PPTA
Plasma Protein Therapeutics Association

July 19, 2011

Reference No. FASC11042

CDR Krista Pedley
Director, Office of Pharmacy Affairs
Health Systems Bureau
Health Resources and Services Administration
5600 Fishers Lane
Parklawn Building, Room 10C-03
Rockville, MD 20857

ELECTRONIC DELIVERY (opaorphan@hrsa.gov)

Re: RIN 0906-AA94, Exclusion of Orphan Drugs for Certain Covered Entities Under the 340B Program

Dear CDR Pedley,

The Plasma Protein Therapeutics Association ("PPTA") would like to thank you for the opportunity to comment on the Health Resources and Services Administration's ("HRSA") proposed rule implementing section 340B(e) of the Public Health Service Act.[1] As the first act of rulemaking by the agency in the nearly 20 years of the 340B Drug Pricing Program, we appreciate the significance of this proposed rule. Because the therapy portfolio of the plasma protein therapeutics industry is almost exclusively for the treatment of rare diseases, disorders, and conditions, PPTA is particularly sensitive to policies that may hinder patient access to the therapeutic intervention best suited for the individual needs of the patient; thus, PPTA recommends the following changes to the proposed rule:

1. HRSA must implement the orphan drug exclusion in a manner consistent with the plain language of the law.
2. HRSA must implement appropriate safeguards to ensure covered entity compliance.
3. HRSA should withhold finalizing the rule until the Centers for Medicare & Medicaid Services ("CMS") expressly excludes from the definition of "best price" for the purpose of title XIX of the Social Security Act the sales of orphan designated drugs for use for common indications, rare disease indications that lack orphan designation, and off-label conditions to the new categories of 340B hospitals that are subject to the 340B orphan drug exclusion.

[1] *See* Exclusion of Orphan Drugs for Certain Covered Entities Under 340B Program, 76 Fed. Reg. 29183 (May 20, 2011). This proposed rule implements changes to the statute made by the Patient Protection and Affordable Care Act ("PPACA"), as amended by the Health Care and Education Reconciliation Act of 2010 ("HCERA") and the Medicare and Medicaid Extenders Act of 2010. Collectively, the PPACA and HCERA are known as the Affordable Care Act ("ACA").

PPTA believes these recommendations, if implemented in the final rule, will be an important first step in equitably shaping the program for all participants.

PPTA represents human plasma collection centers and the manufacturers of lifesaving medicinal therapies, including albumin, alpha$_1$-proteinase inhibitor, antithrombin III, blood clotting factors, C1 esterase inhibitor, fibrin sealant, immune globulin, hyperimmune immune globulin, and protein C concentrate, from this human plasma.[2] 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 ("U.S.") currently includes Baxter, Biotest, Cangene, CSL Behring, Grifols, and Talecris.

Excluding albumin and fibrin sealant, plasma protein therapies are solely approved for marketing in the U.S. by the Food and Drug Administration ("FDA") for the treatment of rare diseases, disorders, and conditions. In the U.S., a "rare disease or condition" is generally defined as a disease or condition that affects less than 200,000 people.[3] The majority of the rare conditions that require treatment with plasma protein therapies are genetic, chronic, and life threatening, including alpha-1 antitrypsin deficiency, chronic B-cell lymphocytic leukemia, chronic inflammatory demyelinating polyneuropathy, hereditary angioedema, hereditary antithrombin III deficiency, protein C deficiency, primary immune deficiency diseases, such as common variable immunodeficiency, X-linked agammaglobulinemia (Bruton's disease), DiGeorge syndrome, Wiskott-Aldrich syndrome, Nezelof's syndrome, severe combined immunodeficiency, and graft-versus-host diseases, and bleeding disorders, such as hemophilia A, hemophilia B, congenital fibrinogen deficiency, Von Willebrand's disease, and factor XIII deficiency. Cytomegalovirus disease associated with transplant patients, hepatitis B reinfection in liver transplant patients, idiopathic thrombocytopenic purpura,[4] infant botulism, Kawasaki's disease, rabies, rhesus incompatible pregnancies, and tetanus are examples of acute rare conditions that are treated with plasma protein therapies.

As representatives of a segment of the drug industry with considerable experience in treating rare diseases, disorders, and conditions, PPTA recognizes the important policy rationale for establishing the orphan drug exclusion. We believe our comments urging its proper implementation will benefit all program participants.

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[2] 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.

[3] *See* 21 U.S.C. § 360bb(a)(2) (2006).

[4] ITP can also be a chronic condition.

I. The Proposed Rule Conflicts with the Plain Language of the Statute

Notwithstanding the sound policy rationale for protecting the financial incentives for enrolling in the 340B program and the desire to be consistent with the Orphan Drug Act incentives, PPTA strongly disagrees with HRSA's proposal to limit the orphan drug exclusion in section 340B(e) of the Public Health Service Act to "uses for the rare disease or condition for which the orphan drug was designated under section 526 of the [Federal Food, Drug, and Cosmetic Act ("FFDCA")]."[5] A federal agency does not have the authority to effectively amend a statute during the rulemaking process,[6] even if it believes it is promulgating good policy.[7]

The statute expressly states that "the term 'covered outpatient drug' shall not include a drug designated by the Secretary under section 526 of the [FFDCA] for a rare disease or condition."[8] In this statute (unlike others noted below), Congress does not limit the orphan drug exclusion to the approved orphan designated indications for the drug, but applies the exclusion to the drug as a whole and without any limitation. The plain language of the statute is clear, so this is not a situation in which there is discretion vested in the agency to which *Chevron* deference would apply. Rather, the agency is charged with following the statute as written,[9] not in a narrower fashion as HRSA proposes.

The agency's attempt to artificially manufacture congressional intent based on the Orphan Drug Act cannot override the plain language of the statute. Specifically, HRSA argues that the financial incentives established under the Orphan Drug Act only apply to orphan designated indications (i.e., an orphan drug is only eligible to receive seven years of market exclusivity for the approved orphan designated indication, not other approved indications).[10] The agency is seemingly taking the view that the orphan drug exclusion from the 340B program is an extension of the Orphan Drug Act and its incentives.[11] If Congress truly intended for the orphan drug exclusion from the 340B program to mirror the Orphan Drug Act, it could have expressly spoken at the indication level, as it did in another section of the ACA where it established an orphan drug exclusion from the annual pharmaceutical fee. In section 9008(e)(3) of the PPACA, Congress excludes the sales of certain products from the determination of a company's annual pharmaceutical fee liability, mandating an examination of the indications of

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[5] 76 Fed. Reg. at 29184.
[6] *See* California Cosmetology Coalition v. Riley, 110 F.3d 1454, 1460 (9th Cir. 1997).
[7] *See* Electric Power Supply Ass'n v. F.E.R.C., 391 F.3d 1255, 1266 (D.C. Cir. 2004) (suggesting that the courts will unlikely give any consideration to the motives of a federal agency in disregarding its obligation to appropriately promulgate a statute as called for by Congress, even if such motives are altruistic).
[8] HCERA § 2302, Pub. L. No. 111-152, 124 Stat. 1029, 1082 – 1083, *amended by* Medicare and Medicaid Extenders Act of 2010 § 204, Pub. L. No. 111-309, 124 Stat. 3285, 3289 – 3290 (codified at Public Health Service Act § 340B(e)).
[9] *See* Chevron U.S.A., Inc. v. Natural Resources Defense Council, Inc., 467 U.S. 837, 842-843 (1984).
[10] *See* 76 Fed. Reg. at 29184-29185.
[11] *Id*. (arguing that implementing the statute according to its plain language "appears to be overly inclusive," suggesting it is contrary to the congressional intent).

orphan designated drugs to determine whether sales of the product should be excluded from the annual fee calculation. Thus, Congress clearly makes considered determinations as to whether it is addressing orphan designated drugs by indication or not. PPTA firmly believes that HRSA lacks the authority to implement the orphan drug exclusion on an indication basis when Congress drafted the statutory language by reference simply to an orphan designated drug, and not by reference to different indications for such products. As such, PPTA urges HRSA to withdraw this proposal and implement the orphan drug exclusion in a manner consistent with the plain language of the statute.

II. HRSA Should Not Finalize the Proposed Rule Until it Can Ensure 340B Covered Entity Compliance with the Orphan Drug Exclusion

The proposed method of implementing the orphan drug exclusion not only exceeds HRSA's statutory authority, but also would, if finalized, create significant operational barriers to compliant implementation for these newly eligible categories of hospitals. Under the agency's proposal, manufacturers are required to continue to offer orphan drugs at the 340B price to free-standing cancer hospitals, critical access hospitals, sole community hospitals, and rural referral centers, but the proposed rule will only permit these hospitals to dispense or administer these orphan designated drugs purchased at the 340B price in treating common indications, rare disease indications that lack orphan designation, and off-label conditions.[12] In order to be compliant with the proposed rule, these 340B hospitals must be able to distinguish the use of each unit of drug it purchases at the 340B ceiling price.

HRSA has directed the covered entities to create separate purchasing accounts and maintain auditable records demonstrating their orphan designated drug use, but is not establishing a standard method for doing so.[13] This "flexible" approach to establishing these safeguards is highly problematic. The absence of clearly stated standards will create significant uncertainties for those covered entities acting in good faith while enabling bad actors to defend their actions based on the lack of any clear requirements for compliance.

Accurately determining the use of the orphan designated drug in each instance it is administered or dispensed by the 340B hospital is impossible without a thorough examination of the patient's medical record. Such an arduous process will not even guarantee the necessary information can be located. For simplicity, these hospitals would instead likely attempt to use diagnosis codes to identify the disease for which the hospital dispensed or administered a drug or biological in treating the patient. The U.S. currently uses the *International Classification of Diseases, Ninth Revision* ("ICD-9 codes"). ICD-9 codes, however, are outdated. Most countries began using the Tenth Revision ("ICD-10 codes") nearly twenty years ago. The U.S. will not transition to ICD-10 codes until October 1, 2013. Although the National Institutes of Health has identified

[12] *Id*. at 29186
[13] *Id*.

more than 7,000 rare diseases and conditions,[14] most rare diseases cannot be identified by ICD-9 code. Identifying rare diseases by ICD-10 codes will be equally difficult upon the transition.

If the 340B hospital is unable to identify the disease for which the orphan designated drug is being used, it will be unable to maintain separate inventories or maintain records of any value for audit purposes. Moreover, the identification of the disease will, in most instances, be even more difficult at the time of purchase because most 340B covered entities do not purchase drugs and biologicals on a specific patient or use basis, but rather purchase larger quantities of products to establish an inventory to have available should they need to administer or dispense a particular drug. In short, separate purchasing accounts are not a sufficient safeguard, so manufacturer audits, even if they were a viable option, will do little to ensure compliance.

The proposed rule provides that manufacturers have the authority to audit covered entity records demonstrating compliance with the orphan drug exclusion.[15] Manufacturer audits are not, however, a viable enforcement tool. Existing program guidance currently limits the manufacturer's right to audit to the covered entity's compliance with the prohibitions against product diversion and duplicate discounts, and so covered entities could deny audit requests on the basis that existing audit guidelines do not apply to the orphan drug exclusion.[16] Moreover, even if a covered entity did permit such an audit, this right to audit under the current guidance is at great expense to the manufacturer, primarily because of the requirement that the manufacturer retain an independent third party accountant to conduct the audit.[17] Additionally, manufacturer audits are a burdensome, time consuming process because of the requirements that a manufacturer submit an audit work plan for agency review and establish reasonable cause prior to conducting it.[18]

Although we do not believe it is appropriate for the agency to finalize this proposed rule until it can ensure covered entity compliance with the orphan drug exclusion, when finalizing the rule, PPTA urges HRSA to develop one standard audit guideline in regulation for all covered entity compliance issues, including the orphan drug exclusion. In doing so, the agency should modify the current manufacturer audit guidelines to permit a manufacturer's in-house personnel to audit 340B covered entities. A manufacturer's in-house personnel are likely to have significantly greater familiarity with a covered entity's operational structure and could conduct the audit in a more effective and efficient manner, benefiting both parties.

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[14] *See Frequently Asked Questions,* OFFICE OF RARE DISEASES RESEARCH, NAT'L INSTITUTES OF HEALTH, http://rarediseases.info.nih.gov/AboutUs.aspx (last visited June 22, 2011).
[15] *See* 76 Fed. Reg. at 29186
[16] *See* Manufacturer Audit Guidelines and Dispute Resolution Process 0905-ZA-19, 61 Fed Reg. 65406, 65409 (Dec. 12, 1996).
[17] *Id*.
[18] *Id*.

III. HRSA Should Not Finalize the Proposed Rule Until CMS Has Issued Guidance Expressly Stating that Sales of Orphan Designated Drugs for Non-Orphan Uses at the 340B Price Are Exempt from Best Price

Section 1927(a) of the Social Security Act compels a manufacturer seeking federal reimbursement for its covered outpatient drugs from both Medicaid and Medicare Part B to participate in both the 340B Drug Pricing Program and the Medicaid Outpatient Drug Rebate Program. The rebate program generally requires manufacturers to provide to each state Medicaid program a rebate on the manufacturer's covered outpatient drugs that the state has reimbursed.[19] CMS calculates the rebate amount for most drugs and biologicals as the greater of the minimum rebate percentage of the average manufacturer price (AMP) reported for the product (23.1% for most branded prescription drugs) or the difference between the AMP and the "best price" reported, plus any "additional rebate amount."[20] Manufacturers are to exclude sales at the 340B ceiling price to 340B covered entities from its calculation of its reported best price.[21] PPTA urges HRSA to refrain from finalizing this proposed rule until CMS has issued guidance expressly excluding from the best price calculation 340B sales of orphan designated drugs for use for common indications, rare disease indications that lack orphan designation, and off-label conditions to free-standing cancer hospitals, critical access hospitals, sole community hospitals, and rural referral centers.

IV. Conclusion

PPTA greatly appreciates the opportunity to provide comments to HRSA on its proposed rule implementing the orphan drug exclusion from the 340B Drug Pricing Program. We are very concerned about HRSA's proposal and urge the agency to refrain from finalizing the proposed rule until it has given careful consideration to the concerns we have expressed with regard to the agency's lack of authority, the resulting operational challenges coupled with a lack of enforcement capabilities, and the potential effect the proposal could have on best price for the purpose of the Medicaid outpatient drug rebate. Please do not hesitate to contact me at 202-789-3100 or by email (jgreissing@pptaglobal.org) if you have any questions.

Sincerely,

John E. Greissing

John E. Greissing
Sr. Director, Federal Affairs

[19] *See* 42 U.S.C.S. § 1396r-8(b)(1)(A) (LexisNexis 2011).
[20] *Id.* at § 1396r-8(c).
[21] *Id.* at § 1396r-8(c)(1)(C)(i)(I).