Plasma Protein Therapeutics Association

Privileged and Confidential
HL Draft 11/20/2015

December [21], 2015

Captain Krista M. Pedley, PharmD, MS, USPHS
Director
Office of Pharmacy Affairs, Healthcare Systems Bureau
Health Resources and Services Administration
5600 Fishers Lane, Mail Stop 08W05A
Rockville, MD 20857

By Electronic Submission

Re: Information Collection Request: Enrollment and Re-Certification of Entities in the 340B Drug Pricing Program and Collection of Manufacturer Data to Verify 340B Drug Pricing Program Ceiling Price Calculations [OMB No. 0915-0327—Revision]

Dear Captain Pedley:

The Plasma Protein Therapeutics Association ("PPTA") is pleased to have this opportunity to submit comments in response to the proposed Information Collection Request ("Proposed ICR") that the Health Resources and Services Administration ("HRSA") published in the Federal Register on October 20, 2015 regarding the 340B Drug Pricing Program ("340B Program").[1]

PPTA represents human plasma collection centers and leading manufacturers of plasma protein therapies, including Baxalta, Biotest, CSL Behring, Grifols Inc., and Kedrion SpA. PPTA is committed to ensuring that patients living with chronic and rare diseases who rely on plasma protein therapies for their lifesaving treatment have appropriate and timely access to the therapy and care that best suits their health status. [HL Note: We took this description from the last comment letter. PPTA to confirm accuracy.]

PPTA firmly supports the implementation of guidelines that advance patient access, reflect the vital importance of continuity of care for plasma protein patients, and ensure that the benefits of 340B discounts accrue to the intended beneficiaries of the 340B program—the most needy and vulnerable patient populations. PPTA members frequently sell their products to hemophilia treatment centers and other entities

[1] 80 Fed. Reg. 63,560 (Oct. 20, 2015).

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participating in the 340B Program as covered entities, and PPTA therefore has significant interest in the program and how it is administered.

In particular, PPTA asks that HRSA:

1. Treat the "must offer" provision as a binding requirement only after a manufacturer's Pharmaceutical Pricing Agreement has been amended to include the "must offer" provision,
2. Implement the must offer provision consistently with HRSA's longstanding non-discrimination guidance, and
3. Clarify the scope of the must offer provision in any final amendment to the Pharmaceutical Pricing Agreement or through related guidance.

In addition, PPTA urges HRSA to clarify that any amendment to the PPA implementing the must offer provision would be effective prospectively only.

I. Background Regarding PPTA

Most of the rare conditions that require treatment with plasma protein therapies are genetic, chronic, and life-threatening, including alpha-1 proteinase inhibitor deficiency, hemophilia, von willebrand disease, and primary immune deficiency diseases ("PIDDs").[2] Plasma protein therapies include albumin, alpha$_1$-proteinase inhibitor, antithrombin III, plasma-derived and recombinant blood clotting factors,[3] C1 esterase inhibitor, fibrin sealant, immune globulin, hyperimmune immune globulin, prothrombin complex concentrate and protein C concentrate.[4]

Due to their unique nature, plasma protein therapies face distinct challenges and regulatory treatment, and some of these particular aspects may be impacted by their treatment under the 340B Program. One such unique characteristic of plasma protein is that its manufacturers depend upon human donated plasma as the raw material for

[2] Diseases treated with plasma protein therapies also include chronic B-cell lymphocytic leukemia, chronic inflammatory demyelinating polyneuropathy, hereditary angioedema, hereditary antithrombin III deficiency, protein C deficiency, PIDDs, such as common variable immunodeficiency, X-linked agammaglobulinemia (Bruton's disease), DiGeorge syndrome, Wiskott-Aldrich syndrome, Nezelof's syndrome, severe combined immunodeficiency, graft-versus-host diseases, and bleeding disorders, such as hemophilia A, hemophilia B, congenital fibrinogen deficiency, and factor XIII deficiency. Cytomegalovirus disease associated with transplant patients, hepatitis B reinfection in liver transplant patients, idiopathic thrombocytopenic purpura, infant botulism, and Kawasaki's disease. Rabies, rhesus incompatible pregnancies, and tetanus are examples of acute rare conditions that are treated with plasma protein therapies.

[3] Recombinant blood clotting factor therapies are those created using recombinant DNA technologies, which entail the integration of genes coding for the production of human blood clotting factor proteins into laboratory cell cultures. The cell cultures produce the blood clotting factor proteins, which are subsequently collective, purified, and further refined into safe and effective biologic medicines.

[4] Human plasma is the clear liquid portion of blood that remains after the red cells, leukocytes, and platelets are removed. Due to its human origin, complexity, and richness in therapeutically useful proteins, human plasma is a unique biological material. *See* Thierry Burnouf, *Plasma Proteins: Unique Biopharmaceuticals – Unique Economics*, *in* 7 PHARMACEUTICALS POLICY AND LAW, BLOOD, PLASMA AND PLASMA PROTEINS: A UNIQUE CONTRIBUTION TO MODERN HEALTHCARE 209 (2005, 2006).

therapeutic production. The process for collecting human donated plasma is highly regulated, resource-intensive, and time-consuming, with a production process spanning seven to nine months. Further, only a small number of people living in the U.S. who are eligible to donate blood or source plasma actually donate. Plasma protein therapies by their very nature are therefore available only in limited quantities.

The non-interchangeable nature of plasma protein therapies further complicates the supply situation of these therapies. Distinct fractionation processes are used to generate each brand within a plasma protein therapeutic class. This results in plasma protein therapies that are non-interchangeable, sole source biologicals that produce different therapeutic outcomes depending on the patient. Each patient requires uninterrupted access to a particular brand of plasma protein therapy, which means that the patient population as a whole requires access to the full spectrum of plasma protein products. [HL Note: We revised this introduction to focus on the limited supply. PPTA to review and confirm.]

II. 340B Program Background

The 340B Program was created by the enactment of section 602 of the Veterans Health Care Act of 1992 (Public Law No. 102-585), which added Section 340B of the Public Health Service Act.[5] Most recently, the Patient Protection and Affordable Care Act ("ACA") amended Section 340B in 2010.[6]

As a condition of coverage for its covered outpatient drugs under Medicaid and Medicare Part B, a manufacturer must participate in both the Medicaid Drug Rebate Program and the 340B Program.[7] In order to participate in the 340B Program, the 340B statute requires manufacturers to enter into a Pharmaceutical Pricing Agreement ("PPA") with the Department of Health and Human Services. Pursuant to the PPA, the manufacturer agrees to charge statutorily defined "covered entities" no more than a discounted ceiling price[8] for its covered outpatient drugs.[9] Importantly, the 340B statute does not directly apply 340B Program requirements to participating manufacturers. Instead, the 340B statute sets forth the program requirements that must be contained in the PPA, and it is by entering into the PPA that the manufacturer agrees to be bound by the terms of the PPA.

The ACA amended the 340B statute to provide that the PPA "shall require that the manufacturer offer each covered entity covered outpatient drugs for purchase at or below the applicable ceiling price if such drug is made available to any other purchaser at any price," often referred to as the "must offer" provision.[10] HRSA to date has not

[5] Section 340B of the PHSA is codified at 42 U.S.C. § 256b.
[6] ACA, § 7102, Pub. L. No. 111-148 (2010).
[7] 42 U.S.C. § 1396r-8(a)(5).
[8] Id. at § 256b(a).
[9] The defined term "covered outpatient drug" includes, among other things, biological products other than vaccines. Plasma protein therapies are therefore included in the 340B program. *See* 42 U.S.C. § 1396r-8(k)(2)(B).
[10] 42 U.S.C. §256b(a)(1).

implemented the provision by amending the PPAs that are in place with manufacturers or releasing a new form PPA.[11] HRSA has now issued the Proposed ICR proposing to implement the must offer provision in the PPA through an addendum.[12]

III. The 340B Statute's "Must Offer" Provision is Not Currently Binding and, Once Binding, Should Apply Prospectively Only

As PPTA recently expressed in a comment letter to HRSA dated October 27, 2015,[13] the "must offer" provision currently is not binding, and will be binding on a manufacturer only after the manufacturer's PPA has been amended to include the must offer provision or the manufacturer enters into a new PPA that includes the must offer provision. HRSA has repeatedly asserted that this provision is binding on manufacturers, most recently in the proposed "omnibus" guidance,[14] despite the fact that HRSA to date has not implemented the provision by amending the PPAs that are in place with manufacturers or by releasing a new form PPA.[15]

The current form PPA expressly states that it "will not be altered except by an amendment in writing signed by both parties," and its terms therefore may not be unilaterally revised.[16] Further, unlike the form agreement pursuant to which manufacturers participate in the Medicaid Drug Rebate Program, the PPA in its current form also does not contain any provision to the effect that the contract terms will automatically conform to future statutory changes. The Medicaid Drug Rebate Program form agreement, on the other hand, does require manufacturers to comply with changes to the Medicaid statute.[17]

As stated in the Proposed ICR, HRSA now intends to implement the must offer provision in the PPA through an addendum.[18] Nevertheless, the current form PPA, and the PPAs that are currently in place with manufacturers, do not include the must offer provision. Unless and until manufacturers have entered into a PPA that contains such a requirement, the must offer provision continues to be not binding on manufacturers—which HRSA now has implicitly acknowledged by suggesting in the Proposed ICR that an addendum to the PPA is necessary to implement the provision.

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[11] HRSA's current form PPA is available at: http://www.hrsa.gov/opa/manufacturers/pharmaceuticalpricingagreement.pdf (last visited Nov. 20, 2015).
[12] 80 Fed. Reg. 63,560 (Oct. 20, 2015).
[13] The letter is available at: http://www.regulations.gov/#!documentDetail;D=HRSA-2015-0002-0520 (last visited Nov. 20, 2015).
[14] 80 Fed. Reg. 52,300 at 52,311 (Aug. 28, 2015).
[15] HRSA's current form PPA is available at: http://www.hrsa.gov/opa/manufacturers/pharmaceuticalpricingagreement.pdf (last visited Nov. 20, 2015).
[16] PPA § VII(h).
[17] CMS's form Medicaid Drug Rebate Program Agreement, at § II(c), *available at*: http://www.medicaid.gov/medicaid-chip-program-information/by-topics/benefits/prescription-drugs/downloads/samplerebateagreement.pdf (last visited Oct. 5, 2015).
[18] 80 Fed. Reg. 63,560 (Oct. 20, 2015).

PPTA urges HRSA to clarify that, where a manufacturer enters into a PPA addendum or a new PPA that includes the must offer provision, that provision is binding prospectively only. The 340B statute does not directly apply 340B program requirements to participating manufacturers and instead sets forth the program requirements that must be contained in the PPA.[19] It is by virtue of entering into the PPA that the manufacturer agrees to be bound by its terms. The must offer provision is not binding on a manufacturer until the provision is implemented through the PPA that the manufacturer has entered into, and HRSA should clearly acknowledge that the must offer provision applies prospectively only.

IV. The "Must Offer" Provision Embodies HRSA's Non-Discrimination Guidance and Its Scope Is Limited to Prohibiting Discrimination

HRSA issued its longstanding "non-discrimination" guidance in 1994.[20] That guidance provides that manufacturers "may not single out covered entities from their other customers for restrictive conditions that would undermine the statutory objective."[21] In other words, 340B covered entities are to be placed on the same footing as a manufacturer's commercial customers. The intent of the ACA in adding the must offer provision to the 340B statute was to embody the non-discrimination policy in the statute. HRSA itself acknowledged as much in the 2012 program notice entitled "Clarification of Non-Discrimination Policy" (the "2012 Notice"), where HRSA states that the non-discrimination policy is "consistent with" the 340B statute's must offer provision.[22]

PPTA is concerned that the Proposed ICR obfuscates and improperly broadens the scope of the must offer provision. The "Abstract" section of the Proposed ICR paraphrases the text of the statutory must offer provision: "A manufacturer subject to a PPA must offer all covered outpatient drugs at no more than the ceiling price to a covered entity listed in the 340B Program database."[23] However, it omits the key qualifying phrase included in the statutory language: "…if such drug is made available to any other purchaser at any price."[24] It is the very language that HRSA omitted that makes clear what the must offer provision requires—that manufacturers treat 340B covered entities in the same manner as "other purchasers." As paraphrased in the "Abstract" section, the must offer provision goes beyond the scope of the 340B statute itself, and PPTA urges HRSA to accurately reflect the statutory language in any final PPA amendment.[25]

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[19] 42 U.S.C. § 256b(a)(1).
[20] 59 Fed. Reg. 25,110 (May 3, 1994).
[21] Id. at 25,111.
[22] HRSA, 340B Drug Pricing Program Notice: Clarification of Non-Discrimination Policy, Release No. 2011-1.1 (May 23, 2012).
[23] 80 Fed. Reg. 63,560 (Oct. 20, 2015).
[24] 42 U.S.C. §256b(a)(1).
[25] Another example of HRSA's overly broad reading of the must offer provision came in the "omnibus" guidance, where HRSA cited the must offer provision as the basis for its erroneous assertion that manufacturers are required to submit limited distribution plans to HRSA for approval. 80 Fed Reg. 52,312 (Aug. 28, 2015).

V. The Limited Scope of the "Must Offer" Provision Should Be Clarified in Any Final PPA Amendment Or Through Contemporaneous HRSA Guidance

HRSA implicitly acknowledges in the 2012 Notice and in the omnibus guidance that there are practical limitations inherent in the must offer provision. For example, where a manufacturer has only a limited supply of a drug available, and does not receive a request from a 340B covered entity for the drug until the manufacturer has exhausted its supply, the manufacturer would factually be unable to sell the drug to a 340B covered entity if one were to request the drug at the ceiling price. The 2012 Notice accordingly requires that allocation procedures must demonstrate that 340B covered entities "are treated the same" as non-340B customers.[26] The omnibus guidance similarly states that the limited distribution plan must indicate that the manufacturer "will impose these restrictions equally on both 340B covered entities and non-340B purchaser."[27]

Any PPA amendment that implements the must offer provision should clearly set forth this limited scope, namely that the must offer provision requires that 340B covered entities be treated in the same manner as commercial customers, but that 340B covered entities are not entitled to preferential treatment. Given the supply limitations inherent in plasma protein therapies, HRSA must forestall the possibility that if the most offer provision becomes binding through the PPA, covered entities use it as a basis to purchase the limited available quantities of plasma protein therapies. HRSA should do so by expressly stating the limited nature of the must offer provision in any PPA amendment, or by issuing guidance contemporaneously with the release of any PPA amendment. In the absence of such safeguards, the result could be to the detriment of patients whose wellbeing is dependent on the availability of plasma protein therapies from particular manufacturers.

PPTA believes that stakeholders should be afforded the opportunity to comment on any final PPA addendum or guidance addressing the must offer provision to give stakeholders the opportunity to share their concerns or comments with HRSA. PPTA therefore urges HRSA to make the PPA addendum and any guidance available for public review and comment before they become effective.

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PPTA welcomes the opportunity to comment on the Proposed ICR. Please feel free to contact Thomas B. Lilburn, Director of Government Relations, at (443) 458-4682 or tlilburn@pptaglobal.org if you have any questions or would like to discuss these comments further.

Sincerely,

[26] HRSA, 340B Drug Pricing Program Notice: Clarification of Non-Discrimination Policy, Release No. 2011-1.1 (May 23, 2012).
[27] 80 Fed. Reg. 52,300 at 52,321 (Aug. 28, 2015).

Thomas B. Lilburn
Director, Government Relations