Plasma Protein Therapeutics Association

March 14, 2013
Reference No.: FDAA13011 **VIA EMAIL**

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

Re: Comments on FDA Drug Shortages Task Force Strategic Plan Concept (Docket No. FDA-2013-N-0124)

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 2013 request for public comment from interested persons on certain questions related to drug and biological product shortages to assist FDA in drafting a strategic plan on drug shortages as required by the Food and Drug Administration Safety and Innovation Act ("FDASIA" or "Act").[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 Most recently, in May 2012, PPTA filed comments on FDA's Draft Guidance on Drug Shortage Reporting.[2] In 2011, PPTA filed comments on FDA's Medical Product Shortages Report[3] and also made a statement at FDA's Drug Shortages Workshop[4] in December and September, respectively. On all three 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.

With this background in mind, the Association now offers its views on the development and implementation of a strategic plan for enhancing the Agency's response to preventing and mitigating drug shortages, which consist of both general comments – on, for example, the value of voluntary reporting and participation by multiple stakeholders – and input on specific issues raised in the FR Notice. It should be noted that, because plasma protein therapies are

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1 Food and Drug Administration Drug Shortages Task Force and Strategic Plan; Request for Comments, 78 Fed. Reg. 9928 (Feb. 12, 2013) ("FR Notice").
2 PPTA Comments on FDA Draft Guidance on Drug Shortage Reporting ("Guidance Comments") (Attachment 1).
3 PPTA Comments on FDA Drug Shortages Report ("Report Comments") (Attachment 2).
4 PPTA Statement at FDA Drug Shortages Workshop ("Workshop Statement") (Attachment 3).

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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"). However, PPTA understands that the Center for Biologics Evaluation and Research is represented on the Drug Shortages Task Force and notes that, although FDASIA refers only to a drug shortages plan, FDA "anticipate[s] that the strategic plan will consider prevention and mitigation of both drug and biological shortages."[5]

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; 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 is well 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]

The early warning system for the plasma protein therapies industry – PPTA's data program – provides shortage-related product supply 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

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5 FR Notice, *supra* note 1, at 9929.
6 Report Comments, *supra* note 2, at 3-4; Workshop Statement, *supra* note 3, at 1.
7 Report Comments, *supra* note 2, at 4.

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.[8] 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.[9]

Input on Specific Issues

The FR Notice notes that, to assist with drafting the FDASIA-mandated strategic plan, the Task Force would appreciate input on a few specific issues. With that invitation in mind, PPTA now offers its thoughts on four of those issues: coordination, timeliness, partnering/voluntary industry efforts, and communication.

1. Coordination

The FR Notice states that the Task Force's strategic plan must include "[p]lans for enhanced . . . intra-agency coordination."[10] PPTA writes briefly on this topic to address only two points.

First, PPTA commends the Task Force for clearly asserting that "we are interested in receiving comments on these questions from all parties, including those with an interest in biological products."[11] PPTA agrees that shortages are an important public health concern across the spectrum of medicinal products, and is pleased that FDA has included a CBER representative on the Task Force.

Second, however, we note with caution that effective intra-agency coordination requires more than each FDA Center reviewing, and signing off on, an omnibus plan. Rather than such rigid uniformity, effective coordination requires careful consideration of the important differences between, and unique circumstances surrounding, the products regulated by each Center. In the shortage context, this means understanding and respecting existing industry preparedness mechanisms, such as the PPTA data program developed in cooperation with CBER, which are already effectively addressing FDA and stakeholder concerns. We are hopeful that such programs will be embraced by the Task Force's strategic plan, rather than disrupted through the imposition of one-size-fits-all policies and rules. Indeed, this approach is consistent with the FDASIA legislation's requirement that any further regulation pursuant to the Act "shall take into account any [existing] supply reporting programs" and "shall aim to reduce duplicative notification."[12]

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[8] Report Comments, *supra* note 2, at 5.

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

[10] FR Notice, *supra* note 1, at 9928.

[11] *Id.* at 9929.

[12] FDC § 506C(i)(3), as amended by FDASIA §1001(a)

2. Timeliness

The FR Notice also notes that FDASIA requires the Task Force's strategic plan to include "[p]lans for ensuring that drug shortages are considered when the Secretary initiates a regulatory action that could precipitate a drug shortage or exacerbate an existing drug shortage."[13] This is an area in which we believe that the PPTA data program embodies shortage-preparedness "best practices" that can be instructive to the Task Force. Indeed, we believe that, with respect to reporting shortage-related information in a timely manner, the PPTA data program is superior to the shortage notification regime currently applicable to drug products, though not biologicals, in FDASIA.

This conclusion is based on the fact that manufacturers participating in the PPTA data program report distribution data for covered products on an ongoing, regular basis. Specifically, each participating manufacturer reports its own data to an independent data aggregator on a monthly basis, and the aggregate reports are subsequently published after a 3-month lag.[14] In contrast, under the FDASIA notification regime for drug products, individual manufacturers report only to FDA and only when there is a problem potentially affecting supply.

The difference in the timeliness of the information is thus substantial. In the event that FDA believes there is a problem affecting an individual manufacturer of plasma protein therapies, before taking regulatory action that may impact supply the Agency can quickly consult the most recent report of industry-wide aggregate distribution data, available through the PPTA program, to determine whether such action will potentially create a problem. In contrast, a manufacturer's individual company notification under FDASIA provides FDA with no information on the aggregate supply situation at all. In practical terms, it merely functions as a signal to the Agency that it must now begin scrambling to put together the industry-wide picture that the PPTA data program provides at the outset. The former is unquestionably a stronger basis for assessing the potential shortage ramifications of FDA regulatory action than the latter.

3. Partnering/Voluntary Industry Efforts

The FR Notice further requests input on the use of a "qualified manufacturing partner program" similar to the one used under the Biomedical Advanced Research and Development Authority ("BARDA"), but notes that there are important potential differences between the BARDA program and the use of a parallel program to address shortages.[15] PPTA understands this to be a request for input on the general topic of partnering/voluntary industry efforts and gratefully accepts the invitation. Here too we believe that PPTA's data program embodies "best practices" and constitutes a useful, real world example for the Task Force's consideration.

As the FR Notice observes, "FDA does not have funding to pay manufacturers to participate in a

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[13] FR Notice, *supra* note 1, at 9928-29.

[14] For a more complete description of the operational details of PPTA's data program, *see* Report Comments, *supra* note 2, at 4-6.

[15] FR Notice, *supra* note 1, at 9929.

drug shortages qualified manufacturer program."[16] Given current federal budget and agency funding concerns, this is not at all surprising. Operating a qualified manufacturing partner program, a shortage-related early warning system, or any other sort of preparedness mechanism 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 the Agency oversees.[17] In light of that fact, partnering and industry voluntary efforts provide an important opportunity for burden sharing.

Operation of the PPTA data program, for example, is hardly as simple as submitting a few figures and adding them up. Keeping the program going requires the continuing efforts of company data contacts, PPTA staff, personnel at an independent economics consulting firm, and legal counsel. Though all of this is accomplished in close consultation with FDA staff, neither PPTA nor the participating companies have ever requested that the Agency contribute to the program's funding. This approach not only represents industry stepping up to its responsibility to the public, but reflects a simple recognition of the fact that FDA is not in a positive to effectively address the problem of drug shortages on its own.

With that industry commitment in mind, it is important to remember that partnering/voluntary efforts require a commitment from FDA as well. On this score, the FR Notice helpfully asks "Are there incentives that FDA can provide to encourage manufacturers . . . to create . . . conditions to prevent or mitigate shortages?"[18] One such incentive that the Agency can provide, perhaps so fundamental that it is often unstated, is to recognize and value manufacturers' existing, ongoing voluntary efforts in this area.

The need for such recognition has been highlighted most recently by the discussion surrounding potential extension of FDASIA's mandatory manufacturer notification provisions, currently applicable to drug manufacturers only, to manufacturers of biologicals as well. While PPTA takes no position on the extension of these requirements to other biological products, the Association believes strongly that extension of these provisions to plasma protein therapies would be inappropriate and counter-productive. The plasma protein therapies industry has an existing shortage-preparedness mechanism in place, designed and implemented in consultation with FDA and stakeholders that has been functioning effectively for over a decade. With that background in mind, extending the FDASIA requirements to manufacturers of plasma protein therapies at this point – essentially, subjecting them to the same regulatory treatment as other pharmaceutical sectors that have done nothing to address shortages – would certainly send the wrong message, and potentially diminish industry enthusiasm for future voluntary efforts across the board.

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[16] *Id.*

[17] Even if FDA had the 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. *See* Guidance Comments, *supra* note 2, at 3.

[18] FR Notice, *supra* note 1, at 9929.

4. Communication

Finally, the FR Notice states that FDA uses a variety of means – including, most notably, the Agency's public shortages Web sites – to send "targeted notifications" to stakeholders, defined broadly to include "health care professionals, manufacturers, distributors, patients, and others."[19] The Notice then requests input on whether there are additional communication tools that FDA should use to share shortage-preparedness information."[20] PPTA commends FDA on this approach and suggests that the Task Force should carefully consider opportunities to maximize the sharing of shortage-preparedness information by encouraging and supporting voluntary communications efforts by industry.

By way of example, PPTA's data program provides "targeted communications" to a specialized, niche audience: individuals involved in the manufacture, distribution, or use of plasma protein therapies – products intended, almost without exception, for the treatment of extremely rare conditions. The program provides shortage-related product supply information not only to FDA and HHS but, in the aggregate, to participating manufacturers. Through reporting on the Association's Web site, the data is reported 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 information who may identify concerns that, for whatever reason, the Agency does not.

PPTA is pleased to see that the Task Force recognizes, through the FR Notice's broad conception of interested stakeholders, that effective shortage-related communications are valuable to a wide variety of individuals and groups, not just to FDA. As a starting point, manufacturers must have access to shortage-related information 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. Patient access to such information is no less critical. As individuals who are dependent on drug and/or biological 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 an actual shortage situation develops, patient access to this information and 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.

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 drafting a strategic plan on drug shortages 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 an effective shortage-preparedness mechanism.

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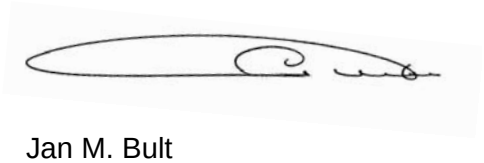
[19] *Id.*

[20] *Id.*

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

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 all 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

PPTA
Plasma Protein Therapeutics Association

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.

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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.

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[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 member[12] and non-member[13] 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

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[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 resources[18] 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

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[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,

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[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).

PPTA Statement on
PPTA's North America Data Program: A System to Monitor Availability of Life-Saving Plasma Protein Therapies

FDA Drug Shortage Workshop
September 26, 2011

Good morning. My name is Jan Bult. I am President & CEO of the Plasma Protein Therapeutics Association (PPTA). PPTA is the international trade association for the world's major producers of plasma-derived and recombinant analog therapies.

History of PPTA Data Program

PPTA's North American data program was developed in response to a shortage of intravenous immune globulin (IVIG) products in the late 1990s. For many users of these products, their health depends on regular IVIG infusions. They demanded information on the scope, likely duration, and causes of the shortage. The shortage was also the subject of Congressional hearings and substantial media attention.

To address this situation, as well as potential future shortages of plasma protein therapies, the Advisory Committee on Blood Safety and Availability (ACBSA) made a specific recommendation to FDA regarding an industry-wide supply data reporting program. The key elements were that: (1) the industry trade association – PPTA – should be directly involved in the program; (2) the program should involve collection *and dissemination* of standardized information; (3) the information reported should be quite detailed; and (4) the data should be reported monthly. By the Spring of 1998, FDA. PPTA, and manufacturers of the therapies – including both PPTA members and non-members – had all complied with ACBSA's recommendation.

Operational Aspects of the Program

PPTA's data program provides monthly, aggregate data on the supply of certain plasma protein therapies, including Ig, albumin, and hemophilia clotting factors. This information is reported directly to manufacturers that contribute data, FDA, and HHS. The information is also reported publicly, via PPTA's Web site, where it is available to patient advocacy groups, healthcare providers, and individual patients.

Antitrust compliance has been a priority since the program's inception, and it incorporates many competitive safeguards. These safeguards include the use of an independent, third party vendor to collect the individual company data. As a result of this firewall, individual company data is *not* made available to PPTA or to any manufacturer of plasma protein therapies. Both PPTA and manufacturer personnel receive aggregate, industry-wide data only.

Providing the data *only* to industry and regulators, however, is not enough. Patients also require access. In addition to the substantial benefit of providing peace of mind with respect to product supply, the PPTA data program empowers patients, and their physicians, to make better-informed decisions regarding treatment.

Benefits to Patients and Regulators

PPTA's data program has proven to be very helpful in times of real shortage. We experienced this with immune globulins in the late 1990s and with recombinant Factor VIII around 2000. For

example, the PPTA data helped many hemophilia patients make decisions regarding the timing of elective surgery.

The PPTA program is also very helpful when there are unsubstantiated rumors regarding shortages. In these situations, PPTA has been able to provide factual data to eliminate any potential concern. For example, in 2005-2006, the data was useful in distinguishing a mere supply disruption – resulting from changes in federal reimbursement policy that forced patient site-of-service changes and related IVIG access problems – from a true product shortage.

One thing we have learned is that, for a supply data reporting system to provide value to patients and regulators as part of a shortage-response framework, industry must make a sustained commitment. Implementing a reporting program only when there is a perceived shortage, and discontinuing it when it appears that supply is sufficient, will not work. In order to be there when needed, the system must be maintained continuously.

As a final note, collecting, aggregating, and reporting supply data takes time and expertise. In other words, it costs money. A data program must also be run in an antitrust compliant manner, which requires ongoing legal input and imposes another layer of expense. As we all know, FDA is already operating under substantial resource constraints and is not in a position to manage shortage-related early warning systems for the multitude of drug products it currently oversees on its own. The PPTA data program is an example of industry stepping up to lighten this burden.

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 for over a decade. The program is an example of highly successful FDA-industry collaboration, and we hope that it can serve as a model to others.