Plasma Protein Therapeutics Association

May 29, 2012
Reference No.: FDAA12013 **VIA EMAIL**

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

Re: Comments on FDA Draft Guidance on Drug Shortage Reporting (Docket No. FDA-2012-D-0140)

Dear Sir or Madam:

The Plasma Protein Therapeutics Association ("PPTA" or "Association") commends the Food and Drug Administration ("FDA" or "Agency") for addressing the critical issue of drug shortages through its February 2012 draft Guidance to industry, "Notification to FDA of Issues that May Result in a Prescription Drug or Biological Product Shortage" ("Draft Guidance").[1] The plasma protein therapies industry is a leader in the area of shortage-preparedness and takes the issue very seriously.

Although, thankfully, there have been no recent shortages of plasma protein therapies, PPTA has nevertheless been active in the public policy discussions on shortage preparedness spurred by current shortages in other pharmaceutical sectors. Most recently, in December 2011, PPTA filed comments on FDA's Medical Product Shortages Report.[2] Earlier in the year, in September 2011, the Association also made a statement at FDA's Drug Shortages Workshop.[3] On both occasions, PPTA took the opportunity to explain the history, function, and benefits of its North American data program, which provides industry-wide aggregate data on the supply of life-sustaining plasma protein therapies to FDA and the Department of Health and Human Services ("HHS"), manufacturers, and other stakeholders (*e.g.*, patients, providers, and hospitals). The data program has now been in operation for over a dozen years, during which time there has not been a single confirmed shortage of plasma protein therapies. Based on this record of success, PPTA believes that the program can serve as a model to others.

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1 *See* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292426.pdf.

2 PPTA Comments on FDA Drug Shortages Report ("Report Comments") (Attachment 1).

3 PPTA Statement at FDA Drug Shortages Workshop ("Workshop Statement") (Attachment 2).

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With this background in mind, the Association now offers its views on the Draft Guidance, which consist of both general comments – on, for example, the value of voluntary reporting and participation by multiple stakeholders – and specific issues and concerns. It should be noted that, because plasma protein therapies are biological products, PPTA's member companies are not subject to the mandatory notification requirements of section 506C of the Food, Drug, and Cosmetic Act ("FD&C Act").[4] Consequently, the Association's comments pertain to the sections of the Draft Guidance on voluntary notification only.

About PPTA

PPTA represents source plasma collection centers and the manufacturers of medicinal therapies derived from this plasma including, but not limited to: albumin, alpha1-proteinase inhibitor, antithrombin III, blood clotting factors, C1 esterase inhibitor, fibrin sealant, immune globulin ("Ig"), hyperimmune Ig, and protein C concentrate. Some of our members also use recombinant DNA technology to produce blood clotting factors. Collectively, these therapies – both plasma-derived and recombinant – are known as "plasma protein therapies." The manufacturer membership of PPTA in the United States currently includes: Baxter BioScience; Biotest Pharmaceuticals; Cangene Corporation; CSL Behring; Grifols USA, Inc.; and Kedrion Biopharmaceuticals.

Excluding albumin and fibrin sealant, plasma protein therapies are exclusively indicated for the treatment of complex rare diseases, disorders, and conditions. Most of these disorders are genetic, chronic, life-threatening conditions that require patients to receive regular infusions or injections of plasma protein therapies for the duration of their lives. Due to the rare nature of these diseases, plasma protein therapies are quite often not only medically necessary, but the only viable treatment option for these patients.

General Comments

PPTA agrees with many of the general principles and recommended approaches set forth in the Draft Guidance. The Association further notes that many of these principles have already been incorporated into its North American data program and that, with respect to specific implementation, in some ways the PPTA data program represents an even more effective approach to manufacturer notification and shortage-preparedness.

For example, PPTA agrees that supply adequacy is a public health issue and that "[d]rug shortages can create significant public health concerns."[5] PPTA is well

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[4] Draft Guidance, *supra* note 1, at 10 ("Unlike mandatory notification, voluntary notification includes prescription biological products licensed under a BLA.").

[5] *Id*. at 2.

aware of the risks that shortages can pose to patient health. Indeed, PPTA's North American data program was developed in response to a shortage of intravenous Ig in the late 1990s. In order to assist the plasma protein therapies industry in responding to this, and potential future, public health emergencies, PPTA complied with the specific recommendation of HHS's Advisory Committee on Blood Safety and Availability ("ACBSA") that the Association develop and implement an industry-wide supply data reporting system.[6] PPTA continues to operate the program as a public health resource to the entire industry, rather than as a service to its member companies, as shown by the ongoing participation of such PPTA non-members as Bayer, BPL, and Pfizer.[7]

PPTA also agrees that voluntary manufacturer notification of potential shortages is critical because, "while mandatory notification of permanent discontinuances [under section 506C] is helpful in preventing or mitigating some drug shortages, this limited requirement is not sufficient to address the magnitude of the current drug shortage problem."[8] As previously noted, PPTA's North American data program was developed and implemented in response to ACBSA's specific recommendation that the plasma protein therapies industry begin voluntarily reporting shortage-related product supply data. This approach not only represents industry stepping up to its responsibility to the public, but reflects a simple recognition that FDA is not in a position to effectively address the problem of drug shortages on its own. Operating a shortage-related early warning system requires resources and expertise that FDA could not bring to bear even with respect to the plasma protein therapies industry, much less with respect to *every* pharmaceutical sector and group of products that it oversees.[9] Even if it had the additional resources, limitations on the Agency's legal authority to share information received from manufacturers would likely hamper its ability to communicate shortage-related supply data to other industry stakeholders rapidly and effectively.[10]

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6 Report Comments, *supra* note 2, at 3-4; Workshop Statement, *supra* note 3, at 1.

7 Report Comments, *supra* note 2, at 4.

8 Draft Guidance, *supra* note 1, at 4. *See also id*. at 1-2 ("On October 31, 2011, FDA sent a letter to manufacturers . . . encouraging them to voluntarily report to the agency any disruptions in supply that could lead to a product shortage, even beyond those situations covered by mandatory reporting."), 10 ("The Agency encourages manufacturers of all prescription drug or biological products to voluntarily notify the Agency of any issue that may result in a shortage or potential disruption in supply of that product in the U.S. market . . . . [W]e encourage voluntary notification for <u>all</u> prescription drug and biological products.") (emphasis in original), 11 ("We reiterate that FDA encourages manufacturers to be over-inclusive and to report any issue that reasonably could be expected to have an impact on the manufacturer's ability to supply the market and/or could lead to a product shortage.").

9 Report Comments, *supra* note 2, at 5; Workshop Statement, *supra* note 3, at 2.

10 Report Comments, *supra* note 2, at 5. *See also* Draft Guidance, *supra* note 1, at 13 (noting that FDA cannot "disclose . . . confidential commercial information that we receive from manufacturers in connection with a drug shortage unless authorized by law").

FDA notes that "[w]e are particularly interested in obtaining information and comment regarding the appropriate scope of voluntary reporting,"[11] which PPTA is happy to provide. FDA's Draft Guidance appears to contemplate a system of voluntary reporting of individual, potentially shortage-related events by individual manufacturers.[12] This piecemeal approach has a number of limitations, some of which are potentially significant. First, it is impossible to enumerate *every* type of manufacturing incident that could conceivably impact product supply and therefore have shortage implications – something that FDA staff likely realized as they struggled to draft a sufficiently comprehensive list of "reportable" shortage-related events. Second, it is extremely difficult to determine the potential shortage significance of any of the specific events set forth in the Draft Guidance based on information received from only one company. In contrast, the approach embodied in the PPTA data program – periodic reporting of aggregate, industry-wide supply – provides a more useful basis for making a shortage assessment.[13] If overall supply remains adequate, for example, then an incident affecting a single manufacturer may not be cause for alarm. Third, the piecemeal approach of the Draft Guidance, whereby FDA receives a report of an incident from a single manufacturer, then feverishly works the phones or otherwise gathers information from additional manufacturers to assess the incident's significance, may be too slow to provide the rapid, actionable shortage information that industry stakeholders need.[14] In contrast, the PPTA data program provides aggregate, industry-wide supply data at the outset, giving FDA both a faster, and a more accurate, basis for shortage assessment.

Finally, PPTA agrees that any effective shortage-preparedness effort must involve manufacturers as well as other industry stakeholders (*e.g.*, patients, providers, and hospitals), not just FDA.[15] The early warning system for the plasma protein therapies industry – PPTA's data program – provides shortage-related product supply

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[11] HHS and FDA, Draft Guidance for Industry on Notification to Food and Drug Administration of Issues that May Result in a Prescription Drug Shortage, 77 Fed Reg. 11,551 (Feb. 27, 2012).

[12] Draft Guidance, *supra* note 1, at 10-11 (providing non-comprehensive list of reportable manufacturing issues that could potentially lead to a shortage).

[13] Report Comments, *supra* note 2, at 6 (providing specific examples of use of the PPTA data program to evaluate potential shortage concerns); Workshop Comments, *supra* note 3, at 2 (same).

[14] Draft Guidance, *supra* note 1, at 11 ("Early notification is critical to the Agency's ability to respond effectively to potential shortage situations . . . . The sooner FDA is notified, the better the chance of averting shortages of important products and minimizing disruptions in patient access to the product.").

[15] *Id*. at 12 ("Communication and cooperation between the Agency *and industry* is vital to successfully combating the drug shortage crisis.") (emphasis added), 13 (describing FDA's shortage-preparedness efforts as encompassing "communicating with healthcare providers, patients, and other third parties").

information not only to FDA and HHS, but in the aggregate to participating manufacturers and, through reporting on the Association's Web site, to all other interested industry stakeholders as well. As a result, FDA is not left with exclusive responsibility for identifying a potential shortage, but rather is aided by a multitude of other recipients of the PPTA data who may identify concerns that, for whatever reason, the Agency does not. In addition to assisting with shortage identification, manufacturers must have access to the aggregate data for the simple reason that, as the only entities capable of ramping up production, they are the best situated to engage in an effective shortage response.[16] Patient access to the data is no less critical. As individuals who are dependent on plasma protein therapies for their continued good health, knowledge that the supply of these therapies is adequate to meet patient need provides them with peace of mind. In the event that there is an actual shortage concern, patient access to the data becomes even more important, as it enables patients to make informed decisions about their own care, such as moderating their use of a particular therapy or re-scheduling a surgical procedure.[17]

Specific Issues and Concerns

In addition to these general comments on the Draft Guidance, the Association has a few specific issues and concerns.

First, the Draft Guidance does not provide a definition of the term "shortage," nor does it set forth any guidelines to assist manufacturers in determining when a supply disruption crosses the threshold from a routine fluctuation in the production process to a "shortage" requiring notification and corrective action. Depending on the nature of the drug or biological products at issue, the medical condition or illness it is being used to address, and the specific patient population being served, the circumstances constituting a "shortage" could vary significantly. PPTA recommends that FDA staff provide greater clarification on this issue in the final Guidance.

Second, the Draft Guidance does not discuss or describe any mechanism for FDA follow-up once the Agency has informed stakeholders that it has received manufacturer notification of an actual or potential shortage. This is a serious shortcoming if a potential shortage never materializes or an actual shortage is resolved quickly. Without some degree of follow-up FDA communication to establish that the shortage concern has passed and that the situation has returned to normal, a prolonged and unnecessary sense of alarm could be allowed to persist in affected patient communities. Burdensome and disruptive corrective measures, such as rationing and

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[16] Report Comments, *supra* note 2, at 5. *See also* Draft Guidance, *supra* note 1, at 13 ("Manufacturers play a primary role in preventing or responding to drug or biological product shortages, because they make the products needed by doctors and patients.").

[17] Report Comments, *supra* note 2, at 5-6; Workshop Statement, *supra* note 3, at 1.

export controls, could also be left in place long after their utility as shortage response mechanisms has expired.

Third, on page 14 of the Draft Guidance, under the heading "Additional Considerations for Manufacturers," FDA cites its own analysis showing that 60% of shortages could have been avoided or mitigated if manufacturers had undertaken "enhanced redundancy" or contingency planning. The Draft Guidance goes on to encourage manufacturers to make contingency plans, including "building redundancy into manufacturing capabilities." PPTA is concerned that this recommendation, if included in the final Guidance, could put FDA on a path toward *requiring* manufacturers to maintain excess capacity. As a practical matter, it is not clear how such a requirement could be implemented, as an individual manufacturer's determination of how much production capacity will be needed during a certain time period is necessarily based on judgments about future demand that are essentially estimates, ranging from cautiously uncertain to highly speculative. Furthermore, it is not clear that imposing such a requirement is within the scope of FDA's authority under the FD&C Act.

Conclusion

PPTA member companies are committed to providing safe and efficacious plasma protein therapies to patients who need them. Part of that commitment is ensuring that there is an adequate supply of therapies to meet patients' needs. PPTA's North American data program has been a key component of this effort. Consequently, as the process of finalizing the Draft Guidance moves forward, we believe that the Association's data program – with a track record of success now extending over a decade – can serve as a useful reference point and a real world model of effective manufacturer shortage notification.

PPTA welcomes from FDA any questions regarding these comments and/or requests for additional information. Thank you for your consideration.

Sincerely,

Jan M. Bult
President & CEO
Plasma Protein Therapeutics Association

Attachments