric trial design: A Case Study of Guillan-Barré Syndrome. Presented to the FDA Workshop Bayes workshop on 20 May 2004, On www. Accessed on 1 March 2009.
[19] A Bayesian approach to the assessment of inhibitor risk in studies of factor VIII concentrates, *Haemophilia* **11** (2005), 5–12.
[20] G. Guyatt, Preface, in: *Users' Guides to the Medical Literature: A Manual for Evidence-Based Clinical Practice*, G. Guyatt and D. Rennie, eds, AMA Press, Chicago, IL, 2002, p. xiv.
[21] D.R. Zucker, C.H. Schmid, M.W. McIntosh, R.B. D'Agostino, H.P. Selker and J. Lau, Combining Single Patient (N of -1) Trials to Estimate Population Treatment Effects and to Evaluate Individual Patient Responses to Treatment, *J Clin Epidemiol* **50**(4) (1997), 401–410.
[22] S. Todd, A. Whitehead, N. Stallard and J. Whitehead, Interim analyses and sequential designs in phase III studies, *J Clin Pharmacol* **51**, 394–399.

[23] D.A. Berry, Bayesian Design & Analysis Of Drug & Device Trials. Presented to joint FDA/NIH Workshop on Can Bayesian approaches to studying new treatments improve regulatory decision making? On http://www.cfsan.fda.gov/˜frf/bayesdl.html. Accessed on 1 March 2009.
[24] P. Noguchi, Simple Complexity in an Evolving World: Rising to the Challenge. On http://74.125.77.132/search?q=cache:SLJxIAVjNs...+Noguchi+ppt+humility&hl=en&ct=clnk&cd=1&gl=be. Accessed on 1 March 2009.