UNITED STATES DISTRICT COURT FOR THE DISTRICT OF COLUMBIA

PHARMACEUTICAL RESEARCH AND MANUFACTURERS OF AMERICA, Plaintiff, vs. UNITED STATES DEPARTMENT OF HEALTH AND HUMAN SERVICES, et al., Defendants.	)	Case No. 1:13-cv-01501

***AMICUS CURIAE* BRIEF OF THE SAFETY NET HOSPITALS FOR PHARMACEUTICAL ACCESS, AMERICA'S ESSENTIAL HOSPITALS, AND NATIONAL RURAL HEALTH ASSOCIATION IN SUPPORT OF DEFENDANT'S MOTION FOR SUMMARY JUDGMENT, IN OPPOSITION TO PLAINTIFF'S MOTION FOR SUMMARY JUDGMENT, AND IN OPPOSITION TO PLAINTIFF'S MOTION FOR PRELIMINARY INJUNCTION**

TABLE OF CONTENTS

TABLE OF AUTHORITIES

Cases

Statutes

Regulations

Federal Registers

Other Authorities

Max Nisen, *$300,000 A Year 'Orphan Drugs' Are Becoming A Hugely Profitable Business*, Business Insider, Jan. 31, 2013, *available at* http://www.businessinsider.com/the-business-of-orphan-drugs-2013-1 (last accessed Dec. 9, 2013) 12

Michael J. Berens and Ken Armstrong, *PhRMA's Windfall: The Mining of Rare Diseases*, Seattle Times (Nov. 9. 2013), *available at* http://apps.seattletimes.com/reports/pharma-windfall/2013/nov/9/mining-rare-diseases/ (last accessed Dec. 9, 2013) 3, 11, 13

Nat'l Cmty Pharmacists Assoc., *Medication Adherence in America: A National Report Card*, http://www.ncpanet.org/pdf/reportcard/AdherenceReportCard_Full.pdf (last accessed Dec. 12, 2013) 34

Olivier Wellman-Labdie, Youwen Zhou, *The US Orphan Drug Act: Rare disease research stimulator or commercial opportunity?*, Health Policy 95 (2010) 216-228 ..... 3, 4, 19, 25

Response to HRSA, Office of Pharmacy Affairs FAQ, *What Outpatient Facilities Are Hospitals Required to Register On the 340B Database? available at* http://www.hrsa.gov/opa/faqs/ (last accessed Dec. 20, 2013) 43

Thompson Reuters, *The Economic Power of Orphan Drugs*, 2012, *available at* http://thomsonreuters.com/products/ip-science/04_013/1001450.pdf (last accessed Dec. 9, 2013) 12

I. INTERESTS OF *AMICI*

Safety Net Hospitals for Pharmaceutical Access ("SNHPA") is a 501(c)(6) non-profit organization of nearly 1,000 public and private non-profit hospitals and health systems throughout the United States that participate in the 340B program. SNHPA, which was originally named the Public Hospital Pharmacy Coalition, was formed in 1993 as an advocacy group within America's Essential Hospitals (then named the National Association of Public Hospitals and Health Systems or NAPH), to increase the affordability and accessibility of pharmaceutical care for the nation's poor and underserved populations. In 2007, SNHPA was established as a separate corporation. Its mission is to serve as the leading advocate and resource for those providers who serve their communities through participation in the 340B drug pricing program. SNHPA is the only national organization that focuses its efforts on matters related to the 340B program. Among SNHPA's members are roughly 300 hospitals that are subject to the Orphan Drug Rule.

America's Essential Hospitals represents more than 200 hospitals and health systems dedicated to high-quality care for all, including the most vulnerable. America's Essential Hospitals was established in 1981 to initiate, advance, and preserve programs and policies that help its public and nonprofit hospital members ensure access to care for the country's vulnerable patient populations. The association's members are vital to their communities, providing primary care, trauma care, disaster response, health professional training, research, public health programs, and other services. They innovate and adapt to lead the broader health care community toward more effective and efficient care. The vast majority of America's Essential Hospitals' member hospitals participate in the 340B program, including health systems with hospitals affected by the Orphan Drug Rule.

The National Rural Health Association ("NRHA") is a national nonprofit membership organization with more than 20,000 members. The association's mission is to provide leadership on rural health issues. NRHA membership consists of a diverse collection of individuals and organizations, including hospitals subject to the Orphan Drug Rule, all of whom share the common bond of an interest in rural health.

II. INTRODUCTION

The Department of Health and Human Services ("HHS") promulgated a regulation that is required by the statutory language that it implements and, even if it were not compelled by the language of the statute, is a perfectly reasonable interpretation of that statute. Congress enacted the 340B program to lower drug costs for eligible hospitals and their patients, and Congress then expanded the program to include certain rural hospitals while exempting these hospitals from receiving discounts on drugs that are designated to treat a rare disease or condition ("orphan drugs"). HHS's regulation promotes the two central goals embodied in this statutory scheme—lowering costs for hospitals and patients while ensuring that orphan uses are not discounted. PhRMA would have this Court eliminate much of the program's benefit to these hospitals, turning a drug discount program into one that freezes the high cost of many of the most expensive, commonly used medications. For these reasons, and as discussed in more detail below, *amicus curiae* SNHPA, America's Essential Hospitals, and NRHA request that this Court grant the motion for summary judgment of HHS and deny the motion for summary judgment of the Pharmaceutical Research and Manufacturers of America ("PhRMA" or "Plaintiff").

Congress enacted the 340B program in 1992 to require manufacturers to offer discounts on outpatient drugs to certain health care providers as a condition of the manufacturers' drugs being eligible for reimbursement under the Medicaid program and the Medicare Part B program.

Congress expanded the categories of hospitals eligible for the 340B program in 2010, but narrowed the obligation of manufacturers to offer 340B discounts for these new categories of hospitals by excluding orphan drugs. HHS adopted a regulation, effective October 1, 2013, to implement the statutory provision that excludes 340B pricing for orphan drugs when they are used for their orphan drug indications (the "Orphan Drug Rule").

Provisions of the Federal Food, Drug, and Cosmetic Act ("FFDCA"), known as the Orphan Drug Act, offer significant financial incentives to pharmaceutical manufacturers to develop orphan drugs.[1] The incentives offered to manufacturers for development of orphan drugs include tax credits, research grants, an exemption from the new drug application user fee, and a marketing exclusivity period. One study published in 2010 found that 43 brand name drugs with orphan designations each reached global annual sales of greater than $1 billion (known as "blockbuster" drugs).[2] Many of these drugs have an orphan indication but are more commonly used for non-orphan indications.[3] For example, Prozac (generic name Fluoxetine), which is commonly used to treat depression, has two orphan drug indications: for the treatment of body dysmorphic disorder in children and adolescents and for the treatment of autism.[4] Some pharmaceutically active agents can obtain up to 33 orphan designations each.[5]

The Orphan Drug Rule must be upheld because the plain language of the statute limits the orphan drug exclusion only to orphan uses and does not sweep in the many non-orphan uses

[1] Michael Berens & Ken Armstrong, *PhRMA's Windfall, The mining of rare diseases, Berens, M. and Armstrong K*, Seattle Times, Nov. 9, 2013, *available at* http://apps.seattletimes.com/reports/pharma-windfall/2013/nov/9/mining-rare-diseases/.
[2] Olivier Wellman-Labdie & Youwen Zhou, *The US Orphan Drug Act: Rare disease research stimulator or commercial opportunity?*, Health Policy 95 (2010) 216, 221-222, Table 3.
[3] *Id*. at p. 222.
[4] *See* HRSA, Orphan Drug Designations and Approvals List as of 12-02-2013, http://www.hrsa.gov/opa/programrequirements/orphandrugexclusion/orphandruglist.pdf.
[5] Olivier Wellman-Labdie & Youwen Zhou, *The US Orphan Drug Act: Rare disease research stimulator or commercial opportunity?*, Health Policy 95 (2010) 216, 225.

for which medications may be prescribed. Congress excluded "a drug designated by the Secretary under section 526 of the Federal Food, Drug, and Cosmetic Act ["FFDCA"] for a rare disease or condition." Health Care and Education Reconciliation Act of 2010, Pub. L. No. 111-152, § 2302; 42 U.S.C. § 256b(e). Designation under section 526 of the FFDCA applies only for purposes of specific diseases or conditions and does not apply for all uses of the drug. 21 U.S.C. § 360bb(a)(1). HHS's regulation is, therefore, compelled by the plain meaning of the statute, which applies the orphan drug exclusion only when the drugs are used to treat a rare disease or condition.

Even if the Court concludes that the statute is ambiguous, the regulation must also be upheld because it reasonably interprets the orphan drug exclusion to carry out Congress's goals behind the 340B program—to lower drug costs for certain safety-net hospitals and allow them to better serve their vulnerable patients. Invalidating the regulation and implementing the orphan drug exclusion in the manner suggested by PhRMA would eliminate many of the benefits of the 340B program for hospitals subject to the Orphan Drug Rule and their patients while retaining burdensome administrative costs. HHS's regulation is reasonable because it is consistent with congressional intent behind the orphan drug exclusion and balances the goals of the Orphan Drug Act and the 340B program.

In addition, the Court should not take the extraordinary step of issuing a preliminary injunction. PhRMA has not met the high standard necessary for a court to grant a preliminary injunction. Most fundamentally, it cannot show that its members will be irreparably harmed because retroactive adjustment payments can be made to drug manufacturers if PhRMA were to prevail in this litigation. An injunction also is not warranted because non-parties—hospitals and patients—would be harmed by losing important discounts. Hospital drug costs will increase,

leading to reduced services and increased drug costs for patients, and patients will find it more difficult to access certain types of care. Such harm to hospitals and patients cannot be rectified after the fact. An injunction during the pendency of this litigation would also be contrary to the public interest by raising costs to the Medicare and Medicaid programs.

III. BACKGROUND

A. Standard of Review for Agency Rulemaking

Judicial review of an agency's construction of a statute it administers is governed by *Chevron U.S.A., Inc. v. Natural Resources Defense Council, Inc.*, 467 U.S. 837 (1984); *see also United States v. Mead Corp.*, 533 U.S. 218 (2001). Under *Chevron*, there are two steps to a court's review: first, the court must determine whether Congress "has directly spoken to the precise question at issue." *Chevron*, 467 U.S. at 842-43. When analyzing a statute under *Chevron* step one, a court employs "traditional tools of statutory construction." *Chevron*, 467 U.S. at n.9. If Congress's intent is clear, then "that is the end of the matter; for the court, as well as the agency, must give effect to the unambiguously expressed intent of Congress." *Id.* If the statute is ambiguous, however, a court must uphold an agency's interpretation so long as it is "based on a permissible construction of the statute." *Id.*

B. Preliminary Injunctions

A preliminary injunction is an "extraordinary remedy" that may only be awarded upon a clear showing that the requestor is entitled to such relief. *Winter v. Natural Res. Def. Council., Inc.*, 555 U.S. 7, 22 (2008). A party is not entitled to a preliminary injunction unless it can show: (1) a substantial likelihood of success on the merits; (2) irreparable injury if the injunction is not granted; (3) that there will be no substantial injury to other interested parties, and (4) that the public interest would be served by the injunction. *Winter*, 555 U.S. at 20; *Sherley v. Sebelius*, 644 F.3d 388, 392 (D.C. Cir. 2011). Although courts apply these factors flexibly, a movant must

show some irreparable injury. *Chaplaincy of Full Gospel v. England*, 454 F.3d 290, 297 (D.C. Cir. 2006); *see also Sherley*, 644 F.3d at 393. A movant must meet a "high standard" to demonstrate irreparable injury by showing that the asserted injury is "certain and great" and "beyond remediation." *Chaplaincy of Full Gospel Churches*, 454 F.3d at 297.

C. The 340B Program and the Orphan Drug Rule

Congress enacted the 340B drug discount program in November 1992. Veterans Health Care Act of 1992, Pub. L. No. 102-585, § 602, 106 Stat. 4943, codified as Section 340B of the Public Health Service Act at 42 U.S.C. § 256b. The program, named for section 340B of the Public Health Service Act ("PHSA"), requires pharmaceutical manufacturers seeking reimbursement for their drugs under the Medicaid or Medicare Part B programs to enter into a pharmaceutical pricing agreement ("PPA") with HHS. 42 U.S.C. § 1396r-8. The terms of the PPA require manufacturers to provide discounts on "covered outpatient drugs" purchased by specified safety-net providers, known as "covered entities," that serve the nation's most vulnerable patient populations.[6] Health Resources and Services Administration ("HRSA"), Pharmaceutical Pricing Agreement, *available at* http://www.hrsa.gov/opa/manufacturers/pharmaceuticalpricingagreement.pdf. "Covered entities" include hospitals serving low-income or otherwise vulnerable patients as well as several other types of safety-net providers including community health centers, state and local health departments, HIV clinics, and hemophilia treatment centers. 42 U.S.C. § 256b(a)(4). To be eligible for 340B pricing, all hospital types must be "owned or operated by a unit of state or local government, a public or private non-profit corporation which has been formally granted governmental powers by a unit of state or local government, or a private non-profit hospital with

[6] Health care providers that treat a large number of particularly vulnerable people, such as those with low incomes, the elderly, or disabled, are commonly referred to as "safety-net providers."

a contract with a state or local government to provide health care services to low-income individuals who are not entitled to benefits under [Medicare or Medicaid]." 42 U.S.C. 256b(4)(L)(i).

Under the original 340B statute, eligible hospitals included only those designated under the Medicare program as disproportionate share hospitals ("DSH")—hospitals that treat a high percentage of low-income patients—and that have a DSH adjustment percentage of greater than 11.75%. Veterans Health Care Act of 1992, Pub. L. No. 102-585, § 602; 42 U.S.C. § 256b(a)(4)(L). In 2005, Congress expanded the program to include free-standing children's hospitals with a payer mix that would give them a DSH adjustment percentage of greater than 11.75%. Deficit Reduction Act of 2005, Pub. L. No. 109-171, § 6004.

As part of the Patient Protection and Affordable Care Act ("ACA"), Congress expanded the 340B program to include four additional categories of hospitals: 1) critical access hospitals ("CAHs"); 2) rural referral centers ("RRCs") with a DSH adjustment percentage of at least 8%; 3) sole community hospitals ("SCHs") with a DSH adjustment percentage of at least 8%; and 4) free-standing cancer hospitals with a payer mix that would give them a DSH adjustment percentage of greater than 11.75%.[7] ACA, Pub. L. No. 111-148, § 7101; 42 U.S.C. § 256b(a)(4)(M); 42 U.S.C. § 256b(a)(4)(N); 42 U.S.C. § 256b(a)(4)(O). Collectively, hospitals

[7] Under the Medicare program, a hospital may be designated as a CAH, RRC, SCH, or free-standing cancer hospital if the hospital meets certain criteria, and the designation generally allows the hospital more favorable Medicare reimbursement. Generally, a CAH must be located in a rural area that does not otherwise have ready access to hospital services, have 25 or fewer inpatient beds, and have an average length of stay of 96 hours or less. 42 C.F.R. § 485 Subpart F. RRCs are hospitals located in rural areas that either have 275 or more beds or that admit at least 50% of patients from other hospitals or from non-staff physicians and serve a large proportion of patients who live at least 25 miles away. 42 U.S.C. § 1395ww(d)(5)(C)(i); 42 C.F.R. § 412.96. SCHs are hospitals that are located more than 35 miles from other similar hospitals or are located in a rural area and meet other criteria related to the need for the hospital in its geographic area. 42 U.S.C. § 1395ww(d)(5)(D)(iii); 42 C.F.R. § 412.92. A free-standing cancer hospital is one that has been recognized by the National Cancer Institute of the National Institute of Health as a comprehensive cancer center or clinical cancer research center as of certain dates and meets other criteria or that HHS designated as a cancer hospital before 1990. 42 U.S.C. § 1395ww(d)(1)(B)(v).

registered in the 340B program under these categories accounted for approximately 3.13% of all 340B drug sales in fiscal year 2012. Final Rule, Exclusion of Orphan Drugs for Certain Covered Entities Under 340B Program, 78 Fed. Reg. 44,016, 44,026 (July 23, 2013).

One week after the ACA's passage, Congress enacted an amendment applicable to CAHs, RRCs, SCHs, and cancer hospitals ("affected hospitals") that excluded from 340B pricing "a drug designated by the Secretary under section 526 of the Federal Food, Drug, and Cosmetic Act ["FFDCA"] for a rare disease or condition." Health Care and Education Reconciliation Act of 2010, Pub. L. No. 111-152, § 2302; 42 U.S.C. § 256b(e). Section 526 of the FFDCA, 21 U.S.C. § 360bb, permits the Secretary of HHS to designate a drug as a drug for a rare disease or condition, defined as a disease that either affects fewer than 200,000 people in the United States or more than 200,000 if there is no reasonable expectation that the costs of developing a drug for the condition would be recouped. 21 U.S.C. § 360bb(a)(2).

Some examples of commonly used orphan drugs are Prozac, Herceptin, Remicade, Avastin, and Rituxan. In granting these drugs an orphan designation, HHS's Food and Drug Administration ("FDA") has said that these drugs have the potential to treat a number of rare diseases and conditions. Nevertheless, these drugs are often used to treat indications other than the indications for which they received their orphan designations, some of which are quite common. For example, Herceptin is commonly used to treat breast and stomach cancer, but its rare orphan indications are for an advanced stomach cancer and for a particular pancreatic cancer. Avastin is commonly used to treat colorectal and lung cancer, but its rare orphan indications include a particular stomach cancer. FDA, Search Orphan Drug Designations and Approvals, *available at* http://www.accessdata.fda.gov/scripts/opdlisting/oopd/ (last accessed Dec. 17, 2013) ("FDA Database").

In selling these and other orphan drugs for use in treating both rare and common diseases, drug manufacturers make significant profits. Recent media coverage of orphan drug development has focused on how manufacturers reap large profits on orphan drugs that are often, if not primarily, used to treat common disorders. For example, Botox has an orphan designation but is well-known to be used to remove wrinkles and generated $1.8 billion last year in sales. Rituxan brought in over $7 billion in revenue last year, the most of any orphan drug, and is commonly used to treat rheumatoid arthritis, multiple sclerosis and autoimmune anemia. Michael J. Berens and Ken Armstrong, *PhRMA's Windfall: The Mining of Rare Diseases*, Seattle Times (Nov. 9. 2013), *available at* http://apps.seattletimes.com/reports/pharma-windfall/2013/nov/9/mining-rare-diseases/ (last accessed Dec. 9, 2013).

Researchers have found that even though orphan drugs may treat a small number of patients as compared to the total patient population, manufacturers stand to generate as much revenue from orphan drugs as they do from non-orphan drugs because of the incentives available to develop orphan drugs and the exorbitant prices at which manufacturers sell them. Thompson Reuters, *The Economic Power of Orphan Drugs*, 2012, *available at* http://thomsonreuters.com/products/ip-science/04_013/1001450.pdf (last accessed Dec. 9, 2013); Kiran N. Meekings, Cory S.M. Williams & John E. Arrowsmith, *Orphan drug development: an Economically Viable Strategy for Biopharma R&D*, Drug Discovery Today, July 2012, *available at* http://csmres.co.uk/cs.public.upd/article-downloads/Meekings-Reuters-paper.pdf (last accessed Dec. 9, 2013). Many of these drugs can cost patients up to $300,000 per year or more. *See* Max Nisen, *$300,000 A Year 'Orphan Drugs' Are Becoming A Hugely Profitable Business*, Business Insider, Jan. 31, 2013, *available at* http://www.businessinsider.com/the-business-of-orphan-drugs-2013-1 (last accessed Dec. 9, 2013); Jonathan D. Rockoff, *Drug Makers See Profit*

Potential in Rare Diseases, Wall Street Journal, Jan. 30, 2013, *available at* http://online.wsj.com/news/articles/SB10001424127887323926104578273900197322758 (last accessed Dec. 9, 2013). In the last year, there have been an increasing number of news media accounts of large drug manufacturers pursuing orphan drug development to increase their profits. *See Id.*; Michael J. Berens and Ken Armstrong, *PhRMA's Windfall: The Mining of Rare Diseases*, Seattle Times, Nov. 9. 2013, *available at* http://apps.seattletimes.com/reports/pharma-windfall/2013/nov/9/mining-rare-diseases/ (last accessed Dec. 9, 2013); Katie Thomas, *Making "Every Patient Count" a Business Imperative*, New York Times, Jan. 30, 2013, *available at* http://www.nytimes.com/2013/01/31/business/orphan-drugs-for-rare-diseases-gain-popularity-with-pharmaceutical-companies.html?partner=rss&emc=rss&_r=1& (last accessed Dec. 11, 2013).

On July 23, 2013, HRSA published the Orphan Drug Rule, a final regulation to implement the ACA's orphan drug exclusion for affected hospitals, which went into effect October 1, 2013. 78 Fed. Reg. 44,016. The Orphan Drug Rule makes clear that 340B pricing is not available to affected hospitals for an orphan drug when the drug is used to treat the rare disease or condition for which the drug received its orphan designation. *Id.* at 44,027. More specifically, the Orphan Drug Rule defines the orphan drug exclusion to apply to "orphan drugs that are transferred, prescribed, sold, or otherwise used for the rare condition or disease for which that orphan drug was designated" as orphan by the FDA, making these drugs ineligible for 340B pricing when used for an orphan indication. *Id.* Discounted 340B pricing is available, however, for an orphan drug when the hospital uses it to treat indications other than the rare disease or condition for which the drug received its designation. *Id.* Stated differently, the Orphan Drug Rule allows affected hospitals to use 340B pricing for orphan drugs that are "transferred,

prescribed, sold, or otherwise used for any medically-accepted indication other than treating the rare disease or condition for which the drug was designated" as an orphan drug by the FDA. *Id.* In the case of Prozac, for example, an affected hospital could purchase the drug at 340B discounts if it were used to treat depression, its common purpose, but an affected hospital would have to purchase the drug outside the 340B program if it were used to treat either of its two orphan indications. Under the interpretation of the orphan drug exclusion advanced by PhRMA, affected hospitals would not be able to purchase Prozac at 340B discounts under any circumstances, regardless of how the drug is used.

Acknowledging the critical importance of compliance, HHS's Orphan Drug Rule requires hospitals to maintain auditable records to verify that each orphan drug that it purchases at a 340B price is used for a purpose other than the rare disease or condition for which the drug received its designation. *Id.* at 44,028. If a hospital cannot, or does not, wish to maintain this detailed documentation, it can elect to purchase orphan drugs at non-discounted prices regardless of the indication for which it used the drug. *Id*. The former hospitals are generally referred to as "opt-in" hospitals and the latter are referred to as "opt-out" hospitals.

The Orphan Drug Rule requires an affected hospital to notify HRSA of its opt-in or opt-out choice so that HRSA can make this information available on its website to stakeholders. *Id.* Each hospital will be required to verify its choice annually.[8] *Id*. at 44,018-19. Affected hospitals that are new to the program are required to notify HRSA of their choices during the registration

[8] Health Resources and Serv. Admin., OPA Database Guide for Public Users-Recertification, 12 (Aug. 2013), *available at* http://opanet.hrsa.gov/opa/Manuals/OPA%20Database%20Guide%20for%20Public%20Users%20-%20Recertification.pdf (last accessed Oct. 19, 2013).

process.[9] Hospitals may change their opt-in/opt-out decisions on a quarterly basis by notifying HRSA. 78 Fed. Reg. at 44,028.

IV. THE COURT SHOULD GRANT HHS'S SUMMARY JUDGMENT MOTION AND DENY PHRMA'S SUMMARY JUDGMENT MOTION BECAUSE THE ORPHAN DRUG RULE VALIDLY IMPLEMENTS THE STATUTE

A. The Orphan Drug Rule Is Compelled by the Plain Meaning of the Statute

The Orphan Drug Rule is compelled by the plain meaning of the statute and must, therefore, be upheld under *Chevron* step one, 467 U.S. at 842-43.[10] The statutory orphan drug exclusion is clear because it incorporates section 526 of the FFDCA (21 U.S.C. § 360bb) which states that an orphan drug designation is specific to the rare disease or condition for which the designation is granted. 21 U.S.C. § 360bb. More specifically, the 340B orphan drug exclusion applies to "a drug designated by the Secretary *under section 360bb of Title 21 for a rare disease or condition*." 42 U.S.C. § 256b(e) (emphasis added). Section 526 of the FFDCA, codified at 21 U.S.C. § 360bb(a)(1), uses identical language, requiring the Secretary to grant orphan designation "for a rare disease or condition." The condition-specific designation in Section 526 of the FFDCA is incorporated into the 340B orphan drug exclusion. HHS's Orphan Drug Rule merely carries out this plain statutory mandate, and the rule must be upheld under *Chevron* step one.[11]

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[9] Health Resources and Serv. Admin., OPA Database Guide for Public Users-Covered Entity, 26 (Aug. 2013), *available at* http://opanet.hrsa.gov/opa/Manuals/OPA%20Database%20Guide%20for%20Public%20Users%20-%20Covered%20Entity.pdf (last accessed Dec. 19, 2013).

[10] Although neither party has argued that the Orphan Drug Rule must be upheld under *Chevron* step one, PhRMA argues the contrary, that the Rule should be invalidated under *Chevron* step one. Accordingly, the *Chevron* step one issue is squarely before the Court, and "the court, as well as the agency, must give effect to the unambiguously expressed intent of Congress." *Chevron*, 467 U.S. at n.9. Moreover, a Court may consider an argument first raised in an *amicus* brief. *Teague v. Lane*, 489 U.S. 288, 300 (1989).

[11] PhRMA cites several statements by SNHPA indicating that the statutory orphan drug exclusion should be "interpreted" to apply only to orphan indications. Memo. of Pt.s & Auth. in Supp't of Pl.'s Mot. for S.J. (PhRMA's Brief") at 6-8, 24-25 [Dkt. No. 25]. Subsequent research and analysis of the interplay between the 340B statute and section 526 of the Orphan Drug Act revealed that no interpretation is necessary because the statute unambiguously

An orphan drug designation is for a single rare disease or condition and not for all diseases or conditions that the drug might treat. The Secretary designates a drug as "a drug for a rare disease or condition" under the FFDCA only if she "finds that a drug [or biologic] for which a request is submitted . . . is being or will be investigated for a rare disease or condition and . . . the approval, certification, or license [of the drug or biologic] would be for use for such disease or condition." 21 U.S.C. § 360bb(a)(1). If all requirements are met, "the Secretary shall designate the drug as a drug for such disease or condition." *Id.* If the Secretary later approves the drug to be marketed for that orphan condition, the Secretary may not approve another application "for such drug for such disease or condition" for another manufacturer for seven years.[12] *Id.* § 360cc(a). The Congress that enacted the Orphan Drug Act was clear that an orphan drug designation is specific to a particular use of the drug: "Many of the currently marketed drugs for rare diseases are also used in common diseases. The designation process established by the bill avoids this confusion *by designating the use of the drug which is for a rare disease or condition*. H.R. Rep. No. 97-840 at 9 (1982) (emphasis added).

The Fourth Circuit held that the statutory phrase "for such disease or condition" in the FFDCA expresses Congress's unambiguous intent that the manufacturer protections for orphan drugs are "disease-specific, not drug-specific." *Sigma-Tau Pharm. v. Schwetz*, 288 F.3d 141, 145 (4th Cir. 2002); *see also Baker Norton Pharm., Inc. v. U.S. Food & Drug Admin.*, 132 F. Supp. 2d 30, 37 (D.D.C. 2001) ("the market exclusivity rights are limited in time to seven years,

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applies the exclusion only to orphan indications. In any event, PhRMA's emphasis on prior statements by "stakeholders" is a red herring that is wholly irrelevant to the Court's analysis of the plain language of the statute.

[12] The FDA grants orphan designation to a drug separately from approving the drug to be marketed for its orphan indication. Nevertheless, both approvals are condition-specific. The FDA grants an orphan designation to a drug for a particular use, 21 U.S.C. § 360bb, and if the FDA later approves "such drug" to be marketed "for such disease or condition," the FDA may not grant marketing approval to another manufacturer for that drug for the *same* use for seven years. *Id.* § 360cc(a). *See also Sigma-Tau Pharm. v. Schwetz*, 288 F.3d 141, 145 (4th Cir. 2002). The FDA could, however, grant marketing approval to another manufacturer for that drug for a *different* use. *Id.*

and granted only for a particular drug for a particular use. Nothing prevents subsequent applicants from obtaining FDA approval for the same drug for a different use, or a different drug for the same use, or a clinically superior drug with the same active moiety for the same use."). The court upheld the Secretary's disease-specific interpretation of the FFDCA under *Chevron* step one because "the statute as written protects uses, not drugs for any and all uses." *Sigma-Tau Pharm.*, 288 F.3d at 145.

The Secretary's regulations under the FFDCA interpreting the incentives available to manufacturers to develop orphan drugs also limit those protections to specific orphan uses. The Secretary's regulations permit multiple manufacturers to have simultaneous marketing exclusivity for the same drug, but for different conditions. 21 C.F.R. § 316.31(b) (stating that "[o]rphan-drug exclusive approval protects only the approved indication or use of a designated drug"); *see also* 21 C.F.R. § 316.20(a) (regarding multiple sponsors submitting requests for orphan designations on the same drug). As stated above, Prozac has two orphan drug indications. The FDA granted one orphan indication, to treat body dysmorphic disorder in children and adolescents, to Eric Hollander, M.D. and a second indication, to treat autism, to Neuropharm, Ltd.[13] Accordingly, an orphan designation is only for the particular use of the drug for which it received its orphan designation.

Statements by key members of Congress knowledgeable of both the 340B program and the Orphan Drug Act confirm that the statutory orphan drug exclusion applies only to orphan uses. Senator Tom Harkin and Representative Henry Waxman, the Chairmen of the committees with jurisdiction over the 340B program when Congress enacted the orphan drug exclusion, supported HHS's proposed rule to implement the orphan drug exclusion because it was

[13] Olivier Wellman-Labdie & Youwen Zhou, *The US Orphan Drug Act: Rare Disease Research Stimulator or Commercial Opportunity?*; 95 Health Policy 216, 225 (2010).

"consistent with legislative intent, which was that the exclusion of orphan drugs from the 340B program for affected entities be construed as a narrow exclusion, applying only when drugs are legitimately used for rare diseases or conditions designated under Section 526 [of the FDCA]." Administrative Record ("AR"), at 335. Senators Harkin and Waxman also noted that an orphan designation under Section 526 includes:

> two components: the drug itself and the indication for which it is designated under Section 526. The same drug can be either a Section 526 designated drug or not a Section 526 designated drug depending on whether it is used for the indication described in Section 526 for that drug.

Id. These statements show that Congress understood the orphan drug exclusion to apply only to orphan uses of designated drugs. Although Congress made a technical amendment to the orphan drug exclusion several months after its initial passage, Congress had no reason to amend the exclusion to limit it to particular uses because the statute already included this limitation.[14] Medicare and Medicaid Extenders Act of 2010, Pub. L. No. 111-309, § 204.

The 340B statutory orphan drug exclusion, which incorporates FFDCA § 526, unambiguously applies only to drugs that are used for their orphan conditions and does not exclude those same drugs when used for other conditions. HHS complied with this statutory mandate in the Orphan Drug Rule by excluding orphan drugs from 340B pricing only when they are used for the rare disease or condition for which they were designated. To do otherwise, and to exclude all orphan drugs regardless of use, would ignore the plain statutory language that specifically refers to "a rare disease or condition" and incorporates the disease-specific

[14] Although children's hospitals were eligible under the Social Security Act for 340B pricing prior to the ACA, the ACA made children's hospitals eligible for 340B under the same subsection of the Public Health Service Act (PHSA) where all other 340B eligibility standards are listed. This had the effect of including children's hospitals under the orphan drug exclusion, though they were not technically new to the program as affected hospitals. The technical amendment had the effect of allowing children's hospitals to remain eligible for 340B discounts on all orphan drug uses, just like all other hospitals that were part of 340B prior to the ACA.

limitations of FFDCA § 526. HHS's Orphan Drug Rule complies with the plain language of the statute by applying the orphan drug exclusion only to orphan drugs when they are used for their orphan indications. The Orphan Drug Rule must be upheld under *Chevron* step one. *Chevron*, 467 U.S. at 842-43.

B. Even if the Statutory Orphan Drug Exclusion Were Ambiguous, HHS's Interpretation Is Reasonable and Must Be Upheld Under *Chevron* Step Two

PhRMA contends that the Orphan Drug Rule is invalid because the statute unambiguously requires exclusion of orphan drugs even when they are administered for a non-orphan purpose. As explained above, the incorporation of FFDCA § 526 in the 340B statute's orphan drug exclusion compels the opposite conclusion—drugs may only be excluded when used for an orphan indication. But, even if the Court should disagree that the Orphan Drug Rule must be upheld under *Chevron* step one, it must then proceed to *Chevron* step two. Under the highly deferential *Chevron* step two analysis, a court must uphold HHS's regulation so long as it is reasonable and even if the Court concludes that other constructions of the statute would be permissible or even more desirable. *Chevron*, 467 U.S. at 843 n.11. When assessing the reasonableness of an agency interpretation under *Chevron* step two, a court should consider the purpose of the statute and any relevant legislative history. *Chevron*, 467 U.S. at 845. The Orphan Drug Rule must be upheld under *Chevron* step two because the Rule reasonably aligns the 340B statute with the FFDCA and furthers the purpose of the 340B statute to lower costs for hospitals and patients and to increase patient access to life-saving treatments.

1. The Orphan Drug Rule Reasonably Interprets the Statute Because It Aligns the 340B Orphan Drug Exclusion With the FFDCA

HHS's interpretation of the statutory orphan drug exclusion is clearly reasonable. It is entirely rational for HHS, which administers both the 340B program and the FFDCA, to have interpreted the exclusion to apply only when an orphan drug is used for its orphan indication.

Therefore, even if there are other permissible interpretations of the statutory exclusion, the Court must uphold HHS's interpretation. *See, e.g., Chevron*, 467 U.S. at 843 n.11; *Nat'l Cable & Telecom. Ass'n v. Brand X Internet Servs.*, 545 U.S. 967, 980 (2005) (citing *Chevron*, 467 U.S. at 843–844) ("If a statute is ambiguous, and if the implementing agency's construction is reasonable, *Chevron* requires a federal court to accept the agency's construction of the statute, even if the agency's reading differs from what the court believes is the best statutory interpretation."); *Covad Comc'ns Co. v. FCC*, 450 F.3d 528, 537 (D.C. Cir. 2006) (applying *Brand X* in the D.C. Circuit to a Federal Communications Commission interpretation of a statute previously held to be ambiguous). Moreover, the Orphan Drug Rule reasonably balances the congressional intent to expand the 340B program to affected hospitals while maintaining the Orphan Drug Act's incentives for manufacturers to develop orphan drugs.

Both the FDA and HRSA are subcomponents of HHS. Because HHS is the federal agency empowered to implement both the 340B statute and the FFDCA, *Chevron* deference is owed to HHS's interpretation of both acts. *United States v. Mead Corp.*, 533 U.S. 218, 226–27 (2001); *Chevron*, 467 U.S. at 842-43; *see also Gonzales v. Oregon*, 546 U.S. 243, 258 (2006). HHS has reasonably interpreted the orphan drug exclusion consistently with its interpretation of the FFDCA to limit orphan designations to particular diseases or conditions and not to apply to non-orphan uses of drugs.

As HHS explained in the preamble to the Orphan Drug Rule, one purpose of the regulation is to "protect the financial incentives for manufacturing orphan drugs designated for a rare disease or condition as indicated in the Affordable Care Act and intended by Congress." 78 Fed. Reg. at 44,017. The FFDCA provides a number of incentives to manufacturers to encourage the development of these products, including "(1) 7-year market exclusivity to

sponsors of approved orphan products; (2) a tax credit of 50 percent of the cost of conducting qualified human clinical trials; (3) Federal research grants for clinical testing of these new therapies to treat and/or diagnose rare diseases; and (4) an exemption from the usual drug application 'user' fees charged by the FDA." *Id.*

HHS explained that the incentives to manufacturers to develop orphan drugs only apply with regard to use of the drug for its orphan indication and, quite logically, HHS determined that the orphan drug exclusion should also apply only to those instances. In the preamble to the final rule, HHS stated:

> First, the marketing exclusivity only applies if the drug has been approved by the FDA to be marketed for an orphan rare disease or condition, even if it has been approved by FDA for a common condition (non-rare use). Second, the tax credit must relate to testing of the drug for the rare disease or condition underlying the orphan designation and not for other diseases or conditions (non-rare uses). Third, the Federal research grants are for testing the treatment of rare diseases and not for other indications. Finally, the exemption from FDA user fee payments only applies to user fees charged when seeking marketing approval to treat the orphan designated rare disease or condition. The incentives associated with orphan drug designation do not apply to any indication for a disease or condition that has not itself received orphan drug designation (the product would not be considered to be an ''orphan drug'' for such additional uses).

78 Fed. Reg. at 44,017. Permitting 340B discounts on orphan drugs used for common indications does not reduce the financial incentives awarded by the government to help bring orphan drugs to the market. The purpose of providing these incentives is to help manufacturers that want to bring to market a drug to treat the rare disease or condition for which it receives an orphan designation. *Id.* In no way are those incentives connected to a manufacturer's marketing and selling of a drug for a common indication.

PhRMA is wrong that the Orphan Drug Rule undermines the incentives provided in the FFDCA to develop new orphan drugs. PhRMA presupposes that requiring manufacturers to offer 340B discounts on orphan drugs used to treat non-orphan indications will make it more

difficult for manufacturers to bring new orphan drugs to market. However, most orphan drug designations are held by manufacturers working to develop drugs that are not even on the market. There are 2,986 drugs with an orphan drug designation, but the vast majority of these drugs are not approved by the FDA to be marketed for any indication. Manufacturers of these products are not required to offer 340B discounts on them as they are not yet being sold.[15] FDA, Search Orphan Drug Designations and Approvals, *available at* http://www.accessdata.fda.gov/scripts/opdlisting/oopd/ (last accessed Dec. 19, 2013) ("FDA Database"). That means that the Orphan Drug Rule can have no financial impact on these drugs, because manufacturers may not market or sell these drugs. The Orphan Drug Rule can only impact drugs that are already approved and being marketed. Requiring manufacturers to provide 340B discounts on orphan drugs used for common indications would have no impact on a manufacturer's ability to develop most orphan products and eventually bring them to market.

PhRMA also ignores that drug manufacturers have been required to give 340B discounts on orphan drugs since the inception of the 340B program on all categories of covered entities (except the newly added affected hospitals) with no adverse impact on the development of new drugs to treat rare diseases or condition. The orphan drug exclusion applies only to a subset of 340B hospitals: CAHs, RRCs, SCHs, and cancer hospitals. According to HHS, these affected hospitals accounted for approximately 3.13% of all 340B drug sales in fiscal year 2012. 78 Fed. Reg. 44,016, 44,026. The exclusion does not apply to the large majority of hospitals and other categories of health care providers that were already eligible for 340B discounts when the ACA

[15] Of the 2,986 drugs with an orphan designation, 457 have been approved by the FDA to be marketed for the orphan indication. In conversations SNHPA has had with industry stakeholders, it has been told that there may be approximately 100 other drugs with an orphan designation that the FDA has not approved to be marketed for the orphan indication but have market approval for common indications. Therefore, under the final regulation, manufacturers are required to offer 340B discounts on only roughly 550 of the 2,986 drugs with an orphan designation, and even for those 550 drugs, only when they are used to treat a common indication.

was enacted, which have always received 340B discounts on orphan drugs, including when the drugs are used for orphan conditions. PhRMA presents no evidence that the 340B program has inhibited the development of orphan drugs. A 2010 study shows that orphan drug approvals have fluctuated since the inception of the 340B program in 1992, but approvals were higher in most years from 1993-2007 than they were in 1992, indicating that there is no relationship between the 340B program and incentives to develop orphan drugs. *The US Orphan Drug Act: Rare Disease Research Stimulator or Commercial Opportunity*, 220, Figure 3. In addition, the FDA's database shows that orphan designations have been robust during the life of the 340B program. http://www.accessdata.fda.gov/scripts/opdlisting/oopd/.

Regardless of the Orphan Drug Rule, manufacturers will continue to access incentives from the FDA to help develop these drugs and bring them to market. The impact of the Orphan Drug Rule on manufacturers is minimal, but the stakes for affected hospitals are significant. The Orphan Drug Rule balances the needs of these two stakeholder groups and the congressional intent behind the 340B and Orphan Drug programs. HHS gave a supremely rational explanation for its interpretation of the bounds of the orphan drug exclusion. HHS's Orphan Drug Rule is a reasonable interpretation of the statutory orphan drug exclusion and must be upheld.

2. The Orphan Drug Rule Reasonably Interprets the Statute Because It Carries Out the Purposes of the 340B Program

Congress intended the 340B program to benefit safety-net hospitals, not pharmaceutical companies. *See Univ. Med. Ctr. of S. Nev. v. Shalala*, 173 F.3d 438, 439 (D.C. Cir. 1999). When Congress debated the creation of the 340B program, the House Energy and Commerce Committee issued a lengthy report discussing the program and its purpose.[16] H.R. Rep. No. 102-

[16] The committee's report accompanied H.R. 2890, 102nd Cong. (1992). H.R. 2890 was passed by the House of Representatives on September 22, 1992 and was incorporated into H.R. 5931, which became the Veteran's Health

384(II) (1992), *reprinted in* 1992 WL 239341. The report stated that the statute's "purpose is to enable" covered entities to "obtain lower prices on the drugs that they provide to their patients." *Id.* at *7. The report also noted that Congress was concerned because drug prices had "increased substantially over the past two years," which "have in turn reduced the level of services and the number of individuals that these hospitals and clinics are able to provide with the same level of resources." *Id.* at *11. Thus, Congress concluded that "the Federal government simply cannot continue to allow" covered entities "and their patients to remain unprotected against manufacturer price increases." *Id.* The 340B statute is intended to accomplish Congress's goal of lowering drug costs to these safety-net providers and allowing them to better serve their vulnerable patients: "In giving these 'covered entities' access to price reductions the Committee intends to enable these entities to stretch scarce Federal resources as far as possible, reaching more eligible patients and providing more comprehensive services." *Id.* at *12.

a. The Orphan Drug Rule Reduces Drug Costs for Hospitals

The Orphan Drug Rule furthers Congress's statutory purpose to lower costs for affected hospitals. SNHPA conducted an electronic survey of its member hospitals that are subject to the Orphan Drug Rule, which 111 hospitals completed. Exhibit 2.[17] SNHPA's survey found that affected hospitals electing to "opt-in" for the Orphan Drug Rule as of October 1, 2013, and purchase orphan drugs through the 340B program expected to save significant sums over the next year, ranging from $20,000 to over $2 million, with the median expected savings around $100,000. Exhibit 2, page 4. Affected hospitals also reported that, if they could not use 340B pricing for non-orphan indications of orphan drugs, their total outpatient drug spending over the

Care Act of 1992, Pub. L. No. 102-585. Joint Expl. Statement on H.R. 5193, *reprinted in* 1992 U.S.C.C.A.N. 4186. The 340B provisions in the final bill that was signed into law relied primarily on H.R. 2890. *Id.* at 4211.

[17] An Affidavit from SNHPA General Counsel Maureen Testoni explaining the survey results is attached as Exhibit 1.

next year would increase by 19%. Exhibit 2, pages 24-26. Similarly, an independent study published in 2012 found that CAHs participating in the 340B program estimated that annual average savings on orphan drugs in 2010 would have been 14% of their total drug budgets, or $171,000 per hospital. Madeline Carpinelli Wallack and Todd Sorensen, *Excluding Orphan Drugs From the 340B Drug Discount Program: The Impact on Critical Access Hospitals*, 3 Innovations in Pharmacy 1, 3 (2012), *available at* http://www.pharmacy.umn.edu/innovations/prod/groups/cop/@pub/@cop/@innov/documents/article/cop_article_376464.pdf. CAHs represent 842 of the 1,012 affected hospitals, which is the vast majority of hospitals subject to the orphan drug exclusion.[18]

Access to 340B discounts for orphan drugs when they are used for common indications has a significant impact on hospital savings because orphan drugs are more expensive than non-orphan products and therefore account for a large percentage of total hospital outpatient drug spending. The Wallack and Sorensen study found that for the CAHs surveyed, orphan drugs were eight to nine times more expensive than non-orphan drugs. *Id.* Even though orphan drugs accounted for only 5% of the drugs purchased by the surveyed hospitals, orphan drug spending represented 44% of the hospitals' total drug spending.[19] *Id.*

SNHPA surveyed opt-in hospitals purchasing orphan drugs through the 340B program about their use of four frequently-used orphan drugs, and the hospitals reported using the drugs for common indications more than 50% of the time for three of these drugs.[20] Exhibit 2, pages

[18] These figures were derived by review of the OPA database November 20, 2013. Health Resources and Serv. Admin., OPA Covered Entity Database, *available at* http://opanet.hrsa.gov/opa/CESearch.aspx (last accessed Dec. 19, 2013).
[19] Drugs are identified by their national drug codes or NDCs, which are a universal product identifier for drugs. A list of NDCs is available on the website of the Food and Drug Administration. FDA, *National Drug Code Directory*, http://www.fda.gov/drugs/informationondrugs/ucm142438.htm (last accessed on Dec. 20, 2013).
[20] When asked how frequently they use Prozac, Herceptin, Remicade, Avastin and Rituxan to treat common indications, opt-in hospitals reported the following: 69% use Prozac for a common purpose at least half the time,

11-15. Because hospitals generally use orphan drugs to treat common indications more often than rare diseases, HHS's Orphan Drug Rule would greatly benefit affected hospitals by reducing the cost of the relatively small number of expensive orphan drugs purchased by affected hospitals. Conversely, the interpretation promoted by PhRMA would significantly undermine the benefit to affected hospitals and their patients of participation in the 340B Program.

b. The Orphan Drug Rule Allows Hospitals to Stretch Their Resources to Better Serve Vulnerable Patients

The Orphan Drug Rule also furthers Congress's goal of providing safety net hospitals with the resources necessary to serve their vulnerable patients. As noted above, the purpose of the 340B program is to allow eligible health care providers, "to stretch scarce Federal resources as far as possible, reaching more eligible patients and providing more comprehensive services." H.R. Rep. No. 102-384 (II), at 12 (1992). The Orphan Drug Rule carries out this goal, and if the Court were to invalidate it, 340B hospitals and their patients would be negatively impacted in a number of ways. SNHPA's survey results show how invalidating the Orphan Drug Rule would be inconsistent with Congress's goal of serving vulnerable patients. A significant percentage of affected hospitals would consider withdrawing from the 340B program if HHS were not able to

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with 56% using the drug for a common purpose nearly all the time. Prozac is commonly used to treat depression, whereas its orphan indications are autism and body dysmorphic disorder in children and adolescents. Sixty-three percent use Herceptin for a common purpose at least 50% of the time, with 39% using the drug for a common purpose almost all the time. Herceptin is commonly used to treat breast and stomach cancer, and its orphan indications are HER2-overexpressing advanced adenocarcinoma of the stomach, including gastroesophageal junction and pancreatic cancer that overexpresses p185HER2. Sixty-one percent use Remicade for a common purpose at least half the time. Remicade is commonly used to treat rheumatoid arthritis, but its orphan indications are chronic sarcoidosis, pediatric Crohn's Disease, pediatric ulcerative colitis, giant cell arteritis, Crohn's disease and juvenile rheumatoid arthritis. Lastly, 52% use Avastin for a common purpose at least half the time, with 24% using the drug for a common purpose almost all the time. Avastin is commonly used to treat colorectal and lung cancer, but its orphan indications are stomach cancer (in combination with a platinum and 5-FU or capecitabine), melanoma stages IIb through IV as part of a combination chemotherapy regimen, malignant glioma, renal cell carcinoma, fallopian tube carcinoma, pancreatic cancer and primary peritoneal carcinoma. Only with regard to Rituxan did respondents report not using the drug to treat a common indication at least half the time, with only 32% of respondents reporting a common use at least 50% of the time. Rituxan is commonly used to treat certain types of cancer, including leukemia and lymphoma, as well as rheumatoid arthritis. Its orphan indications are anti-neutrophil cytoplasmic antibody-associated vasculitis (Wegener's Granulomatosis, Microscopic Polyangiitis, and Churg-Strauss Syndrome), chronic lymphocytic leukemia and immune thrombocytopenic purpura.

implement the Orphan Drug Rule, which would force them to curtail staff and services, increase costs to patients, and limit access to care for vulnerable patients.[21]

i. The Orphan Drug Rule Allows Hospitals to Provide More Services

The Orphan Drug Rule permits affected hospital to increase the services that they provide to patients. Affected hospitals are willing to bear the administrative complexity and costs of complying with 340B requirements, but withdrawing the critical discounts for non-orphan uses of orphan drugs would severely undermine the benefits, leading many to leave the program altogether. SNHPA's survey results indicate that, of opt-in hospitals (i.e., those that chose to track their orphan drug use so they can be purchased through 340B), 17% would be "very likely" or "somewhat likely" to withdraw from 340B if the Orphan Drug Rule is invalidated. Exhibit 2, page 6. Another 10% indicated that they were not sure if they would withdraw. *Id.* Of those hospitals indicating that they would withdraw, 67% said withdrawing from the program would force them to reduce pharmacy services, 58% reported they would make staff reductions, another 58% reported they would reduce pharmacy-related services, such as medication therapy management and disease management programs, and 50% indicated they would have to institute more restrictive formularies. These hospitals also reported that they would be forced to close outpatient pharmacies and clinics. Exhibit 2, page 7.

Even opt-out hospitals (i.e., those that do not currently purchase orphan drugs through the 340B program) expressed concern that invalidating the Orphan Drug Rule would impact their patients, as many of these hospitals plan to adopt tracking systems in the future so they can use 340B pricing for orphan drugs. For this reason, 22% of opt-out hospitals reported that they were

[21] Note that SNHPA's survey provided respondents a number of choices as to the impact on their patients if PhRMA's lawsuit were successful and affected hospitals could no longer receive 340B discounts on any orphan drugs, regardless of use. The survey invited respondents to select all options that applied to the institution. Therefore, results do not add up to 100%.

"very likely" or "somewhat likely" to withdraw from the 340B program if their hospital no longer had the ability to purchase orphan drugs through 340B in the future because they had expected the future benefit of receiving discounts on non-orphan uses of orphan drugs. Exhibit 2, page 2. Withdrawing from the 340B program would mean losing access to all 340B savings, which would impact the ability of hospitals to serve their patients. Of the hospitals reporting that they would withdraw from 340B, 67% said they would be forced to reduce pharmacy services and 67% also said they would reduce pharmacy-related services. Forty-four percent said they would reduce non-pharmacy-related programs, such as patient outreach and education, another 44% reported they would make staff reductions, and 44% said they would have to institute more restrictive formularies. Exhibit 2, page 3.

Some affected hospitals that are currently buying orphan drugs through the 340B program reported that they would continue to participate in 340B even if they could not access 340B discounts on orphan drugs when used for common indications. However, many of these hospitals reported that they would nevertheless be forced to cut staff and services due to higher drug costs. More specifically, 29% reported that they would be forced to institute more restrictive pharmacy formularies, 28% said they would reduce non-pharmacy-related programs, 26% would reduce pharmacy-related services, another 26% would reduce pharmacy services, and another 24% said they would be forced to make staff reductions. Exhibit 2, page 8.

ii. The Orphan Drug Rule Allows Hospitals to Lower Drug Costs for Patients

The Orphan Drug Rule enables participating hospitals to better serve their patients by lowering costs so that hospitals can afford to offer drugs to low-income patients for free or at reduced prices. Invalidating the Rule would inhibit the ability of hospitals to provide drugs at lower costs. In SNHPA's survey, 17% of opt-in hospitals that would withdraw from the 340B

program if the Orphan Drug Rule is invalidated reported that doing so would directly impact patient costs. Of these hospitals, 83% stated that their uninsured and underinsured patients would experience higher drug costs. Exhibit 2, page 7. A similar impact can be anticipated among opt-out hospitals that are not currently using 340B for orphan drugs but would withdraw if the Rule is invalidated because they had anticipated accessing 340B discounts in the future on non-orphan uses of orphan drugs. Sixty-seven percent of those answering the question said their uninsured and underinsured patients would see higher drug costs. Exhibit 2, page 3.

Even hospitals reporting that they would continue to participate in 340B if they could not access discounts on orphan drugs for any use would still face increased drug costs, and they also reported that their loss of savings would directly impact patient care. Of these hospitals, 52% reported that their uninsured and underinsured patients would face higher drug costs due to the loss of savings. Exhibit 2, page 8.

Lowering drug costs not only saves money for low-income patients, but has clinical benefits as well. A recent survey found that 45% of Americans under 65 who did not have prescription coverage in 2012 did not fill their prescriptions because of the cost, up from 27% the year before. Ann Carins, *Many Struggling With Prescription Drug Costs*, NY Times Bucks Blog (Sept. 13, 2012 1:13 pm), http://bucks.blogs.nytimes.com/2012/09/13/many-struggling-with-prescription-drug-costs/?_r=0 (last accessed Dec. 17, 2013). Whether a patient can afford a drug is one of the key predictors of whether the patient will take a prescribed medication and adhere to the directed treatment. Nat'l Cmty Pharmacists Assoc., *Medication Adherence in America: A National Report Card*, http://www.ncpanet.org/pdf/reportcard/AdherenceReportCard_Full.pdf (last accessed Dec. 12, 2013). Following a health care provider's instructions and adhering to prescribed treatment protocols can lead to improved health outcomes. Reducing the cost of

drugs can help achieve this goal. *Cf.* David M. Cutler & Wendy Everett, *Thinking Outside the Pillbox – Medication Adherence a Priority for Health Care Reform*, 362 N. Engl. J. Med. 1553 (Apr. 29, 2010), *available at*: http://www.nejm.org/doi/full/10.1056/NEJMp1002305 (last accessed Dec. 12, 2013).

iii. The Orphan Drug Rule Allows Hospitals to Improve Access to Care for Vulnerable Patients

The Orphan Drug Rule also furthers Congress's 340B program goal of improving patient care by enabling hospitals to provide high-cost therapies and services to low-income patients who otherwise would not have access to these therapies in their local communities. In response to SNHPA's survey and in conversations with SNHPA, a number of hospitals noted that the Rule will make it easier for patients to access specific life-saving therapies, in particular, certain specialty infusion services such as chemotherapy and treatment for rheumatoid arthritis. The provision of specialty infusion and chemotherapy services in rural hospitals allows patients to access care more conveniently in their local communities. Rural hospitals frequently report that often there are no health care providers offering these services in their communities. Because these infusion products tend to be some of the most expensive on the market, access to discounts on these products through the 340B program can enable rural hospitals to provide these therapies and expand patient access to care.[22] *See* Madeline Carpinelli Wallack & Todd Sorensen, *Excluding Orphan Drugs from the 340B Drug Discount Program: the Impact on 18 Critical Access Hospitals*, 3 Innovations in Pharmacy 1, Table 2 (2012),

[22] The Wallack and Sorenson study of CAH outpatient drug spending in 2010 found that of the top ten products with the highest 340B savings potential, listed in Table 2, all ten were specialty infusion or chemotherapy products. *See* Food and Drug Administration, Drugs@FDA: *FDA Approved Drug Products*, (providing labeling and approval information for each drug in the CAH study and identifying it as a chemotherapy or infusion drug) http://www.fda.gov/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm111085.htm#R (last visited Dec. 11, 2013).

http://www.pharmacy.umn.edu/innovations/prod/groups/cop/@pub/@cop/@innov/documents/article/cop_article_376464.pdf (last accessed Oct. 9, 2013).

For example, one CAH located 50-60 miles from a metropolitan area reported that 340B savings allow the hospital to contract with oncologists to come to the hospital and offer chemotherapy services in its rural community. Under the Orphan Drug Rule, the hospital anticipates saving an additional $200,000 to $300,000 per year by purchasing orphan drugs used to treat non-orphan indications at 340B prices. Most of these savings would come from specialty infusion and chemotherapy products, and because of the increasing costs of these specialty products and the increasing amount of chemotherapy services the hospital is providing, the hospital has planned to use the anticipated savings to continue providing infusion services. However, if the Orphan Drug Rule is invalidated, the hospital's annual spending will increase by $200,000 to $300,000, and it may not be able to provide chemotherapy services. If it can no longer provide these services, patients may be required to travel 50 to 60 miles to receive specialty infusion and chemotherapy treatments.

Another CAH reported a similar impact on patient care related to the use of Remicade, an infusion product commonly used to treat patients suffering from rheumatoid arthritis. The hospital reported using Remicade nearly 100% of the time to treat rheumatoid arthritis, and it does not use Remicade to treat any rare diseases for which the drug has an orphan designation. Most of the patients using the drug are elderly or low-income, and without access to the therapy at a local hospital, they would be required to drive 45 to 60 miles for treatment. Exhibit 2, page 33.[23] If the Court invalidates the Orphan Drug Rule, the hospital would lose access to 340B savings on nearly all of its Remicade purchases and may not continue offering this infusion

[23] Conclusions about this hospital were derived from analyzing the hospital's responses to several questions in the survey.

product in the community. Dropping Remicade from the hospital's formulary would force patients to drive long distances and to pay more for Remicade. In addition, one hospital that is not currently purchasing orphan drugs through the 340B program responded to SNHPA's survey saying it is not currently offering infusion therapy but hopes to offer chemotherapy services in the future, at which time access to 340B discounts on orphan drugs used for common indications will be "very important." Exhibit 2, page 33.

Furthermore, as explained above, if hospitals could not access 340B discounts on any orphan drugs, regardless of use, many hospitals would withdraw from the program. Withdrawing from the 340B program would inhibit the ability of affected hospitals to offer high-cost services and could limit access to care for patients. Of opt-in hospitals, 42% reported that patients would have to travel longer distances to get care if this were to occur. Exhibit 2, page 7. Opt-out hospitals expressed a similar concern about the impact on patient access to care if the Court were to invalidate the Orphan Drug Rule. Even though these hospitals are not currently accessing 340B discounts on any orphan drugs, many of the hospitals told SNHPA that they would like to implement an orphan drug tracking system in the future so they can purchase orphan drugs through 340B when they are used to treat non-orphan indications. If the Court invalidated the Orphan Drug Rule, the hospitals would not have this option in the future, and many would withdraw from the 340B program. Among these hospitals, 44% reported that their patients would have to travel longer distances to get care under these circumstances. Exhibit 2, page 3.

Some opt-in hospitals indicated that even if they could no longer access discounts on any orphan drugs, they would continue to participate in 340B. Nevertheless, these hospitals would face increased drug costs, and also reported that their loss of savings would directly impact

patient care. Of these hospitals, 22% said their patients would have to travel longer distances to receive care due to the loss of savings. Exhibit 2, page 8.

V. THE COURT SHOULD NOT TAKE THE EXTRAORDINARY STEP OF ISSUING A PRELIMINARY INJUNCTION BECAUSE PHRMA FAILS TO DEMONSTRATE THAT IT MEETS ANY OF THE FACTORS TO ISSUE A PRELIMINARY INJUNCTION

PhRMA is not entitled to a preliminary injunction because it has not shown that its members will be irreparably harmed, which is a required element for a preliminary injunction. *Chaplaincy of Full Gospel v. England*, 454 F.3d 290, 297 (D.C. Cir. 2006); *see also Sherley*, 644 F.3d at 393. PhRMA also cannot meet the other standards for a preliminary injunction. PhRMA is not likely to prevail on the merits for the reasons explained in section IV, *supra*, and the *amici* will not repeat those arguments here. The injunction also should be denied because non-parties will be substantially harmed, including hospitals and patients, who will see their drug costs rise. Lastly, an injunction is not in the public interest because it will raise costs to the Medicare and Medicaid programs. *See Winter*, 555 U.S. at 20; *Sherley*, 644 F.3d at 392.

A. PhRMA Members Will Suffer No Irreparable Harm if the Orphan Drug Rule Takes Effect During This Litigation

PhRMA has failed to meet the "high standard" necessary to demonstrate irreparable injury because PhRMA has not shown—and cannot show—that the asserted injury is "certain and great" and "beyond remediation." *Chaplaincy of Full Gospel Churches*, 454 F.3d at 297. An economic injury is not irreparable if the complaining party can recover its alleged losses when the litigation concludes. *Id.* at 297-98; *Davis v. Pension Ben. Guar. Corp.*, 571 F.3d 1288, 1294-95 (D.C. Cir. 2009). PhRMA's members would not be harmed at all if the Orphan Drug Rule remains in effect during this litigation because if the Court were to invalidate the regulation, covered entities could make retroactive payments for any drugs that were purchased pursuant to the Rule. The Orphan Drug Rule would have a very minor financial impact on manufacturers,

and so even if the harm were "beyond remediation," the impact would not be "great." *Chaplaincy of Full Gospel Churches*, 454 F.3d at 297.

Allowing affected hospitals to access 340B savings on orphan drugs used to treat non-orphan indications will have a minimal financial impact on drug manufacturers, especially as compared to the impact on hospitals of withholding the 340B discount. The 2012 Wallack and Sorenson study indicates that if CAHs could not access 340B pricing for orphan drugs in any circumstances, CAHs would see their outpatient drug spending increase on average by 14%, adding $144 million to the collective spending of CAHs (with a corresponding increase in manufacturer revenues of $144 million). *Cf.* Wallack & Sorenson, 3 Innovations in Pharmacy at 3 (stating that hospitals would save $171 per hospital if orphan drugs were listed under 340B, which, multiplied by 842 CAHs nationwide, amounts to $144 million). These sales would have amounted to less than 2.0% of total orphan drug sales in 2010, which were estimated to be approximately $40 billion. *Id.*; Proposed Rule, Exclusion of Orphan Drugs for Certain Covered Entities Under 340B Program, 76 Fed. Reg. 29,183, 29,187 (May 20, 2011). As a percentage of *total* drug sales, manufacturers would have only saved 0.05% of their total drug sales, which were estimated to be $307 billion in 2010. *See* Letter from John E. Dicken, Director Health Care, GAO, to Senator Orrin G. Hatch (Jan. 31, 2012), *available at* www.gao.gov/assets/490/588064.pdf (stating total drug sales in 2010, which was used to calculate manufacturer 340B savings here).

B. A Preliminary Injunction Would Substantially Harm Other Parties, Including Affected Hospitals and Their Patients

Affected hospitals and their patients would be substantially harmed by a preliminary injunction. As required by the Orphan Drug Rule, hospitals currently opting-in and purchasing orphan drugs through 340B have expended resources to ensure that they can track orphan and

non-orphan uses of designated drugs. They did so in anticipation of receiving 340B discounts when orphan drugs are used for non-orphan indications. A preliminary injunction would force opt-in hospitals to forego these discounts, raising costs both for the hospitals and their patients. Moreover, it is not clear that this harm could be undone if the Court ultimately upholds the Orphan Drug Rule. There is no clear mechanism that would provide relief to covered entities that are denied discounts during the period of a preliminary injunction. There is a process used in the industry that allows drug manufacturers to be repaid for errors relating to 340B discounts. Under this process, purchases made through a 340B account may be credited and rebilled through a non-340B account. HRSA's policy is that the credit-rebill process requires "fully informed consent" by manufacturers. Apexus 340B Prime Vendor Program, *340B FAQs, No. 1*, https://docs.340bpvp.com/documents/public/news/flash/flash_1204.html (last accessed Dec. 20, 2013).[24] Manufacturers would either have to consent to pay retroactive discounts or HHS would have to change its policy to force them to pay the discounts.

Covered entities would have to rely on HHS to compel retroactive 340B discounts. The D.C. Circuit has held that covered entities do not have standing in suits against HHS seeking retroactive discounts. *Univ. Med. Ctr. of So. Nev. v. Shalala*, 173. F.3d 438 (D.C. Cir. 1999). The 340B statute also does not provide a private right of action for covered entities to sue manufacturers for failing to pay discounts. *Astra USA, Inc. v. Santa Clara County*, 131 S.Ct. 1342 (2011). Covered entities also may not sue as third-party beneficiaries to seek enforcement of the manufacturers' contracts with HHS. *Id.*

[24] This policy guidance was issued by Apexus, which is a private company under contract with HRSA to assist with certain aspects of administering the 340B program. Apexus's responsibilities include communicating the agency's 340B policies to the public. http://www.hrsa.gov/opa/faqs/ ("HRSA uses the HRSA contracted 340B Prime Vendor Program, managed by Apexus, Health Resources and Serv. Admin., *340B FAQ: General No. 1*, to assist in communicating that policy") (last accessed Dec. 20, 2013).

Congress recently amended the 340B statute to require HHS to establish procedures for manufacturers to issue refunds to covered entities, but HHS has not yet established any procedures for providing retroactive discounts to covered entities. 42 U.S.C. § 256b(d)(1)(B)(ii). Covered entities have no guarantee that any procedures that HRSA establishes would permit retroactive payments for the drugs at issue here. Therefore, no mechanism currently entitles covered entities to obtain retroactive discounts if the Court were to grant the injunction requested by PhRMA, but then later upheld the regulation.

PhRMA argues also that granting an injunction would not harm hospitals and goes even further to say it would help hospitals by relieving them of the compliance burdens they face under the Orphan Drug Rule. Memorandum of Law in Support of Plaintiff's Application for a Preliminary Injunction, at 23-24. PhRMA is mistaken. PhRMA cites the regulation requiring opt-in hospitals to implement a tracking system to identify how their drugs are used. 78 Fed. Reg. at 44,018. However, when asked about their preference in SNHPA's survey, these hospitals overwhelmingly reported that they would rather track orphan drug use so they can use 340B than not have to track orphan drug use and forego access to discounts on all orphan drugs. One hospital said: "I would rather track indication than miss out on 340B discounts at this point." Exhibit 2, page 30.

C. An Injunction Is Not in the Public Interest Because It Would Harm the Medicare and Medicaid Programs

One factor considered by courts in determining whether to grant a preliminary injunction is whether the injunction would further the public interest. *Wash. Metro. Area Transit Comm'n v. Holiday Tours, Inc.*, 559 F.2d 841, 842-43 (D.C. Cir. 1977); *see also CSX Transp., Inc. v. Williams*, 406 F.3d 667, 670 (D.C. Cir. 2005). A preliminary injunction would harm the public

interest by reducing the Medicare trust fund and increasing costs in certain states related to the federal Medicaid program.

As discussed above, CAHs are among the hospitals that are subject to the orphan drug rule. Based on recent data from the HRSA website, 847 CAHs are registered for the 340B program.[25] The Medicare program reimburses most hospitals for outpatient services furnished to Medicare beneficiaries at a prospectively fixed rate.[26] Under the outpatient prospective payment system, hospitals sometimes receive payment that is more than their costs and sometimes receive payment that is less than their costs. 75 Fed. Reg. 71,800, 71,836 (Nov. 24, 2010). In contrast, however, the Medicare program reimburses CAHs for outpatient services at 101% of the CAH's reasonable costs for providing services. 42 U.S.C. §1395m(g)(1). Therefore, when a CAH purchases a drug for outpatient use with a 340B discount, the Medicare program receives the benefit of those 340B savings because it reimburses the CAH at the discounted price, plus 1%.

If the Court were to grant PhRMA a preliminary injunction, CAHs will not receive 340B discounts on orphan drugs in any circumstance. Instead, the CAH will purchase orphan drugs from PhRMA's members at non-340B prices, and Medicare will ultimately pay the CAH at 101% of that higher cost. Accordingly, the loss of 340B discounts to the CAH is also a loss to the Medicare program.

[25] This figure was derived by SNHPA's analysis of the OPA database Nov. 20, 2013. This figure does not include "child sites" of the CAHs. A child site is an outpatient facility that is part of the hospital but registered on the 340B database under the hospital's registration. HRSA requires that outpatient sites that are located outside the hospital facility and that dispense 340B drugs to register as child sites. Outpatient sites located in the hospital facility have the option whether to register as child sites. *See* Response to HRSA, Office of Pharmacy Affairs FAQ, *What Outpatient Facilities Are Hospitals Required to Register On the 340B Database? available at* http://www.hrsa.gov/opa/faqs/ (last accessed Dec. 20, 2013).

[26] The Balanced Budget Act of 1997 (BBA), Pub. L. 105-33, added § 1833(t) to the Social Security Act, authorizing implementation of a prospective payment system for hospital outpatient services. 42 U.S.C. § 1395l(t). The outpatient prospective payment system was first implemented for services furnished on or after August 1, 2000. Implementing regulations are located at 42 C.F.R. parts 410 and 419.

State Medicaid agencies and the federal Medicaid program also stand to lose money if the Court were to stop implementation of the Orphan Drug Rule. Many state Medicaid agencies reimburse covered entities at lower rates for outpatient drugs knowing that they are purchased at the lower 340B prices. If affected hospitals were forced to purchase all orphan drugs at non-340B prices, states would pay these hospitals for orphan drugs at higher rates.[27] Thus, 340B reduces Medicaid expenditures. If the Court were to prevent implementation of the Orphan Drug Rule, affected hospitals would be forced to purchase all orphan drugs outside 340B, and states would reimburse the hospitals for these drugs at their higher, regular rates. States would be unable to recoup the difference through the Medicaid rebate program, thereby resulting in higher Medicaid expenditures.

VI. CONCLUSION

For the foregoing reasons, *amici curiae* Safety Net Hospitals for Pharmaceutical Access, America's Essential Hospitals, and National Rural Health Association urge this Court to uphold the Orphan Drug Rule and to deny PhRMA's request for a preliminary injunction

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[27] States collect rebates from drug manufacturers on non-340B drugs, but these rebates are not enough to offset the lower rates established for 340B participants. Per Congressional Budget Office ("CBO") estimates, the Medicaid net final price of a drug (the amount Medicaid pays net rebates) is 64 percent of a drug's average wholesale price ("AWP"), and the 340B ceiling price is 51 percent of AWP. Therefore, as a percentage of the 340B ceiling price, the Medicaid net final price is 25 percent higher than the 340B price. CBO, Prices for Brand-Name Drugs Under Selected Federal Programs, 11 (June 2005), *available at*: http://www.cbo.gov/sites/default/files/cbofiles/ftpdocs/64xx/doc6481/06-16-prescriptdrug.pdf (last accessed Dec. 17, 2013).

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CERTIFICATE OF SERVICE

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