

December 22, 2011
Reference No.: FDAA11021

VIA WEB

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

SUBJECT: Comments on FDA Medical Product Shortages Report
[Docket No. FDA-2011-N-0690]

Dear Sir or Madam:

The Plasma Protein Therapeutics Association (“PPTA” or “Association”) commends the Food and Drug Administration (“FDA” or “Agency”) for its September 26, 2011 public workshop on the issue of drug shortages,¹ as well as the subsequently issued report, “A Review of FDA’s Approach to Medical Product Shortages.”² PPTA agrees with FDA that drug shortages are “a significant public health problem” and one that “deserves the concerted attention of government and industry.”³ We write now to offer our views, based on over a decade of experience, on an important tool for combating shortages: manufacturer notification. Many of the “immediate actions” recommended in the FDA Report specifically focus on the issue of manufacturer notification,⁴ and we agree with the Agency’s assessment that notification can be properly understood as a form of “secondary prevention.”⁵

We note with encouragement that FDA has begun a comparison of “best practices” with respect to drug shortages between its various Centers.⁶ As manufacturers of plasma protein therapies, PPTA’s member companies produce medicines that fall into the category of “blood products,” which are regulated by the Center for Biologics Evaluation and Research (“CBER”). We are particularly gratified to see that, in the initial comparison of best practices provided in Appendix 2 of the FDA Report, the effectiveness of CBER’s medical product shortage activities was evaluated quite

¹ Center for Drug Evaluation and Research, Approach to Addressing Drug Shortage; Public Workshop, 76 Fed Reg. 45,268 (July 28, 2011). PPTA participated in the workshop and offered comments on the shortage-preparedness benefits of its North American data program at that time. See Transcript, *FDA Drug Shortage Workshop* 184-187 (Sept. 26, 2011), <http://www.fda.gov/downloads/Drugs/NewsEvents/UCM275801.pdf>

² U.S. Dep’t of Health and Human Servs. (“HHS”) and FDA., *A Review of FDA’s Approach to Medical Product Shortages* (Oct. 31, 2011), <http://www.fda.gov/downloads/aboutfda/reportsmanualsforms/reports/ucm277755.pdf> (“FDA Report”).

³ *Id.* at 3

⁴ *Id.* at 37 (Recommendations 1-4).

⁵ *Id.* at 34.

⁶ *Id.* at 25.

favorably.⁷ We believe that at least part of this success is attributable to PPTA's North American supply data reporting program, which – at the recommendation of the HHS Advisory Committee on Blood Safety and Availability (“ACBSA”) and with the encouragement of CBER – was put in place in response to a shortage of intravenous immune globulin (“IVIG”) products in the late 1990s. Indeed, we believe that, through implementation of the PPTA data program, the plasma protein therapies industry has already accomplished many of the objectives set forth in the FDA Report, and that the industry's example of effective shortage preparedness can serve as a useful model for other pharmaceutical sectors.

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.

History of the PPTA Data Program

In 1997-1998, the plasma protein therapies industry was facing a crisis very similar to that faced by manufacturers of cancer therapies, and other critical pharmaceutical products, today. A shortage of IVIG products attracted the national spotlight. Patients, physicians, hospitals, and FDA all demanded answers from industry. The shortage was

⁷ *Id.* at 43. Appendix 2 notes that, with respect to shortage notification, of the four FDA Centers surveyed, CBER is the most satisfied with manufacturer performance. CBER reports “[g]ood cooperation and early notification received from manufacturers.” In contrast, the Center for Veterinary Medicine (“CVM”) states that it “rarely” receives notification of shortages from industry. Likewise, the Center for Devices and Radiological Health (“CDRH”) “[r]arely, if ever” receives notification from industry and “often finds out about shortages from the media.” Staff of the Center for Drug Evaluation and Research (“CDER”) estimate that “under 50% of product discontinuations are properly reported.” Not surprisingly, Centers reporting less effective manufacturer notification also report a greater number of shortages (e.g., CBER reports “[v]ery few shortages,” while CDER reports 30-40 and CVM reports 6).

the subject of a May 7, 1998 Congressional hearing, and even a segment on “60 Minutes.” However, no individual company was in a position to answer the central question being posed: “How much product is out there?” Each company had data on its own distribution of Ig therapies, but none could provide an aggregate, industry-wide picture. Nor was it simply a matter of each company submitting a figure and FDA summing the total. Developing a program to collect comparable data, at regular intervals, in an antitrust-compliant manner, with procedures for error correction and reporting to appropriate stakeholders would require substantial resources – resources that FDA did not have.

To address this situation, a meeting of the ACBSA was convened to discuss how industry could collect and report more useful shortage-preparedness data on product supply. Manufacturers of certain biological products, including plasma protein therapies, were already required to periodically report product distribution data to FDA pursuant to the Agency’s broad authority under an existing regulation, 21 C.F.R. § 600.81, but the objective of the meeting was to encourage industry to do more.⁸

Following its April 1998 meeting, ACBSA issued a number of shortage-response recommendations. The very first item on the list expressly called for PPTA’s involvement in a data program featuring both more frequent and more detailed reporting of supply information than was then required of PPTA’s member companies under § 600.81. Specifically, the recommendation stated that:

The Food and Drug Administration, the International Plasma Producers Industry Association [now PPTA], and individual manufacturers and distributors of plasma derivatives and their recombinant analogs should, on a monthly basis, collect and disseminate standardized information on production, distribution, and demand for intravenous immunoglobulin, clotting factors (recombinant and plasma-derived), and alpha-1 antitrypsin.⁹

The key elements of the ACBSA recommendation were that: (1) the industry trade association – PPTA – should be directly involved in the data program; (2) the program should involve collection *and dissemination* of standardized information; (3) the information reported should be quite detailed (*i.e.*, production, distribution, and demand – not just distribution); and (4) the data should be reported at frequent, regular intervals. Although the PPTA data program has been modified periodically since 1998, the Association adheres closely to these four elements to this day.

⁸ This approach is not unusual. As the FDA Report notes, all Centers reported “exercising regulatory discretion” in attempting to resolve shortages. *Id.* at 25.

⁹ ACBSA, *Blood Safety Recommendations – April 1998* (May 8, 1998), <http://www.hhs.gov/ash/bloodsafety/advisorycommittee/recommendations/resapr98.html>

A publicly available ACBSA follow-up report issued shortly after the April 1998 meeting confirms that both FDA and PPTA did, in fact, comply with the Committee's data program recommendation.¹⁰ In the ensuing thirteen years, FDA has continued to receive and review product supply data via the PPTA program, and has regularly contacted the Association with data-related inquiries.

Operational Aspects of the Data Program

Manufacturers participating in the PPTA data program report data on the supply of certain plasma protein therapies – specifically, Ig, albumin 5%, albumin 25%, plasma-derived Factor VIII, and recombinant Factor VIII – on a monthly basis. The company-specific information is then aggregated, and industry aggregate supply data for each product category is reported back to FDA (which also receives company-specific data), HHS, and participating manufacturers. The information is also reported publicly, via PPTA's Web site,¹¹ where it is available to patient advocacy groups, healthcare providers, and individual patients.

It bears noting that the Association does not operate the data program as a service to its members, but as a public health resource for the entire industry. Consequently, the list of participating manufacturers currently includes both PPTA member¹² and non-member¹³ companies.

The FDA Report asserts, correctly, that, “[p]erhaps the major impediment to disclosure of impending drug shortages is manufacturers’ concern that such disclosures run counter to competitive business practices.”¹⁴ However, this need not be the case. Antitrust compliance has been a priority since the PPTA data program's inception, and the program incorporates many competitive safeguards. One of the most notable is the use of an independent, third party vendor – Georgetown Economic Services (“GES”) – to collect the individual company data. As a result of GES's involvement, individual company data is *not* made available to PPTA or to any manufacturer of plasma protein therapies. PPTA, manufacturers, and all other stakeholders receive aggregate, industry-wide data only.

Armed with this data, industry and regulators can rapidly and accurately assess, and respond to, any potential shortage situation before it results in adverse outcomes for patients. As FDA is learning anew in other sectors of the pharmaceutical industry, without accurate, reliable information on what is happening with respect to the supply

¹⁰ ACBSA, *Follow Up*, (Aug. 3, 2000), (“[m]onthly reports [have been] distributed by [PPTA] since 10/21/98”).

¹¹ See PPTA North American Supply Data, <http://www.pptaglobal.org/program/data.aspx>

¹² Baxter, CSL, Grifols, Kedrion, and Octapharma.

¹³ Bayer, BPL, and Pfizer.

¹⁴ FDA Report, *supra* note 2, at 28.

situation, it is nearly impossible to mount an effective shortage response effort.¹⁵

FDA also candidly acknowledges that the Agency cannot go it alone. As the FDA Report explains, it is critical for manufacturers to have access to any shortage notification mechanism as well because, “from a public health perspective, advanced warning of an expected disruption or discontinuation of production by any party would prove useful to other manufacturers who might be able to increase production of similar products.”¹⁶ FDA not only needs manufacturers’ assistance in identifying potential shortage situations but, more importantly, in addressing them. As the FDA Report notes, perhaps at the risk of stating the obvious, “FDA has no capacity or authority to manufacture medications.”¹⁷

Just as FDA does not have the capacity to manufacture medical products, it does not have the capacity to manage an industry data program. Collecting, aggregating, and reporting supply data requires time, personnel, and expertise. A data program must also be run in an antitrust compliant manner, which requires ongoing legal input and imposes another layer of expense. As the FDA Report explains, the Agency is already operating under substantial limitations, in terms of both resources¹⁸ and legal authority,¹⁹ and is simply not in a position to manage shortage-related early warning systems for the multitude of drug products it currently oversees. The PPTA data program is an example of industry stepping up to lighten this burden, as the FDA Report recommends.

Benefits to Stakeholders

While regulator and industry participation is the cornerstone of any shortage-related data program, providing data *only* to FDA and manufacturers is not enough. As the FDA Report acknowledges, addressing the drug shortage problem will require “involving multiple stakeholders,” most of these stakeholders desire “greater transparency” with respect to shortage information, and many of them “find this [information] difficult to obtain from manufacturers.”²⁰

Hospital and physicians also require access to the data, but perhaps patients – the individuals who rely on these therapies on a day-to-day basis for their continued good

¹⁵ *Id.* at 26 (“The absence of readily analyzable data limits FDA’s ability to assess the adequacy of its responses to shortages, to identify steps it can take to reduce the likelihood of shortages, and, potentially, to predict future shortages.”).

¹⁶ *Id.* at 28.

¹⁷ *Id.* at 20.

¹⁸ *Id.* at 34 (noting that improving shortage notification “requires resource-intensive efforts”) and 37 (requesting additional shortage notification-related staffing resources).

¹⁹ *Id.* at 3 (“The agency is . . . limited in its current authorities as it formulates a response to the [drug shortage] problem.”) and 39 (“[G]enerally, the Agency cannot disclose [shortage] information without the permission of the manufacturer” because it may constitute “confidential commercial information.”).

²⁰ *Id.* at 27, 36.

health – most of all. In addition to the substantial benefit of providing peace of mind with respect to product supply, PPTA's Web-based data reporting empowers patients to take control of their own health decisions in the event of a shortage by, for example, providing them with adequate notice to secure alternative sourcing or to change their site of service. This is certainly preferable to patients learning of a shortage for the first time upon arriving at the pharmacy, or physician's office, and discovering that the shelves are bare.

Thankfully, there have been no recent shortages of plasma protein therapies. However, this hardly suggests that the PPTA data program has outlived its utility.²¹ Even in the absence of a true shortage, the program has demonstrated its utility in promoting and ensuring patient access to plasma protein therapies, as two recent examples illustrate.

First, in 2005-2006, in response to an increase in patient complaints regarding access to IVIG, HHS conducted an investigation into a possible shortage. PPTA's data program was instrumental in demonstrating that, during the time period in question, the U.S. supply of IVIG was at historically high levels. The subsequently published HHS report confirmed that supply had "almost doubled" between 1998 and 2005.²² Consequently, the report explained, any access difficulties experienced by patients were attributable to causes other than a true shortage. Two months later, this conclusion was confirmed a second time by a parallel report issued by HHS's Office of Inspector General.²³

Second, in August 2010, Octapharma announced a voluntary withdrawal of its Ig product in the U.S. market. Naturally, this raised concerns with both patients and regulators regarding the short term supply situation. Once again, however, PPTA's data program was available to reassure both groups. Rather than being forced to "fly blind," patients and regulators were able to quickly assess the situation and make the welcome determination that shortage-response efforts were not needed.

Conclusion

Ultimately, both the drug shortage workshop and the subsequent research underlying the FDA Report led the Agency to the conclusion that, as good corporate citizens,

²¹ *Id.* at 5 (noting that efforts to address the shortage problem will need to be "sustained over the long term") and 25 ("the nature of the drug shortage problem suggests that shortages are not likely to abate in the near-term").

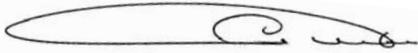
²² HHS, Office of the Assistant Secretary for Planning and Evaluation, *Analysis of Supply, Distribution, Demand, and Access Issues Associated with Immune Globulin Intravenous (IGIV)* viii (Feb. 2007), <http://aspe.hhs.gov/sp/reports/2007/IGIV/report.pdf> (In 1998, total IGIV available for distribution was 15.2 million grams. In 2005, it was 28.3 million grams).

²³ HHS, Office of Inspector General, *Intravenous Immune Globulin: Medicare Payment and Availability* iii (Apr. 2007), <http://oig.hhs.gov/oei/reports/oei-03-05-00404.pdf> (attributing product access difficulties to off-label use, coding, and "plasma industry economics," understood to mean that "[t]he production of IVIG requires substantial resources not typically associated with other pharmaceutical products").

manufacturers *must*: (1) notify FDA of potential disruptions to the supply of drugs rapidly and voluntarily (*i.e.*, even when not required to do so by regulation); and (2) work to maximize disclosure of drug shortage information to the public.²⁴ By reporting company-specific product supply data to FDA, and industry aggregate data to all other stakeholders, this is precisely what the plasma protein therapies industry is already doing.

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 for over a decade. We believe that the program already incorporates the key recommendations of the FDA Report with respect to manufacturer notification, and hope that it can serve as a model to others.

Sincerely,



Jan M. Bult
President & CEO
Plasma Protein Therapeutics Association

²⁴ FDA Report, *supra* note 2, at 36-37 (Recommendation 1) and 39 (Recommendation 11).