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Regional Administrator, Region IX.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

42 CFR Part 10

RIN 0906-AA94

Exclusion of Orphan Drugs for Certain Covered Entities Under 340B Program

AGENCY: Health Resources and Services Administration (HRSA), Department of Health and Human Services (HHS).

ACTION: Notice of proposed rulemaking.

SUMMARY: The “Veterans Health Care Act of 1992,” enacted section 340B of the Public Health Service Act (PHSA) “Limitation on Prices of Drugs Purchased by Covered Entities.” Section 340B implemented a drug pricing program by which manufacturers who participate in Medicaid are required to sell covered outpatient drugs to particular covered entities listed in the statute and must agree to charge a price that will not exceed the amount determined under a statutory formula. The manufacturer’s obligation to sell at no greater than the ceiling price extends only to covered outpatient drugs and does not apply to inpatient drugs. Covered entities are required to ensure that drugs purchased under 340B are used only for outpatients. The Patient Protection and Affordable Care Act expanded the types of covered entities eligible to participate in the 340B Drug Pricing Program (340B Program) under the PHSA to include certain free standing cancer hospitals, rural referral centers, sole community hospitals, critical access hospitals, and children’s hospitals. Of these entities, children’s hospitals were already eligible to participate in the 340B drug pricing program under the Deficit Reduction Act of 2005. The Health Care and Education Reconciliation Act (HCERA) (the Patient Protection and Affordable Care Act and HCERA collectively hereinafter will be referred to as the “Affordable Care Act”), as amended by the Medicare and Medicaid Extenders Act of 2010, contained a provision that limits the types of drugs that free standing cancer hospitals, rural referral centers, sole community hospitals and critical access hospitals could obtain through the 340B Program. Under the changes made by the Affordable Care Act, orphan drugs, when used for the

rare condition or disease for which that orphan drug was designated under the Federal Food, Drug, and Cosmetic Act (FDCA), are excluded from the definition of covered outpatient drug for the specified newly-eligible covered entity types for purposes of the 340B Program. This regulatory action details how these exclusions will be implemented under the 340B Program.

DATES: Comments on this proposed rule must be submitted by July 19, 2011.

ADDRESSES: You may submit comments, identified by the Regulatory Information Number (RIN) 0906-AA94, by any of the following methods:

- *Federal eRulemaking Portal:* <http://www.regulations.gov>. Follow the instructions for submitting comments.

- *E-mail:* opaorphan@hrsa.gov. Include RIN 0906-AA94 in the subject line of the message.

- *Mail:* CDR Krista Pedley, Director, Office of Pharmacy Affairs (OPA), Healthcare Systems Bureau (HSB), Health Resources and Services Administration (HRSA), 5600 Fishers Lane, Parklawn Building, Room 10C-03, Rockville, Maryland 20857.

All submissions received must include the agency name and RIN for this rulemaking. All comments received will be available for public inspection and copying without charge, including any personal information provided, at Parklawn Building, 5600 Fishers Lane, Room 10C-03, Rockville, Maryland 20857, weekdays (Federal holidays excepted) between the hours of 8:30 a.m. and 5 p.m.

FOR FURTHER INFORMATION CONTACT: CDR Krista Pedley at the mail address or by telephone at (301) 594-4353.

SUPPLEMENTARY INFORMATION:

I. Background

The purpose of the 340B Program is to permit covered entities “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 340B Program was established by section 602 of the Veterans Health Care Act of 1992 (Pub. L. 102-585) and is codified as section 340B of the PHSA. Section 340B instructs HHS to enter into Pharmaceutical Pricing Agreements (PPA) with drug manufacturers. (42 U.S.C. 256b(a)). If manufacturers sign a PPA, they agree that the prices charged for covered outpatient drugs to covered entities (organizations eligible under section 340B to receive 340B discounted pricing) will not exceed defined ceiling prices, which are based on pricing data reported to the Centers for Medicare &

Medicaid Services (CMS). The 340B ceiling price is calculated by subtracting the Unit Rebate Amount from the Average Manufacturer Price. Drugs purchased by covered entities through the 340B Program may not be sold or transferred to anyone other than the patients of the covered entities. Since 1992, the program has grown; there are currently over 16,000 participating covered entity sites in the 340B Program.

The Affordable Care Act introduced several changes to the 340B Program. The 340B Program has not previously published codified regulations on the operation of this program, instead relying on published program guidance documents, which were typically finalized after a notice and comment period. However, a number of the provisions of the Affordable Care Act necessitate the development and publication of regulations. This is the first of a series of regulations that will outline certain requirements in the 340B Program.

Section 7101 of the Affordable Care Act added several new categories of eligibility for program participants, allowing them to have access to 340B drug pricing except in the case of an orphan drug when used for a rare disease or condition. The entity types added to the list of eligible entities listed under 340B(a)(4) included: 340B(a)(4)(M) (children’s hospitals and free-standing cancer hospitals), 340B(a)(4)(N) (critical access hospitals), and 340B(a)(4)(O) (rural referral centers and sole community hospitals). As amended by the Affordable Care Act, and section 204 of the Medicare and Medicaid Extenders Act of 2010 (Pub. L. 111-309), section 340B(e) of the PHSA (42 U.S.C. 256b(e)) states the following:

- **EXCLUSION OF ORPHAN DRUGS FOR CERTAIN COVERED ENTITIES**—For covered entities described in subparagraph (M), (other than a children’s hospital described in subparagraph (M)), (N), or (O) of subsection (a)(4), the term ‘covered outpatient drug’ shall not include a drug designated by the Secretary under section 526 of the Federal Food, Drug, and Cosmetic Act for a rare disease or condition.

Congress passed the Orphan Drug Act of 1983 to stimulate the development of drugs for rare diseases. The Food and Drug Administration (FDA), Office of Orphan Products Development, administers the Orphan Drug Act and reviews requests for designations. Orphan status designation by the FDA indicates that the drug has been found “promising” for treating a rare disease. The award of an orphan designation does not alter the standard regulatory requirements and process for obtaining

marketing approval, which is a separate process administered by the FDA Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research. In fact, a large majority of drugs with orphan designations do not have approval to be marketed in the United States. Generally, only outpatient drugs that have been approved for marketing in the United States are included in the 340B Program. Thus, among outpatient drugs that have received an orphan designation, only those that have also received marketing approval by the FDA meet the definition of covered outpatient drugs for the 340B Program.

Rationale for Rulemaking

The purpose of issuing this proposed rule is to clarify HHS's stated effort in: (1) Providing clarity in the marketplace, (2) maintaining the 340B savings and interests to the newly-eligible covered entities; and (3) protecting the financial incentives for manufacturing orphan drugs designated for a rare disease or condition as indicated in the Affordable Care Act as intended by Congress.

First, HHS is aware of confusion in the marketplace, having been notified of such by affected parties, including covered entities and drug manufacturers. This confusion is due to varying interpretations of the statutory exclusion: whether the language prohibits these newly covered entities from purchasing all orphan drugs through the 340B Program or whether the language only prohibits purchase of orphan drugs when used for the rare disease or condition for which the orphan drug is designated. In response to this uncertainty, some manufacturers have ceased selling orphan drugs through the 340B Program to the newly-eligible covered entities to avoid best price implications. Other manufacturers are waiting for Federal policy before taking action, while still other manufacturers have stated that they will stop selling orphan drugs through the 340B Program to newly-eligible covered entities effective immediately. In addition, the affected covered entities are not sure if they are permitted to purchase orphan drug products and, if they are, at what price. These covered entities do not know if they can buy these orphan drugs using group purchasing organizations or if there are additional record-keeping requirements that they must meet for 340B compliance. Other 340B stakeholders such as wholesalers are also not sure which systems need to be in place to ensure compliance with this new statutory provision. HHS has received numerous requests from these affected

parties asking for clear Federal policy on the scope of this provision. The Secretary believes that this proposed rule will provide requested clarity on this issue.

Second, the Affordable Care Act added four newly-eligible covered entity categories to benefit from the 340B Program. As Congress wanted these new covered entities to participate and benefit from the 340B Program "to stretch scarce federal resources as far as possible, reaching more eligible patients and providing more comprehensive services," it is critical that HHS recognizes these covered entities' ability to benefit from the 340B Program savings so there is sufficient value for them to participate in the 340B Program. HHS has been notified by the covered entities that some of the hospitals such as free-standing cancer hospitals are significant purchasers of orphan drugs and if these drugs were excluded from the 340B Program entirely, it is not clear if there would be sufficient financial benefits to participating in the 340B Program. As of October 1, 2010, only 337 hospitals out of approximately 1,500 eligible hospitals have enrolled in the program. Some covered entities are still weighing the benefits while other covered entities are waiting for Federal guidance to clarify how the orphan drug exclusion will impact their organizations. Interpreting the statutory language to exclude all uses of drugs with an orphan designation, including uses for common diseases or conditions, would place a substantial burden on the affected entities and potentially nullify the benefits of the 340B Program for those entities considering enrolling. Thus, this proposed rule would apply an interpretation of the statutory language prohibiting purchase of orphan drugs through the 340B Program by certain newly covered entities that limits the prohibition to uses for the rare disease or condition for which the orphan drug was designated under section 526 of the FFDCFA.

Finally, HHS has to maintain financial incentives for the manufacturing of an orphan drug designated for a rare disease or condition. A drug is designated by the FDA as "a drug for a rare disease or condition" pursuant to section 526 of the Federal Food, Drug, and Cosmetic Act at the request of the sponsor if FDA finds that the drug is being or will be investigated for a rare disease or condition and, if approved by FDA, the approval will be for that disease or condition. 21 USC 360bb(a)(1). This designation is referred to as orphan-drug designation. 21 CFR 316.24. FDA has interpreted the law as permitting the

designation of a drug for a rare disease or condition in situations where the drug is also approved for a different disease or condition that does not qualify for such a designation. 21 CFR 316.23(b). Some drugs may be used to treat multiple diseases or conditions. This designation provides a number of incentives for the development of the orphan drug for the particular disease or condition. These incentives include: (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 new therapies to treat and/or diagnose rare diseases; and (4) an exemption from the usual drug application or "user" fees charged by the FDA. Each of these incentives applies only when the orphan drug is targeted or used to treat a rare disease or condition and not for other indications. First, the marketing exclusion only applies if the drug is the first approved by the FDA to be marketed for an orphan indication and not if the drug is only approved by the FDA for a common condition. 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. Thus, 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). The approach proposed in this rule (in which the exclusion of orphan drugs is limited to uses for the rare disease or condition for which the orphan drug was designated) is consistent with the general application of incentives associated with orphan drug designation, described above.

To the extent Congressional intent was to not undermine pricing for drugs used to treat rare diseases, a broad exclusion appears to be overly inclusive. Drugs that are marketed for a rare disease are in some cases also approved, or used without approval, for other indications and some such drugs are among some of the most widely used today. This rule, as proposed, serves to maintain orphan drugs outside of 340B

pricing when the drug with such a designation is used for a rare disease or condition. This approach is consistent with the implementation of the FFDCA by FDA without generating an unintended benefit for those manufacturers with drugs that have an orphan indication under section 526 of the Federal Food, Drug, and Cosmetic Act, but are widely or even exclusively utilized for common indications. The fact that drugs can have multiple indications, only some of which qualify for designation, has led HHS to conclude that the exemption from the term "covered outpatient drug" under section 340B(e) of the PHS Act only applies to orphan drugs when they are transferred, prescribed, sold, or otherwise used for the rare condition or disease for which the orphan drug was designated.

II. Summary of the Regulation

General Provisions (Subpart A)

In 1992, Congress enacted the Veterans Health Care Act to provide certain purchasers with a process through which they received drug discounts or rebates. Section 602 of the Veterans Health Care Act provided for drug discounts primarily for certain grantees of the Public Health Service. Since 1992, HHS has administratively established through documents published in the **Federal Register** the terms and certain elements of the 340B Program. HHS is now establishing a regulatory structure for the 340B Program and will also be publishing regulations on other provisions of this program. This is the first regulation to be published.

Section 340B(e) of the PHS Act does not alter a manufacturer's obligation to sell covered outpatient drugs at no greater than the ceiling price to the designated covered entities. A manufacturer may not condition the offer of statutory discounts upon a covered entity's assurance of compliance with section 340B provisions. Accordingly, manufacturers cannot condition sales upon receiving prior assurance that the 340B drug will not be used to treat a rare disease or condition. Manufacturers must offer covered entities covered outpatient drugs for purchase at or below the applicable 340B ceiling price if such drug is made available to any other purchaser.

Section 340B(e) of the PHS Act creates no additional obligations or restrictions upon drug manufacturers. As provided under section 340B(a)(10) of the PHS Act, the law does not prohibit manufacturers from charging a price for a drug that is lower than the maximum price that may

be charged under section 340B(a)(1). CMS is delegated the responsibility for regulating the Medicaid best price exemption, and HRSA is working with CMS to develop policy on the treatment of orphan drugs to covered entities under 340B(a)(4)(M) (other than a children's hospital described in subparagraph (M)), (N), and (O) with respect to Medicaid best price. Until HHS issues this policy, which will be prospective in its effect, manufacturers are permitted to make reasonable assumptions regarding the Medicaid best price calculations, including exclusions applicable to those calculations.

Eligibility To Purchase 340B Drugs (Subpart B)

Health care entity types that meet the requirements under section 340B(a)(5) of the PHS Act and which are listed under section 340B(a)(4) of the PHS Act are eligible to enroll in the 340B Program. These safety-net organizations are referred to as "covered entities." Section 7101 of the Patient Protection and Affordable Care Act (Pub. L. 111-148) expanded the types of covered entities eligible to participate in the 340B Drug Pricing Program (340B Program) to include certain free-standing cancer hospitals, rural referral centers, sole community hospitals, and critical access hospitals. After the enactment of the Affordable Care Act, section 340B(a)(4) includes the following entity types: (1) A Federally-qualified health center (as defined in section 1905(l)(2)(B) of the Social Security Act); (2) A family planning project receiving a grant or contract under section 1001 of the Public Health Service Act; (3) An entity receiving a grant under subpart II of part C of title XXVI of the Public Health Service Act (relating to categorical grants for outpatient early intervention services for HIV disease); (4) A state-operated AIDS drug purchasing assistance program receiving financial assistance under title XXVI of the Public Health Service Act; (5) A black lung clinic receiving funds under section 427(a) of the Black Lung Benefits Act; (6) A comprehensive hemophilia diagnostic treatment center receiving a grant under section 501(a)(2) of the Social Security Act; (7) A Native Hawaiian Health Center receiving funds under the Native Hawaiian Health Care Act of 1988; (8) An urban Indian organization receiving funds under title V of the Indian Health Care Improvement Act; (9) Any entity receiving assistance under title XXVI of the Public Health Service Act (other than a state or unit of local government or an entity described in 340B(a)(4)(D)),

but only if the entity is certified by the Secretary pursuant to paragraph 340B(a)(7); (10) An entity receiving funds under section 318 of the Public Health Service Act (relating to treatment of sexually transmitted diseases) or section 317(j)(2) (relating to treatment of tuberculosis) through a state or unit of local government, but only if the entity is certified by the Secretary pursuant to paragraph 340B(a)(7); (11) A subsection (d) hospital (as defined in section 1886(d)(1)(B) of the Social Security Act) that—(i) is owned or operated by a unit of state or local government, is a public or private non-profit corporation which is formally granted governmental powers by a unit of state or local government, or is a private non-profit hospital which has a contract with a state or local government to provide health care services to low income individuals who are not entitled to benefits under title XVIII of the Social Security Act or eligible for assistance under the state plan under this title; (ii) for the most recent cost reporting period that ended before the calendar quarter involved, had a disproportionate share adjustment percentage (as determined under section 1886(d)(5)(F) of the Social Security Act) greater than 11.75 percent or was described in section 1886(d)(5)(F)(i)(II) of such Act; and (iii) does not obtain covered outpatient drugs through a group purchasing organization or other group purchasing arrangement; (12) A children's hospital excluded from the Medicare prospective payment system pursuant to section 1886(d)(1)(B)(iii) of the Social Security Act, or a free-standing cancer hospital excluded from the Medicare prospective payment system pursuant to section 1886(d)(1)(B)(v) of the Social Security Act, that would meet the requirements of subparagraph (L), including the disproportionate share adjustment percentage requirement under clause (ii) of such subparagraph, if the hospital were a subsection (d) hospital as defined by section 1886(d)(1)(B) of the Social Security Act; (13) An entity that is a critical access hospital (as determined under section 1820(c)(2) of the Social Security Act), and that meets the requirements of subparagraph (L)(i); and (14) An entity that is a rural referral center, as defined by section 1886(d)(5)(C)(i) of the Social Security Act, or a sole community hospital, as defined by section 1886(d)(5)(C)(iii) of such Act, and that both meets the requirements of subparagraph (L)(i) and has a disproportionate share adjustment percentage equal to or greater than 8 percent.

Drugs Eligible for Purchase Under 340B (Subpart C)**Drugs Eligible for Purchase Under 340B (§ 10.20)**

In general, covered entities are eligible to purchase any 340B drugs (“covered outpatient drugs”) for their patients. However, as added by the Affordable Care Act, section 340B(e) of the PHSA excludes certain categories of covered entities from purchasing orphan drugs at 340B pricing when used for rare diseases or conditions.

Exclusion of Orphan Drugs for Treating Rare Diseases or Conditions—General (§ 10.21(a))

For the covered entities described in § 10.21(b), a covered outpatient drug does not include orphan drugs that are transferred, prescribed, sold, or otherwise used for the rare condition or disease for which that orphan drug was designated under section 526 of the FFDCA.

However, for these same covered entities, a covered outpatient drug includes designated orphan drugs that are transferred, prescribed, sold, or otherwise used for any indication other than treating the rare disease or condition for which the drug was designated under section 526 of the FFDCA. In other words, the affected entities can purchase these drugs at 340B prices when using them for common conditions for which they are approved or any other lawful use except when using them for the rare condition or disease for which they were given an orphan drug designation by the FDA.

Covered Entities to Which the Orphan Drug Exclusion Applies (§ 10.21(b))

The exclusion of orphan drugs when used for the rare condition or disease for which that orphan drug was designated under section 526 of the FFDCA is applicable only to covered entities qualifying under sections 340B(a)(4)(M), (other than a children’s hospital described in subparagraph (M)) of the PHSA (free-standing cancer hospitals), 340B(a)(4)(N) of the PHSA (critical access hospitals), and 340B(a)(4)(O) of the PHSA (rural referral centers and sole community hospitals). The exclusion does not apply to entities that meet the 340B Program eligibility requirements and are enrolled under sections 340B(a)(4)(A) through 340B(a)(4)(L) or to a children’s hospital described in 340B(a)(4)(M)). For example, if a hospital potentially qualifies both under 340B(a)(4)(L) as a disproportionate share hospital and under 340B(a)(4)(O) as a sole community hospital, then that hospital must select which type and

enroll under the requirements of the type that it selected.

Covered entities enrolled under sections 340B(a)(4)(M) (other than a children’s hospital described in subparagraph (M)), (N), and (O) that fail to ensure that orphan drugs that are purchased through the 340B Drug Pricing Program are not transferred, prescribed, sold, or otherwise used for the rare condition or disease for which orphan drugs are designated under section 526 of the FFDCA shall be subject to all sanctions and penalties applicable to failure to comply with section 340B(a)(5)(B). The covered entities shall put in place tracking and recordkeeping requirements to demonstrate compliance with the limits on the use of orphan drugs. To demonstrate compliance, it will be necessary for the covered entities to create separate purchasing accounts and improve inventory and auditing capacity.

In those few cases where safety-net organizations meet more than one eligibility criteria as covered entities that are eligible under sections 340B(a)(4)(L) through 340(a)(4)(O), these safety-net organizations shall be limited to participating in the 340B Program as only one covered entity type and shall abide by all applicable restrictions and requirements for that entity type.

Covered Entity Responsibility To Maintain Records of Compliance (§ 10.21(c))

The covered entities to which the orphan drug exclusion applies are responsible for ensuring that orphan drugs that are purchased through the 340B Program are not transferred, prescribed, sold, or otherwise used for the rare condition or disease for which orphan drugs are designated under section 526 of the FFDCA. These covered entities are required to provide auditable records upon the written request of the government or government-approved manufacturer audit request that directly pertain to the covered entity’s compliance with this requirement.

Affected covered entities that cannot or do not wish to maintain auditable records sufficient to demonstrate compliance, must purchase all orphan drugs outside of the 340B Program. Entities are required to notify HRSA that they will be purchasing all designated orphan drugs outside the 340B Program when they enroll in the program and during recertification.

Use of Group Purchasing Organizations by Free-Standing Cancer Hospitals (§ 10.21(d))

The covered entities remain responsible for complying with all other 340B requirements and applicable Federal, state, and local law. Free-standing cancer hospitals enrolled under section 340B(a)(4)(M) of the PHSA must comply with the prohibition against using a group purchasing organization under section 340B(a)(4)(L)(iii) of the PHSA for the purchase of any covered outpatient drug.

If auditable records are maintained that demonstrate full compliance with orphan drug purchasing requirements, then free-standing cancer hospitals enrolled under 340B(a)(4)(M) are permitted to use a group purchasing organization to purchase orphan drugs when they are transferred, prescribed, sold, or otherwise used for the rare condition or disease for which that orphan drug was designated under section 526 of the FFDCA, as these drugs are not considered covered outpatient drugs. However, free-standing cancer hospitals enrolled under 340B(a)(4)(M) are prohibited from using a group purchasing organization to purchase orphan drugs when used for any indication other than treating the rare disease or condition for which the drug was designated under section 526 of the FFDCA, as these drugs are considered covered outpatient drugs. To the extent that free-standing cancer hospitals elect to purchase all orphan drugs outside of the 340B Program, covered entities are permitted to use a group purchasing organization for those purchases.

Identification of Orphan Drugs (§ 10.21(e))

Designations under section 526 of the FFDCA are the responsibility of and administered by the FDA. FDA publishes information pertaining to orphan drug designations pursuant to 21 CFR part 316. Manufacturers and covered entities seeking to determine whether a drug is designated under section 526 of the FFDCA and the indication for which it is designated shall rely on the FDA. This list can be accessed by the public at <http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm>.

III. Economic and Regulatory Impact

Executive Order 12866, as amended by Executive Orders 13258 and 13422, directs agencies to assess all costs and benefits of available regulatory alternatives and, when rulemaking is

necessary, to select regulatory approaches that provide the greatest net benefits (including potential economic, environmental, public health, safety, distributive, and equity effects). In addition, under the Regulatory Flexibility Act, if a rule has a significant economic effect on a substantial number of small entities, the Secretary must specifically consider the economic effect of a rule on small entities and analyze regulatory options that could lessen the impact of the rule. Executive Order 12866, as amended by Executive Orders 13258 and 13422, requires that all regulations reflect consideration of alternatives, of costs, of benefits, of incentives, of equity, and of available information. Regulations must meet certain standards, such as avoiding an unnecessary burden. Regulations which are "significant" because of cost, adverse effects on the economy, inconsistency with other agency actions, effects on the budget, or novel legal or policy issues, require special analysis.

Impact of the New Rule

Analysis of Impacts

HHS has examined the impacts of the proposed rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104–4). HHS believes that this proposed rule is not a significant regulatory action under the Executive Order; however, the impact is difficult to fully estimate. HHS invites additional comments on the impact of the proposed rule from affected stakeholders.

The Regulatory Flexibility Act (RFA) requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. For purposes of the regulatory flexibility analysis, we consider all health care providers to be small entities either by virtue of meeting the SBA size standard for a small business, or for being a nonprofit organization that is not dominant in its market. The current SBA size standard for health care providers ranges from annual receipts of \$7 million to \$34.5 million. States and individuals are not considered small entities under the RFA. Because the proposed rule does not create or mandate any new reporting requirements and provides flexibility to entities to voluntarily purchase orphan drugs based on the entities' best interests, the Secretary certifies that the proposed rule will not have a significant economic impact on a substantial number of small entities.

Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires

that agencies prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing "any rule that includes any federal mandate that may result in the expenditure by state, local, and Tribal governments, in the aggregate, or by the private sector, of \$100,000,000 or more (adjusted annually for inflation) in any one year." The current threshold after adjustment for inflation is \$135 million, using the most current (2009) Implicit Price Deflator for the Gross Domestic Product. HHS does not expect this proposed rule to result in any 1-year expenditure that would meet or exceed this amount.

In accordance with Executive Order 12866, we analyzed the potential economic effects of the proposed rule. As stated above, we are unable to quantify the costs of the proposed rule and we are unable to quantify the benefits of the final rule. However, we expect the net benefits to exceed the costs of not promulgating a final rule, as explained below.

HHS has reviewed this proposed rule in accordance with Executive Order 13132 regarding federalism, and has determined that it does not have "federalism implications." This rule would not "have substantial direct effects on the states, or on the relationship between the national government and the states, or on the distribution of power and responsibilities among the various levels of government."

The proposals made in this notice of proposed rulemaking, if implemented, would not adversely affect the following family elements: family safety, family stability, marital commitment; parental rights in the education, nurture and supervision of their children; family functioning, disposable income or poverty; or the behavior and personal responsibility of youth, as determined under section 654(c) of the Treasury and General Government Appropriations Act of 1999.

A. Costs of the Regulation

1. Impact on Covered Entities

The proposed rule will not create any new requirements or costs upon the affected covered entities beyond those imposed by statute. The proposed rule will provide covered entities clarity on the meaning of 340B(e) and provide them flexibility in making their own business case in how to proceed. Under the rule as proposed, covered entities will have the choice to either purchase a drug with an orphan designation under the FFDCAs outside of the 340B Program or purchase such drugs under

the 340B Program while maintaining auditable records required under 340B(a)(5)(C) that show that such drugs are not used for an indication excluded under 340B(e). HHS is not able at this time to estimate the costs of showing compliance for those affected entities that choose to purchase orphan drugs under 340B. HHS does not currently mandate the method of demonstrating compliance and allows flexibility of covered entities to do so.

The proposed rule is expected to result in a net benefit to the affected covered entities, by establishing certainty as to the applicability of the exclusion and ensuring the option of continued access to orphan drugs when used for indications other than those for which the entity received a designation. HHS does not have sufficient information to make a comprehensive assessment. HHS has received anecdotal information suggesting that without this rule, the cost of purchasing orphan drugs for certain covered entities will increase substantially where those drugs are used for indications other than the rare disease for which they received an orphan drug designation. Some drugs with orphan drug designation are used widely for common indications.

The total amount in reduced expenditures of drugs resulting from this rule depends on what the market would do absent this proposed regulation compared with the result from promulgating this rule in final as proposed. We have estimates that the orphan drug market as a whole for both inpatient and outpatient services is approximately \$40 billion. In general, covered entity purchases under the entire 340B Program are estimated to make up less than 2 percent of the prescription drug market. The only covered entities impacted by this proposed rule are the entities listed in 340B(e) which make up a projected 10 percent of the total purchasing volume of all covered entities. The savings for entities purchasing under 340B varies considerably with savings as high as 50 percent. We estimate that the rule as proposed will help ensure access to the 340B ceiling price in 50 to 75 percent of sales where orphan drugs with a designation are used for an indication other than the rare disease or indication for which the orphan drug received its designation. Based upon these estimates, we project that the proposed rule may result in a \$20 to \$30 million reduction in the cost to acquire drugs by the affected covered entities. We have no data on the breakout of inpatient versus outpatient drug use. Thus, this cost reduction would be less if outpatient purchases by these covered

entities are significantly less than inpatient purchases (e.g., if outpatient drugs are 50% of orphan drug purchases then the cost reduction may only be \$10 to \$15 million). We welcome additional information from stakeholders to improve the estimated impact of this rule.

While we are unable to provide a concrete estimate, we conclude that this rule will result in a net economic benefit to the affected covered entities. This conclusion is based upon the assumption that the rule as proposed will result in greater access to 340B pricing on orphan drugs than without the rule and on the grounds that the flexibility provided to covered entities will permit them to utilize the program only where there is a net economic benefit. Without a rule, we anticipate continued uncertainty and variability with a general tendency among many manufacturers to take a broad interpretation of the exclusion and minimize or eliminate savings to the covered entities.

2. Impact on Participating Manufacturers

The proposed rule creates no new reporting or record-keeping requirements for manufacturers that have a 340B Pharmaceutical Pricing Agreement with the Secretary. The proposed rule provides clarity to the meaning of section 340B(e) to assist manufacturers in complying with their statutory responsibilities. As noted above, by definition all 340B covered drugs have marketing approval for at least one indication. There are approximately 350 drugs that have been approved for rare diseases and conditions. Also from the FDA's Rare Disease Repurposing Database, there are another 100 orphan designated drugs that have not been approved for the rare disease but are approved for a common disease. There is relatively little quantitative data published on the orphan drug sector and the data published emphasizes approval for rare indications. Data currently publicly available from the FDA on orphan designated drugs tends to focus on approval for rare indications as opposed to common indications. Of those drugs, only those used for outpatients are eligible for purchase under 340B. The pharmaceutical manufacturers of these orphan designated drugs with at least one marketing approval will be affected by this rule.

The impact of this proposed rule is narrowed by the fact that the orphan drug exclusion only applies to a subset of newly-eligible rural hospitals and freestanding cancer hospitals which are

expected to make up a small fraction of the total purchases of covered outpatient drugs through the 340B Program. The overall economic impact is therefore difficult to estimate. In general, having a drug subject to the 340B ceiling price provides a cost savings to the purchasing covered entities and, if the drug would have otherwise been purchased at higher cost, a loss of that additional revenue to the manufacturer. The impact of this rule would vary considerably from drug to drug depending on such factors as the level of utilization of drugs with orphan designations by the affected covered entities, the elasticity of demand by the affected patient population, and the availability and cost of alternative treatments. Such anticipated cost savings and revenue losses would not apply when orphan designated drugs are purchased for their designated rare uses. HRSA invites comments from manufacturers regarding orphan drugs and the expected impact of the orphan drug exclusion and this proposed rule.

3. Impact on Other Parties

HHS has concluded that the proposed rule will not have a significant impact on those third party firms that do business with covered entities and drug manufacturers. To the extent that third parties are indirectly affected, HHS estimates that this will result in lowered cost due to increased certainty in the marketplace and reduced likelihood of disputes as to whether a covered entity was properly charged, and decrease the number of disputes between wholesalers and manufacturers.

B. Benefits of the Regulation

HHS concludes that the regulation increases clarity for all stakeholders and flexibility for the affected covered entities in how to most efficiently comply with all statutory requirements. The proposed regulation will not create disincentive for manufacturers to pursue designations under section 526 of the FFDCA. It will maintain economic incentives for drugs used for rare diseases, and minimize the increases in health care costs that could result from a broader interpretation of 340B(e) than the one we are offering in the proposed rule.

C. Initial Regulatory Flexibility Analysis

The proposed regulation provides flexibility for the affected covered entities while supporting all statutory requirements and harmonizing with the objectives of encouraging development of drugs for treating rare diseases. A broader interpretation of section 340B(e) would reduce flexibility for covered

entities and particular smaller covered entities and potentially undermine the addition of entities added to section 340B(a)(4) by the Affordable Care Act, by making it economically infeasible for the entities to participate.

Paperwork Reduction Act

The proposed rule contains information-collection activities for certain covered entities that voluntarily choose to purchase designated orphan drugs and that will be required to establish internal data systems to ensure compliance with the regulation. The information collection requirements will assist the covered entity in maintaining program integrity and compliance with the requirements in Section 340B of the PHSA. The information collection activities are based on data collection requirements approved by the Office of Management and Budget (OMB No. 0915-0176 and OMB No. 0915-0327). The proposed rule references statutory requirements to maintain auditable records sufficient to demonstrate program requirements. The currently approved information collection already includes burdens for certification of maintenance and compliance with statutory mandates of the 340B program and for recordkeeping and reporting requirements associated with potential audits.

As required by the Paperwork Reduction Act of 1995 (PRA) (44 U.S.C. 3507(d)), a copy of this proposed rule is submitted to the Office of Management and Budget for its review of the collection of information. Comments concerning information collection requirements are being solicited to: (1) Evaluate whether the proposed information requirement is necessary for the proper performance of functions of the agency, including whether the information will have practical utility; (2) evaluate the accuracy of the Agency's estimate burden; (3) enhance the quality, utility, and clarity of the information to be collected; and (4) minimize the information collection burden on the affected public, including automated collection techniques.

Dated: April 20, 2011.

Mary Wakefield,
Administrator, Health Resources and Services Administration.

Approved: May 16, 2011.

Kathleen Sebelius,
Secretary.

List of Subjects in 42 CFR Part 10

Biologics, Business and industry, Diseases, Drugs, Health, Health care, Health facilities, Hospitals, Orphan drugs, 340B Drug Pricing Program.

For the reasons stated in the preamble, the Department of Health and Human Services, Health Resources and Services Administration proposes to add a new part to 42 CFR part 10 to read as follows:

PART 10—340B DRUG PRICING PROGRAM

Subpart A—General Provisions

Sec.

10.1 Purpose.

10.2 Summary of 340B Drug Pricing Program.

10.3 Definitions.

Subpart B—Eligibility To Purchase 340B Drugs

10.10 Entities eligible to participate in the 340B Drug Pricing Program.

Subpart C—Drugs Eligible for Purchase Under 340B

10.20 Drugs eligible for purchase under 340B.

10.21 Exclusion of orphan drugs for certain covered entities.

Authority: Sec. 340B of the Public Health Service Act (42 U.S.C. 256b), as amended; Sec. 215 of the Public Health Service Act (42 U.S.C. 216), as amended; Sec. 526 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360bb); Sec. 701(a) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 371(a)).

Subpart A—General Provisions

§ 10.1 Purpose.

This part implements section 340B of the Public Health Service Act (PHSA) “Limitation on Prices of Drugs Purchased by Covered Entities.”

§ 10.2 Summary of 340B Drug Pricing Program.

Section 340B of the PHSA instructs the Secretary of Health and Human Services to enter into agreements with manufacturers of covered drugs under which the amount required to be paid to these manufacturers by certain statutorily-defined entities does not exceed the price paid for the drug under title XIX of the Social Security Act reduced by a rebate percentage. Manufacturers participating in the 340B Drug Pricing Program (340B Program) are required to provide these discounts on all covered outpatient drugs.

§ 10.3 Definitions.

Ceiling price means the maximum statutory price established under section 340B(a)(1) of the PHSA.

Covered entity means an entity that meets the requirements under section 340B(a)(5) of the PHSA and is listed within section 340B(a)(4) of the PHSA.

Covered outpatient drug has the same meaning set forth in section 1927(k) of the Social Security Act.

Group purchasing organization (GPO) is an entity that contracts with purchasers, such as hospitals, nursing homes, and home health agencies, to realize savings and efficiencies by aggregating purchasing volume and using that leverage to negotiate discounts with manufacturers, distributors, and other vendors.

Manufacturer has the same meaning as set forth in section 1927(k)(5) of the Social Security Act.

Orphan drug means a drug designated by the Secretary under section 526 of the Federal Food, Drug, and Cosmetic Act (FFDCA).

Participating drug manufacturer means a manufacturer that has entered into a Pharmaceutical Pricing Agreement with the Secretary.

Pharmaceutical Pricing Agreement (PPA) means an agreement described in section 340B(a)(1) of the PHSA.

Section 340B means section 340B of the PHSA.

Subpart B—Eligibility to Purchase 340B Drugs

§ 10.10 Entities eligible to participate in the 340B Drug Pricing Program.

A covered entity means an entity that meets the requirements under section 340B(a)(5) of the PHSA and is listed within section 340B(a)(4) of the PHSA. Covered entities are eligible to purchase covered outpatient drugs under the 340B Program.

Subpart C—Drugs Eligible for Purchase Under 340B

§ 10.20 Drugs eligible for purchase under 340B.

The definition of covered outpatient drug has the meaning given such terms in section 1927(k) of the Social Security Act except as provided in § 10.21 of this chapter.

§ 10.21 Exclusion of orphan drugs for certain covered entities.

(a) *General.* For the covered entities described in paragraph (b) of this section, a covered outpatient drug does not include orphan drugs that are transferred, prescribed, sold, or otherwise used for the rare condition or disease for which that orphan drug was designated under section 526 of the FFDCA. A covered outpatient drug includes orphan drugs when they are transferred, prescribed, sold, or otherwise used for any indication other than treating the rare disease or condition for which the drug was

designated under section 526 of the FFDCA.

(b) *Covered entities to which the orphan drug exclusion applies.* The exclusion of orphan drugs from covered outpatient drugs described in paragraph (a) of this section shall only apply to covered entities qualifying under sections 340B(a)(4)(M) (other than a children’s hospital described in subparagraph (M)) of the PHSA (free-standing cancer hospitals), 340B(a)(4)(N) of the PHSA (critical access hospitals), and 340B(a)(4)(O) of the PHSA (rural referral centers and sole community hospitals). The exclusion does not apply to those entities that meet the 340B Program eligibility requirements and are enrolled under sections 340B(a)(4)(A) through 340B(a)(4)(L) or to children’s hospitals enrolled under section 340B(a)(4)(M) of the PHSA. Where safety-net organizations meet more than one eligibility criteria as covered entities that are eligible under sections 340B(a)(4)(L) through 340(a)(4)(O), these safety-net organizations shall be limited to participating in the 340B Program as only one covered entity type and shall abide by all applicable restrictions and requirements for that entity type.

(c) *Covered entity responsibility to maintain records of compliance.* The responsibility rests with the covered entities listed in paragraph (b) of this section to ensure that orphan drugs that are purchased through the 340B Program are not transferred, prescribed, sold, or otherwise used for the rare condition or disease for which orphan drugs are designated under section 526 of the FFDCA. The covered entities listed in paragraph (b) of this section that purchase orphan drugs under the 340B Program are required to maintain separate purchasing accounts and to provide auditable records upon the written request of the government or government-approved manufacturer audit request that directly pertain to the entity’s compliance with this requirement. The covered entities listed in paragraph (b) of this section that cannot or do not wish to maintain auditable records sufficient to demonstrate compliance, must purchase all orphan drugs outside of the 340B Program. Covered entities are required to notify the Health Resources and Services Administration if they will be purchasing all designated orphan drugs outside the 340B Program.

(d) *Use of group purchasing organizations by free-standing cancer hospitals.* The covered entities remain responsible for complying with all other 340B requirements and applicable Federal, State, and local laws. Free-

standing cancer hospitals enrolled under section 340B(a)(4)(M) must comply with the prohibition against using a group purchasing organization under section 340B(a)(4)(L)(iii) of the PHSA for the purchase of any covered outpatient drug. If auditable records are maintained that demonstrate full compliance with orphan drug purchasing requirements, then free-standing cancer hospitals enrolled under 340B(a)(4)(M) are permitted to use a group purchasing organization to purchase orphan drugs when they are transferred, prescribed, sold, or otherwise used for the rare condition or disease for which that orphan drug was

designated under section 526 of the FFDCa, as these drugs are not considered covered outpatient drugs. However, free-standing cancer hospitals enrolled under 340B(a)(4)(M) are prohibited from using a group purchasing organization to purchase orphan drugs when used for any indication other than treating the rare disease or condition for which the drug was designated under section 526 of the FFDCa, as these drugs are considered covered outpatient drugs. To the extent that free-standing cancer hospitals elect to purchase all orphan drugs outside of the 340B Program, covered entities are

permitted to use a group purchasing organization for those purchases.

(e) *Identification of orphan drugs.* Designations under section 526 of the FFDCa are the responsibility of and administered by the FDA. FDA publishes information pertaining to orphan drug designations pursuant to 21 CFR part 316. Drug manufacturers and affected covered entities seeking to determine whether a drug is designated under section 526 of the FFDCa must consult FDA listings of orphan drugs under section 526.

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