Indian tribes, or on the distribution of power and responsibilities between the Federal Government and Indian tribes.

12. Energy Effects

This rule is not a ''significant energy action'' under Executive Order 13211, Actions Concerning Regulations That Significantly Affect Energy Supply, Distribution, or Use.

13. Technical Standards

This rule does not use technical standards. Therefore, we did not consider the use of voluntary consensus standards.

14. Environment

We have analyzed this rule under Department of Homeland Security Management Directive 023–01 and Commandant Instruction M16475.lD, which guide the Coast Guard in complying with the National Environmental Policy Act of 1969 (NEPA)(42 U.S.C. 4321–4370f), and have determined that this action is one of a category of actions that do not individually or cumulatively have a significant effect on the human environment. This rule is categorically excluded under figure 2–1, paragraph (34)(g), of the Commandant Instruction because it involves the establishment of safety zones. An environmental analysis checklist supporting this determination and a Categorical Exclusion Determination are available in the docket where indicated under **ADDRESSES**.

List of Subjects in 33 CFR Part 165

Harbors, Marine safety, Navigation (water), Reporting and record keeping requirements, Security measures, Waterways.

For the reasons discussed in the preamble, the Coast Guard amends 33 CFR Part 165 as follows:

PART 165—REGULATED NAVIGATION AREAS AND LIMITED ACCESS AREAS

■ 1. The authority citation for Part 165 continues to read as follows:

Authority: 33 U.S.C. 1231; 46 U.S.C. Chapters 701, 3306, 3703; 50 U.S.C. 191, 195; 33 CFR 1.05–1, 6.04–1, 6.04–6, and 160.5; Pub. L. 107–295, 116 Stat. 2064; Department of Homeland Security Delegation No. 0170.1.

■ 2. Add § 165.T09–0192 to read as follows:

§ 165.T09–0192 Tall Ship Safety Zones; War of 1812 Bicentennial Commemoration, Great Lakes.

(a) *Locations.* The following are safety zones:

(1) All navigable waters of the United States located in the Ninth Coast Guard District within a 100 yard radius of the following tall ships: APPLEDORE IV, CHALLENGE, DENIS SULLIVAN, EMPIRE SANDY, FAIR JEANNE, FRIENDS GOOD WILL, HINDU, KAJAMA, LA REVENANTE, LYNX, MADELINE, NIAGARA, PATHFINDER, PEACEMAKER, PLAYFAIR, PRIDE OF BALTIMORE II, RED WITCH, SORLANDET, ST. LAWRENCE II, UNICORN, and the WINDY. These safety zones will be enforced around each tall ship regardless of whether the tall ship is underway, at anchor, or moored.

(2) All navigable waters of the United States located in the Ninth Coast Guard District within a 500 yard radius of each tall ship participating in the re-enactment of the Battle of Lake Erie on September 2, 2013.

(b) Effective and enforcement period. This rule is effective and will be enforced between 12:01 a.m. on July 3, 2013 until 11:59 p.m. on September 10, 2013.

(c) Regulations. (1) In accordance with the general regulations in section 165.23 of this part, entry into a safety zone established by this section is prohibited without the authority of the Ninth District Commander, the cognizant Captain of the Port, or the on-scene designated representative.

(2) The ''designated representative'' of the Ninth District Commander is any Coast Guard commissioned, warrant, or petty officer who has been designated by the Ninth District Commander or the cognizant Captain of the Port to act on his or her behalf.

(3) Permission may be obtained to enter a safety zone established herein by contacting the on-scene designated representative on VHF channel 16.

(4) Each vessel permitted to enter a safety zone established herein must remain at least 25 yards from any tall ships within that zone.

(5) Each vessel permitted to enter a safety zone established by this section must operate at the minimum speed necessary to maintain a safe course and must proceed as directed by the Ninth District Commander, the cognizant Captain of the Port, or the on-scene designated representative.

Dated: June 26, 2013.

M.N. Parks

Rear Admiral, U. S. Coast Guard, Ninth District Commander.

[FR Doc. 2013–17797 Filed 7–19–13; 4:15 pm]

BILLING CODE 9110–04–P

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: Final rule.

SUMMARY: HHS is issuing this final rule to clarify how section 340B(e) of the Public Health Service Act (PHSA) will be implemented. The final rule applies section 340B(e) of the PHSA only to drugs transferred, prescribed, sold, or otherwise used for the rare condition or disease for which the orphan drug was designated under section 526 of the Federal Food, Drug, and Cosmetic Act (FFDCA). The final rule also sets forth that it is the responsibility of the 340B covered entity to maintain auditable records that demonstrate compliance with the terms of the orphan drug exclusion requirements. This rule will provide clarity in the marketplace, maintain the 340B savings for newly-eligible covered entities, and 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.

DATES: This final rule is effective on October 1, 2013.

FOR FURTHER INFORMATION CONTACT: 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, or by telephone at (301) 594–4353.

SUPPLEMENTARY INFORMATION:

I. Background

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 agreements with drug manufacturers of covered outpatient drugs. 42 U.S.C. 256b(a). Pursuant to section 340B(a)(1) of the PHSA, when a manufacturer signs a Pharmaceutical Pricing Agreement (PPA), it agrees 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 taking the Average Manufacturer Price (AMP) and reducing it by the Unit Rebate Amount, which is calculated as indicated in 340B(a)(1) and 340B(a)(2)(A). 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.

The Affordable Care Act and the HCERA made several changes to the 340B Program. The 340B Program generally has relied on published program guidance documents, which are typically finalized after a notice and comment period. However, we have determined that a regulation is necessary to implement these changes. On May 20, 2011, HHS published a notice of proposed rulemaking in the **Federal Register** (76 FR 29183) to provide details about how it proposed to implement section 340B(e) of the PHSA. As stated in the notice, the purpose of issuing this regulation is to: (1) Provide clarity in the marketplace; (2) maintain the 340B savings for newly-eligible covered entities; and (3) 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. (76 FR at 29184).

Section 7101 of the Affordable Care Act added several new categories of eligibility for 340B Program participants, allowing them to have access to 340B drug pricing. 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). It also excluded free-standing cancer hospitals, critical access hospitals, rural referral centers, and sole community hospitals from access to 340B drug pricing for an orphan drug when it is used for a rare disease or condition. 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. A drug is designated by the FDA as ''a drug for a rare disease or condition'' pursuant to section 526 of the FFDCA 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 U.S.C. 360bb(a)(1). This designation is referred to as orphan-drug designation. 21 CFR 316.24. The orphan drug 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 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.

FDA will designate a drug for a rare disease or condition as an orphan drug 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). However, each of the orphan drug incentives applies only when the orphan drug is targeted or used to treat the rare disease or condition and not when used for other indications.

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).

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's 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. Only outpatient drugs that have been approved by FDA 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 can be included as covered outpatient drugs for the 340B Program.

The May 20, 2011, **Federal Register** (76 FR 29183) notice provided a 60-day comment period and HHS received 50 comment letters raising a variety of issues. Comments were received from Members of Congress, manufacturers, 340B entities and providers, and other 340B stakeholders. HHS has carefully considered all comments in developing this final rule, as outlined in Section III, below, presenting a summary of all major comments and agency responses.

II. Summary of the Final Rule

General Provisions (Subpart A)

This final rule establishes a new Part 10 of Chapter 42 of the Code of Federal Regulations, which will include requirements for implementation of certain sections of section 340B of the PHSA ''Limitation on Prices of Drugs Purchased by Covered Entities.'' Additional 340B Program regulations may be published in the future and would be incorporated into this Part.

Eligibility To Purchase 340B Drugs (Subpart B)

Section 10.10 of the final rule establishes that entities meeting the requirements of section 340B(a)(5) of the PHSA and listed within section 340B(a)(4) of the PHSA are eligible to purchase covered outpatient drugs under the 340B Program. 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 (SSA)); (2) An entity receiving a grant under section 340A of the PHSA; (3) A family planning project receiving a grant or contract under section 1001 of the PHSA; (4) An entity receiving a grant under subpart II of part

C of title XXVI of the PHSA (relating to categorical grants for outpatient early intervention services for HIV disease); (5) A state-operated AIDS drug purchasing assistance program receiving financial assistance under title XXVI of the PHSA; (6) A black lung clinic receiving funds under section 427(a) of the Black Lung Benefits Act; (7) A comprehensive hemophilia diagnostic treatment center receiving a grant under section 501(a)(2) of the SSA; (8) A native Hawaiian health center receiving funds under the Native Hawaiian Health Care Act of 1988; (9) An urban Indian organization receiving funds under title V of the Indian Health Care Improvement Act; (10) Any entity receiving assistance under title XXVI of the PHSA (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); (11) An entity receiving funds under section 318 of the PHSA (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); (12) A subsection (d) hospital (as defined in section 1886(d)(1)(B) of the SSA) 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 SSA 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 SSA) greater than 11.75 percent or was described in section 1886(d)(5)(F)(i)(II) of the SSA; and (iii) does not obtain covered outpatient drugs through a GPO or other group purchasing arrangement; (13) A children's hospital excluded from the Medicare prospective payment system pursuant to section 1886(d)(1)(B)(iii) of the SSA, or a free-standing cancer hospital excluded from the Medicare prospective payment system pursuant to section 1886(d)(1)(B)(v) of the SSA, that would meet the requirements of 340B(a)(4)(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 SSA; (14) An entity that is a critical access hospital (as determined under section 1820(c)(2) of the SSA), and that meets the requirements of subparagraph 340B(a)(4)(L)(i); and (15) An entity that is a rural referral center, as defined by section 1886(d)(5)(C)(i) of the SSA, or a sole community hospital, as defined by section 1886(d)(5)(C)(iii) of the SSA, and that both meets the requirements of subparagraph 340B(a)(4)(L)(i) and has a disproportionate share adjustment percentage equal to or greater than 8 percent.

Drugs Eligible for Discounted Purchase Under 340B (Subpart C)

Under § 10.20, covered entities are generally eligible to purchase ''covered outpatient drugs'' as defined in section 1927(k)(2) of the SSA. Under § 10.21, certain drugs are excluded from the definition of ''covered outpatient drugs'' in § 10.20 for certain categories of covered entities. These drugs are orphan drugs used for rare diseases or conditions for which the orphan drug was designated under section 526 of the FFDCA.

As provided under section 340B(a)(10) of the PHSA, 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 has the authority to issue regulations on the Medicaid best price exemption. In the absence of specific guidance, manufacturers may make reasonable assumptions in their calculations, consistent with the general requirements and intent of section 1927 of the Social Security Act, Federal regulations, the Medicaid drug rebate agreement, and their customary business practices.

Section 340B(e) of the PHSA does not alter a manufacturer's obligation to sell covered outpatient drugs at no greater than the 340B ceiling price to the designated covered entities. A manufacturer may not condition the offer of statutory discounts upon a covered entity's assurance to the manufacturer of compliance with section 340B provisions. However, a covered entity is required to be in compliance with the statutory and regulatory provisions of the 340B Program. Failure to do so may result in the entity's obligation to repay a manufacturer for the inappropriate purchase and use of 340B drugs.

Section 10.21(a) establishes that, 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.

Section 10.21(b) describes the covered entities for which the orphan drug exclusion applies when used for the rare condition or disease for which that orphan drug was designated under section 526 of the FFDCA, including covered entities qualifying under PHSA sections 340B(a)(4)(M) (other than a children's hospital described in subparagraph (M)) (free-standing cancer hospitals), 340B(a)(4)(N) (critical access hospitals), and 340B(a)(4)(O) (rural referral centers and sole community hospitals). The exclusion does not apply to covered 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 section 340B(a)(4)(M). Furthermore, if a hospital potentially qualifies under more than one section, such as a 340B(a)(4)(L) disproportionate share hospital and 340B(a)(4)(O) sole community hospital, the hospital must select which enrollment type it chooses to qualify under and comply with the related regulatory and program requirements. During the registration and annual recertification processes, an entity is required to certify that it meets the requirements for such an enrollment type, including the orphan drug exclusion.

Section 10.21(c) establishes that it is the responsibility of the covered entities to which this provision applies 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. These covered entities are required to keep auditable records and provide them upon HRSA's request or upon a government-approved manufacturer audit request that directly pertains to the covered entity's compliance with section 340B(e) of the PHSA. Any HRSA audit of an affected covered entity will include a review of the covered entity's auditable records that demonstrate compliance with this regulation, if applicable. Additionally, in accordance with section 340B(a)(5) of the PHSA, with government approval, a manufacturer has the right to audit an affected covered entity's compliance with this section.

Under § 10.21(c), a covered entity listed in § 10.21(b) that cannot or does not wish to maintain auditable records

sufficient to demonstrate compliance this rule, must notify HRSA and purchase all orphan drugs outside of the 340B Program regardless of the indication for which the drug is used. Once a hospital is enrolled in 340B, it may change its decision to purchase all orphan drugs outside of the 340B Program on a quarterly basis by notifying HRSA. This documentation will be made public. This information will also be verified during the annual recertification process.

Section 10.21(d) clarifies that a free-standing cancer hospital enrolled under section 340B(a)(4)(M) of the PHSA must still comply with the prohibition against using a GPO for covered outpatient drugs under section 340B(a)(4)(L)(iii) of the PHSA. As stated in Section 10.21(a), when an orphan drug is used for the rare condition or disease for which that orphan drug was designated under section 526 of the FFDCA, it is not considered a covered outpatient drug for purposes of the 340B Program. Therefore, a free-standing cancer hospital could use a GPO when an orphan drug is used for a rare disease or condition if it is able to track by indication, as these drugs are not considered covered outpatient drugs and the GPO prohibition only applies to covered outpatient drugs. When an orphan drug is used for a non-rare condition or disease, it is considered a covered outpatient drug and a free-standing cancer hospital cannot use a GPO. If the free-standing cancer hospital is unable track by indication, it would not be able to demonstrate the difference between when an orphan drug is used for a rare disease or condition as compared to a non-rare disease or condition. Therefore, a free-standing cancer hospital must purchase all orphan drugs, regardless of indication, outside of the 340B Program and it is not permitted to use a GPO to purchase those orphan drugs because the hospital would be purchasing orphan drugs that are considered covered outpatient drugs through a GPO.

An enrolled critical access hospital, rural referral center, or sole community hospital is permitted to use a GPO for covered outpatient drugs even if enrolled in the 340B Program. Thus, these types of entities can use a GPO to purchase an orphan drug whether or not it is used for a rare disease or condition, if it chooses not to purchase any designated orphan drugs under the 340B Program.

Section 10.21(e) directs manufacturers and covered entities to information and orphan drug lists that will be published on HRSA's public Web site. Because of the need for recordkeeping and tracking by covered entities which are limited in purchasing orphan drugs for rare conditions, the 340B Program will use the FDA's list of drugs on a quarterly basis. HRSA will publish on its public Web site FDA's section 526 list of drugs on the first day of the month prior to the end of the calendar quarter to govern the following quarter's purchases. Manufacturers and covered entities will use HRSA's published orphan drug list to determine whether a drug is designated under section 526 of the FFDCA and, if so, the rare indication for which it is designated. This information, which includes the name of the drug sponsor, can be accessed by the public at *http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm*.

III. Comments and Responses

HHS received a total of 50 comments in response to the notice of proposed rulemaking published on May 20, 2011, in the **Federal Register** (76 FR 29183). The comments raised numerous issues and included general support of, and general opposition to, the proposed rule implementing section 340B(e) of the PHSA. All comments were considered in developing this final rule.

The following section presents a summary of all major issues raised in the comment letters, grouped by subject, as well as a response to each comment.

1. Interpretation of Statutory Language

Comment: Several commenters supported the proposed rule as clarifying how orphan drugs should be purchased under the 340B Program. Several commenters noted that HRSA's interpretation of the statutory language supports the intent of Congress to improve access to 340B discounted drugs for the newly-eligible entities, while recognizing the issues associated with orphan drug use for rare conditions and diseases, and that a broader interpretation of the prohibition would undermine new covered entity participation and place a substantial burden on affected entities. Commenters asserted that orphan drugs were commonly used for many treatments in addition to the rare condition or disease for which FDA had designated it an orphan drug. Some entities have chosen not to participate in the 340B Program because the costs of paying non-340B prices for all drugs with at least one orphan drug indication could have exceeded the cost saving benefits of other non-orphan designated 340B drugs. Several commenters believe the interpretation of the statutory language reflected in the proposed rule follows the spirit of the 340B Program, giving covered entities access to orphan drugs for non-rare indications under the 340B Program while preserving financial incentives for manufacturers.

Response: HRSA believes the interpretation as set forth in this rule reflects the intent of Congress to expand eligible entities and restrict purchases of certain orphan drugs by both providing 340B savings for newly-eligible covered entities including commonly prescribed uses of orphan drugs and protecting the financial incentives for manufacturing orphan drugs designated for a rare disease or condition.

Comment: Several commenters noted that the limitation of the orphan drug exclusion to FDA-designated orphan drugs when used to treat an orphan indication is consistent with the limitations of the orphan drug statute, implementing regulations, and policy placed on the tax benefits, market exclusivity, and other incentives otherwise given to orphan drug manufacturers. Commenters stated that applying a broader application of the 340B orphan drug exclusion whereby affected entities could not purchase an FDA designated orphan drug for any treatment purpose would be inconsistent with section 526 of the FFDCA, and would limit the covered drugs available to the newly covered entities in the 340B Program in such a way as to significantly limit their ability to participate in the 340B Program.

Response: HRSA agrees with these comments and has proposed a balanced expansion to the 340B discounts to new entities and continued benefits for the development of orphan drugs for rare diseases and conditions.

Comment: Several of the commenters supported the clear statement in the proposed rule that manufacturers are prohibited from placing conditions or limitations on the purchase of orphan drugs for non-orphan conditions.

Response: HRSA has sought to make clear that all orphan drugs that meet the definition of covered outpatient drug for these four types of entities are subject to the same requirements applicable to all other 340B covered outpatient drugs. Therefore, orphan drugs used for common conditions are subject to the same general rules and requirements under the 340B Program as all other covered outpatient drugs (*e.g.,* pricing, availability, etc.). Section 340B(e) of the PHSA 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. At the same time, an affected entity is required to maintain systems that distinguish the use of such drugs for orphan and non-orphan use. If an entity cannot maintain such systems of records, it cannot purchase orphan drugs, regardless of the indication, through the 340B Program. Failure to do so may result in the entity's obligation to repay a manufacturer for the inappropriate purchase and use of 340B orphan drugs for prohibited purposes.

Comment: Several comments from manufacturers included the assertion that the plain text of the 340B orphan drug exclusion does not permit an indication-specific interpretation. Others stated that the statutory language unambiguously applied to drugs and not a particular use of a drug. Some urged HRSA to reach the same conclusion on the grounds that if Congress had intended the statute to be interpreted on the basis of the indication, that the statute would have expressly stated that it only applied when utilized for the rare designation or indication. One commenter stated that when Congress intends to distinguish between different indications of a drug, the term ''indication'' is expressly stated in the statute and that in the absence of express references to particular indications, a reference to ''a drug'' designated under section 526 for a rare disease or condition applies to all uses of the drug. In support of this statement the commenter stated that the relevant provisions of FFDCA section 736(a)(1)(F) and the Patient Protection and Affordable Care Act section 9008(e)(3) contain ''indication-specific'' language.

Response: This rule is consistent with the language of the orphan drug exclusion in 340B(e) of the PHSA, which states that it applies to drugs ''for a rare disease or condition.'' Interpreting the statutory language to exclude all uses of drugs with an orphan designation, including indications for other diseases and conditions, would nullify the benefits of the expansion of the 340B Program for those entities. Therefore, we believe that interpreting the statutory language to exclude all indications for a drug that has an orphan drug designation is contrary to Congressional intent to balance the interests of orphan drug research and the expansion of the 340B Program to new entities. Drugs that are marketed for a rare disease are in some cases also approved for other indications; some of these drugs are among the most widely used today. This rule recognizes the unique issues associated with orphan drugs, when the drug with such a designation is used for a rare disease or condition, by excluding them from the 340B Program for these entities. This approach is consistent with the implementation of the FFDCA by FDA. Some orphan designated drugs have not yet been approved for marketing for the rare condition or disease, but may have marketing approval for other indications. The fact that drugs can have multiple indications, only some of which qualify for orphan designation, has led HHS to conclude, consistent with the statutory language, that the exemption from the term ''covered outpatient drug'' under section 340B(e) of the PHSA applies to orphan drugs only when they are transferred, prescribed, sold, or otherwise used for the rare condition or disease for which the orphan drug was designated.

Comment: Some of the commenters asked the agency to make further clarifications in its interpretation of section 340B(e) of the PHSA. Some asked that HRSA clarify the confusion that will exist because of ''designated'' versus ''designated/approved'' products on the FDA orphan drug list.

Response: HRSA believes that the rule clarifies orphan drug designations as it applies to section 340B(e) of the PHSA. A drug is designated by the FDA as ''a drug for a rare disease or condition'' pursuant to section 526 of the FFDCA if, at the request of the sponsor, FDA finds that the drug is being or will be investigated for a rare disease or condition. This designation is referred to as ''orphan-drug'' designation. The award of an orphan drug designation does not alter the standard regulatory requirements and process for obtaining marketing approval, which is a separate process administered by the FDA's 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. 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 can be included as covered outpatient drugs in the 340B Program.

Comment: Some commenters stated that HRSA should clarify that the 340B orphan drug exclusion will only apply for a drug manufactured by the sponsor of the orphan drug—not generic drugs or other manufacturers of the same drug for non-orphan conditions.

Response: HRSA believes that it is clear that the exclusion only applies to those drugs that match the section 526 listing by the FDA, which includes the name of the drug's sponsor. HRSA has further clarified in the preamble that the exclusion is limited to the drug that is specific to the sponsor listed.

Comment: Some commenters said that the 340B orphan drug exclusion should only apply through the 7-year market exclusivity period granted to orphan drugs. They contend that section 340B(e) of the PHSA should not apply for orphan drugs that have exceeded this exclusivity period.

Response: Given that section 340B(e) of the PHSA makes no mention of marketing exclusivity, HRSA does not interpret the statutory language to only apply through the exclusivity period. Regardless of exclusivity, an orphan drug maintains its designation status by FDA indefinitely, even after the exclusivity period.

2. Administrative Burden

Comment: Nearly all of the comments submitted in support of the proposed rule expressed concern about the potential burdens of maintaining records to demonstrate compliance, as described in proposed § 10.21(c). While many noted it was appropriate that the responsibility for demonstrating compliance remain with the covered entity, most asserted that § 10.21(c) would be challenging for covered entities and asked HRSA to recognize the burdens and allow flexibility regarding the particular approaches covered entities use for compliance. A commenter representing hospitals said its members recognized the challenges but reported they would be able to ensure, on a drug-by-drug basis, compliance with § 10.21(c) of the proposed rule. The commenter asked HRSA to allow hospitals to use alternative compliance systems that do not require separate purchasing accounts. Other commenters asserted that current split-billing software cannot track or provide auditable records regarding patients and their diagnoses.

Response: HRSA recognizes that compliance with this rule may be challenging for the subset of covered entities to which it applies. HRSA's OPA will provide technical assistance to covered entities seeking information concerning the new auditable records requirements. However, to ensure program integrity, the ability of a covered entity to determine which drugs are going to the entity's eligible patients has always been an essential element of covered entity participation. Under this rule, failure to comply with the applicable requirements is treated as violating the prohibition under sections 340B(a)(5)(B) and 340B(a)(5)(C) of the

PHSA. Utilization of the 340B Program is voluntary and covered entities should take into account any burden they may have in ensuring compliance. The covered entity is responsible for ensuring that records that document its compliance are auditable by the government or manufacturers in accordance with section 340B(a)(5)(C) of the PHSA. HRSA has instituted a covered entity audit program, and in these audits HRSA will include a review of covered entities' auditable records that demonstrate compliance with this regulation, when applicable. Additionally, in accordance with section 340B(a)(5) of the PHSA, manufacturers have the right to audit covered entities' compliance with these requirements. As already permitted by this program, the covered entity may also document its compliance by developing an alternative system to tracking each discounted drug through the purchasing and dispensing process. (59 FR 25113 (May 13, 1994)). Alternative tracking systems must be approved and will be considered by HRSA on a case-by-case basis. Under § 10.21(c), affected covered entities that cannot or do not wish to maintain auditable records sufficient to demonstrate compliance with this rule, must purchase all orphan drugs, regardless of indication, outside of the 340B Program.

Comment: While noting it will be burdensome to make necessary adaptations, some commenters stated that their current split-billing software and other systems can be updated to track drug purchases with patient diagnoses to create auditable records that show compliance. One hospital said it will be using ICD–9–CM codes and noted this should be a relatively simple approach that most hospitals should be able to use. The commenter thought this approach would likely be over-inclusive regarding orphan drug transactions, so there would be a low risk of non-compliance. One hospital said it would be difficult, but it would be able to mine data from clinical systems to support an audit trail to comply with the recordkeeping requirements. A few commenters recognized there will be expenses involved in complying with the recordkeeping requirements of § 10.21(c), but believed the costs would be more than offset by realized savings. A few covered entity commenters mentioned they would be ready and willing to respond to government or government-approved manufacturer audit requests, as described under proposed § 10.21(c).

Response: HRSA believes that maintaining auditable records and tracking the use of orphan drugs by indication is achievable. The rule continues to recognize that participation in the 340B Program is voluntary and allows covered entities to determine whether to participate. Likewise, covered entities that are unable or unwilling to respond to an appropriate audit request should not participate in the 340B Program. In addition, covered entities can propose alternative tracking systems for approval by HRSA on a case-by-case basis. While not applicable to all covered entities, HRSA believes the benefits of purchasing orphan drugs in the 340B Program will typically outweigh the costs of implementing these systems.

Comment: Many commenters pointed out that diagnosis codes and other information are not readily available for prescriptions handled in the retail setting. Concerned that resulting costs in the retail setting could outweigh the benefits of participation in the 340B Program, commenters asked HRSA to create alternatives and take the necessary steps in developing the final rule to make certain covered entities have a chance of participating and benefitting from the 340B Program.

Response: HRSA recognizes that these new requirements will require additional procedures and system capabilities. The affected hospitals will need to determine how they will meet these requirements and the cost of ensuring compliance with this rule. HRSA will continue to work with the covered entities to which this provision applies to provide information and technical assistance to find efficient and effective means of participating in the 340B Program. HRSA guidelines (59 FR 25113 (May 13, 1994)) allow the covered entity discretion to develop an alternative system, short of tracking each discounted drug through the purchasing and dispensing process, to prove compliance. If an alternate system of tracking is proposed, it must be approved by HRSA. Each alternate system of compliance will be reviewed on a case-by-case basis (59 FR 25113 (May 13, 1994)). Under § 10.21(c), affected covered entities that cannot or do not wish to maintain auditable records sufficient to demonstrate compliance with this rule, must purchase all orphan drugs, regardless of indication, outside of the 340B Program.

Comment: Many commenters suggested, as an alternative in both hospital and retail settings, that HRSA allow entities to conduct a retrospective review or track historical utilization of orphan drugs as a proxy for current utilization rather than a drug-by-drug analysis. Commenters suggested that covered entities would submit these alternative tracking systems to HRSA for advance approval and said a flexible approach would help ensure broader participation in the 340B Program while maintaining program integrity. One commenter suggested HRSA could limit the burdens by requiring covered entities to maintain records of orphan drugs that are actually used for the orphan indication rather than tracking all uses since orphan drug use is rare by definition.

Response: HRSA believes the legislative language permits an orphan drug to be dispensed only for a non-orphan condition under the 340B Program. In order to ensure compliance, the entity must maintain auditable records sufficient to demonstrate compliance with this rule. A proxy for current utilization will not meet auditable records compliance requirements to determine if the orphan drugs are used for a rare disease or condition. However, HRSA is amenable to alternate recordkeeping systems that would permit such analysis.

Comment: One commenter expressed concern about whether covered entities could comply with proposed § 10.21(c), without additional guidance from HRSA. For instance, the commenter noted that FDA's Web site does not include National Drug Codes (NDCs) for orphan products, and said that HRSA should provide guidance regarding whether all drugs appearing on the FDA orphan drug list would be eligible for purchase for off-label uses.

Response: HRSA believes that the rule provides sufficient direction for covered entities to identify drugs that are subject to the orphan drug provision and will provide additional assistance as appropriate. The rule specifies the circumstances under which an orphan drug meets the definition of covered drug for the purposes of the 340B Program. This information can be accessed by the public at *http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm*. Because of the need for recordkeeping and tracking by covered entities which are limited in purchasing orphan drugs for rare conditions, the 340B Program will use the FDA's list of drugs on a quarterly basis. HRSA will publish on its public Web site FDA's section 526 list of drugs on the first day of the month prior to the end of the calendar quarter to govern the following quarter's purchases. Manufacturers and covered entities will use HRSA's published orphan drug list to determine whether a drug is designated under section 526 of the

FFDCA and, if so, the rare indication for which it is designated.

Comment: One wholesaler noted its position in the middle of the supply chain would likely make it necessary to institute additional compliance activities and/or offer additional assistance to covered entities to help them meet their compliance responsibilities under proposed § 10.21(c). The wholesaler noted this could add costs to its daily operations.

Response: HRSA encourages all stakeholders to develop mechanisms to ensure efficiency and compliance. HRSA will continue to provide technical assistance to stakeholders regarding compliance requirements and implementation of this rule.

Comment: Some commenters expressed that the proposed rule failed to address compliance issues and enforcement of hospital noncompliance. One commenter asserted that manufacturers would be unable to audit covered entities' compliance with section 340B(e) until existing audit guidelines are amended through a notice and comment process.

Response: The rule interprets the meaning of section 340B(e) of the PHSA and makes clear that failure to comply is treated as a failure to comply with the prohibition on transferring drugs to individuals other than patients of the entity under section 340B(a)(5)(B) of the PHSA. This is consistent with previous guidance issued by the Department after notice and comment (59 FR 25113 (May 13, 1994)), which indicates that use of 340B discounted drugs in excluded services (*e.g.,* inpatient setting, ineligible site) is drug diversion and therefore violates section 340B(a)(5)(B) of the PHSA. The current manufacturer audit guidelines (61 FR 65406 (December 12, 1996)) apply to violations of section 340B(a)(5)(B) of the PHSA, and therefore manufacturers have the ability to audit covered entities' compliance with the orphan drug provision pursuant to those guidelines. A hospital's non-compliance with the requirements of this rule will be pursued by the Department similarly to any other violation of sections 340B(a)(5)(A) and 340B(a)(5)(B). HRSA has instituted audits of covered entities, and in future audits, HRSA will include a review of covered entities' auditable records that demonstrate compliance with this regulation, where applicable. In addition, HRSA permits manufacturer audits of covered entities in which the manufacturer demonstrates reasonable cause that the entity is violating statutory prohibitions against duplicate discounts (340B(a)(5)(A)) or diversion (340B(a)(5)(B)).

Comment: Some commenters asserted that, at the time of purchase, a given drug's indication will be unknown and that after the drug is used it will be impossible, under current coding procedures, to determine whether the drug was used for a rare indication or otherwise.

Response: In those cases where a covered entity cannot comply with the requirement to maintain auditable records demonstrating compliance with the orphan drug rule, the rule states the covered entity must purchase all orphan drugs, regardless of indication, outside the 340B Program to ensure compliance. Prior to purchasing orphan drugs, an entity is required to notify HRSA if it is able to comply with this rule and if it will be purchasing all orphan drugs outside the 340B Program. HRSA will add this information for relevant entities to its public Web site so stakeholders are aware of a covered entity's purchasing practices under this rule. Covered entities will have the option of either developing additional documentation, using drugs purchased outside 340B, or developing an alternative method of compliance. Alternate tracking systems will be reviewed for approval by HRSA on a case-by-case basis (59 FR 25113 (May 13, 1994)).

Comment: Several manufacturers asserted that the proposed rule would require manufacturers to participate in a complex new framework in which they would have to sell their orphan drugs to newly-eligible entities through two different accounts; determine whether particular sales were going through proper accounts; monitor the newly-eligible entities, in an effort to ensure that their 340B purchases of orphan drugs were limited to circumstances where the drugs were ultimately used for non-orphan indications; and reduce the risks of payment error by attempting to educate the newly-eligible entities about the rare disease(s) for which the manufacturer's orphan drugs were designated and how those diseases should be identified on claims forms. In the aggregate, the costs of performing these various new functions (including costs of personnel, data systems, services of relevant consultants, *etc.*) would be significant, and would drain resources from tasks central to the company's mission.

Response: The regulation does not create new requirements or mandatory functions for manufacturers that participate in the 340B Program. The 340B Program already includes circumstances where covered entities purchase a drug from the manufacturer both inside and outside of the 340B Program (*e.g.,* drugs that may be either inpatient or outpatient, drugs subject to Medicaid rebate claims, drugs for individuals not eligible as patients).

3. Best Price

Comment: Several manufacturers commented that HRSA cannot require manufacturers to sell orphan drugs to the newly-eligible entities at 340B prices until CMS issues guidance confirming explicitly that sales of orphan drugs to newly-eligible entities at (or below) 340B prices are exempt from Medicaid Best Price determinations.

Response: HRSA does not believe that compliance with the 340B Program is contingent upon implementing regulations expressly addressing the effect on Medicaid Best Price for orphan drugs. As provided under section 340B(a)(10) of the PHSA, 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 has the authority to issue regulations on the Medicaid best price exemption. In the absence of specific guidance, manufacturers may make reasonable assumptions in their calculations, consistent with the general requirements and intent of section 1927 of the Social Security Act, Federal Regulations, the Medicaid drug rebate agreement, and their customary business practices.

4. Must Offer

Comment: One commenter asserted that the proposed rulemaking represents an impermissible attempt to implement the ''must offer'' provision of the Affordable Care Act and that the ''must offer'' provision can only be implemented if it is written into the PPA. Section 340B(a)(1) of the PHSA indicates that the PPA shall require ''. . . that the manufacturer offer each covered entity covered outpatient drugs for purchase at or below the applicable ceiling price if such drug is made available to any other purchaser at any price.'' Several other manufacturers commented on the must offer provision and expressed concerns about how that language would be implemented. One commenter argued that section 340B(a)(1) of the PHSA, as amended by the Affordable Care Act to require manufacturers to ''offer each covered entity covered drugs for purchase at or below the applicable ceiling price if such drug is made available to any other purchaser at any price,'' means that manufacturers ''must sell'' orphan drugs to covered entities under the terms of

the statute, as interpreted by HRSA in the proposed rule.

Response: This regulation is not dependent upon implementation of the ''must offer'' provision, and even if it were, this regulation would be a permissible implementation of that provision. Long before the recent inclusion of the ''must offer'' provision in the 340B statute by the Affordable Care Act, the Department has consistently held that manufacturers may not single out covered entities from their other customers for restrictive conditions that would undermine the statutory objective, and that manufacturers must not place limitations on transactions which would have the effect of discouraging entities from participating in the program (59 FR 25113 (May 13, 1994)). This would include a requirement that manufacturers offer drugs at the 340B discount to 340B covered entities on the same basis as its other customers. A refusal to offer orphan drugs to a 340B covered entity on the basis of 340B Program participation would violate the 340B statutory requirements.

Section 340B(e) of the PHSA does not alter a manufacturer's obligation to sell covered outpatient drugs at no greater than the ceiling price to the designated covered entities. In addition, the ''must offer'' provision would not need to be specifically written into the PPA prior to taking effect. As the U.S. Supreme Court recently confirmed (Astra USA v. Santa Clara County, 131 S.Ct. 1342 (2011)), PPAs are not transactional, bargained-for contracts, but simply serve as the means by which drug manufacturers opt into the statutory framework of the 340B Program.

5. GPO Prohibition

Comment: Several manufacturers commented that the proposed rule permitting the use of a GPO to purchase orphan drugs when used for the orphan designated purpose was contrary to statute and stated that there were no statutory exceptions to the GPO prohibition. Several manufacturers expressed the view that the proposed rule's treatment of the GPO prohibition as applied to free-standing cancer hospitals was inconsistent with prior application and would substantially undermine the GPO prohibition.

Response: Section 340B(a)(4)(L)(iii) of the PHSA requires certain hospitals participating in the 340B Program to ''not obtain covered outpatient drugs through a group purchasing organization or other group purchasing arrangement.'' The 340B statute prevents disproportionate share hospitals, children's hospitals, and free-standing cancer hospitals from obtaining covered outpatient drugs through a GPO. Of those entities, only free-standing cancer hospitals are impacted by the orphan drug exclusion. In this final rule, free-standing cancer hospitals are permitted to use a GPO to purchase orphan drugs only 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 covered outpatient drugs for these hospitals for purposes of the 340B Program. If the free-standing cancer hospital chooses to use a GPO for purchasing orphan drugs when used for a rare disease or condition for which it was designated, it is required to maintain auditable records that demonstrate full compliance with orphan drug purchasing requirements and limitations. If a free-standing cancer hospital does not have the necessary tracking systems in place to ensure compliance with the GPO prohibition for the use of orphan drugs in non-designated situations, it must purchase all orphan drugs, regardless of indication, through a separate purchasing account outside of the 340B Program and would not be permitted to use a GPO for any of those drugs. HRSA agrees that a free-standing cancer hospital prohibited from using a GPO under the 340B Program should not use a GPO for the purchase of all orphan drugs if the hospital cannot or is unwilling to create auditable records concerning orphan drug purchases. Allowing a free-standing cancer hospital to purchase all of its orphan drugs through GPOs would, in effect, allow hospitals to purchase orphan drugs that are included in the definition of ''covered outpatient drugs,'' which is prohibited. The rule has been amended to reflect this distinction.

Comment: Entities and their stakeholder groups generally supported proposed § 10.21(d), which allows a free-standing cancer hospital that decides not to use 340B for orphan drugs to purchase orphan drugs through a GPO instead. One commenter explained that HRSA has the legal authority to interpret the GPO prohibition provision flexibly to permit a free-standing cancer hospital to use a GPO for all orphan drugs if it decides not to track non-orphan use. The commenters stated that this approach provides cancer hospitals, which use a much higher volume of orphan drugs than other affected covered entities, flexibility as they evaluate their compliance options.

Response: HRSA disagrees with the commenters who state that HRSA has the flexibility to permit a free-standing cancer hospital to use a GPO for all orphan drugs if it decides not to track non-orphan use. Under this assertion, the free-standing cancer hospital could use a GPO for any orphan drug, whether used for a common condition or used for the orphan designation. However, as noted above, the statute is clear that certain entities, including a free-standing cancer hospital, cannot use a GPO for obtaining covered outpatient drugs. HRSA has concluded that the statute does not permit the commenter's proposed alternative because orphan drugs being used for non-rare indications are covered outpatient drugs and included in the 340B Program. While HRSA recognizes that the volume of drugs utilized by a free-standing cancer hospital is substantial, and such a hospital has the desire to minimize administrative burden, it does not change the definition of covered outpatient drug for purposes of the GPO prohibition. A hospital can choose not to enroll in the 340B Program if it calculates that the benefits are not sufficient given the program requirements to track purchases.

6. Impact on Orphan Drug Incentives

Comment: Several manufacturers expressed that the proposed rule would significantly undermine financial benefits for manufacturers by sharply reducing economic incentives for the manufacturing of therapies to treat rare diseases. In contrast, other commenters suggest that the rule as proposed would upset the balance in the marketplace by creating incentives for the manufacturer to seek the development of drugs for rare diseases or conditions.

Response: This rule implements the PHSA statute for the 340B Program. It does not, nor does HRSA have the authority, to alter the statutory incentives for orphan drug development under the FFDCA. Manufacturers that seek orphan-drug designations for rare diseases under the FFDCA continue to receive the full statutory benefits for those designations under this rule. The incentives provided to manufacturers of orphan drugs are specific to an orphan drug designation for a rare disease or condition.

Comment: Some covered entity commenters assert that the orphan drug exclusion, as proposed, follows the spirit of the 340B Program, providing new entities access to the program while preserving financial incentives for manufacturers. According to these comments, the proposed rule is consistent with the FDA's approach of

tying tax credits, market exclusivity, orphan drug research grants, user fee exemptions, and other orphan drug incentives to orphan drug indications. One commenter pointed out that the exclusion of orphan drugs from 340B pricing for certain newly-eligible entities is, in effect, yet another incentive to promote investment in drugs for the diagnosis or treatment of rare diseases or conditions. This commenter believes the incentive is properly limited to orphan drugs when used for a rare disease or condition and is consistent with Congressional intent that the 340B orphan drug exclusion protect those drugs used for orphan diseases and populations.

Response: HRSA agrees that the orphan drug exclusion as outlined in this regulation follows the intent of the 340B Program by providing the newly added entities access to the program benefits while preserving financial incentives for manufacturers to develop orphan drugs for rare diseases or conditions.

7. Impact on Covered Entities

Comment: All of the comments from covered entities and their stakeholder groups concurred with HRSA's estimate that the proposed rule would result in a net savings for affected covered entities. Some said the savings would be difficult to quantify, but one commenter noted that orphan drugs made up only 1.5 percent of their pharmacy inventory last year, but accounted for 52 percent of inventory costs. Many comments from covered entities provided HRSA with estimates of potential savings estimated to be between $360,000 and $3,000,000 annually. All of the commenters said that significant savings from the 340B Program are needed to safeguard the financial stability of safety-net providers and allow them to extend improved care to their patients. Another said the funds saved on orphan drugs through the 340B Program are desperately needed to help patients in rural communities. A few commenters said that a broad interpretation of the exclusion that includes drugs used for non-rare indications would so substantially reduce program savings so as to make the overall costs outweigh the benefits of 340B participation.

Response: HRSA continues to believe that although difficult to estimate with specificity, the final rule strikes the appropriate balance between providing 340B covered entity legislatively-required discounts, while preserving the incentives of manufacturers to continue to produce orphan drug products for rare diseases and conditions. The final rule is expected to benefit the affected covered entities by establishing certainty as to the applicability of the exclusion and ensuring the option of continued access to drugs that, although designated as orphan drugs for certain indications, are approved for broader uses.

8. Impact on Patient Populations

Comment: Some comments from manufacturers and manufacturer groups expressed the view that the proposed rule would threaten the well-being of vulnerable populations by decreasing access to needed orphan drugs by delaying the purchase and dispensing of medications due to the need to do so on an indication basis.

Response: Hospitals that participate in the 340B Program are already required to manage drug purchases to ensure that drugs used in the 340B Program are for outpatient purposes only. Participation in the 340B Program is voluntary and covered entities are not prohibited under section 340B from purchasing drugs outside of the 340B Program. Covered entities are never encouraged to delay dispensing drugs in any manner that would threaten the health and safety of a patient.

Comment: Some manufacturers expressed that the proposed rule would jeopardize the economic viability of a product by substantially reducing its commercial marketplace.

Response: HRSA believes that the final rule's interpretation best meets the intent of Congress in the enactment of section 340B(e) of the PHSA, and that implementation of this rule will not result in jeopardizing the economic viability of orphan drug products. The impact of this final rule is narrowed by the fact that the orphan drug exclusion only applies to a subset of newly-eligible entities which are expected to make up a small percentage of the total purchases of covered outpatient drugs through the 340B Program. Covered entity drug purchases under the entire 340B Program are estimated at $6 billion, making up an estimated 2 percent of the total prescription drug market. In fiscal year 2012, the covered entities to which this rule applies comprised an estimated 3.13 percent of total 340B sales for all covered entities. The purchase of orphan drugs would be a subset of these purchases. All other eligible 340B entities may purchase orphan drugs for any disease or condition.

Comment: Several entities commented that they use the additional savings from the purchase of orphan drugs for non-orphan indications at 340B pricing to benefit their patients and communities. One called the proposal an important step in supporting access and comprehensive provision of healthcare for millions of Americans. Certain comments from the four most recently eligible entities noted specific plans to use savings to expand pharmacy services, reduce medication costs for the neediest patients, provide medication therapy management services, and reduce readmission rates at their institutions. Several commenters said they needed the benefits of 340B Program participation to help offset the costs of uncompensated care they provide to their communities each year. One comment asserts the inability of covered entities to obtain orphan drugs under the 340B Program would have a huge negative impact on the ability of patients to treat their diseases when these drugs become too expensive and unattainable.

Response: HRSA believes that this rule's interpretation provides clarity in the marketplace, reflects the intent of Congress to maintain the 340B savings for newly-eligible covered entities, and protects the financial incentives for manufacturing orphan drugs designated for a rare disease or condition.

9. Effective Date/Application on Past vs. Prospective

Comment: Some manufacturers commented that the rule should only be applied prospectively. One stated that a good faith interpretation prior to the finalization of a regulation should be allowed to stand. Some stated that applying the standard to prior sales would be inappropriate and administratively burdensome.

Response: HRSA agrees that attempting to apply the final rule retrospectively would be administratively burdensome and difficult to implement for all stakeholders. The final rule will only apply prospectively.

10. Miscellaneous

Comment: One commenter asked HRSA to clarify how the rule would apply to contract pharmacies of affected covered entities. In particular, the commenter asked HRSA to allow covered entities to use a different compliance approach at their main and contract facilities. Under this scenario, the main facility would maintain auditable records to show compliance under § 10.21(c), while a satellite facility using a contract pharmacy would be allowed not to comply with the recordkeeping requirements and purchase all orphan drugs outside the 340B Program.

Response: Covered entities and their contract pharmacies are required to

keep auditable records and provide them upon either HRSA's request or upon a government-approved manufacturer audit request, provided that audit request directly pertains to the covered entity's compliance with section 340B(e) of the PHSA. Contract pharmacies are under the same compliance requirements with this rule as a covered entity. Affected covered entities with contract pharmacies that cannot or do not wish to maintain auditable records sufficient to demonstrate compliance with this rule, must purchase all orphan drugs, regardless of indication, outside the 340B Program. A covered entity that is listed on the 340B database and compliant with the auditable records requirement for orphan drugs purchased under 340B can have an outpatient facility that chooses not to comply with the recordkeeping requirement if the outpatient facility makes all of its orphan drug purchases outside the 340B Program.

A covered entity that cannot or does not wish to maintain auditable records sufficient to demonstrate compliance with this rule, must inform HRSA and purchase all orphan drugs outside of the 340B Program regardless of the indication for which the drug is used. Once a hospital is enrolled in 340B, it may change its decision to purchase all orphan drugs outside of the 340B Program on a quarterly basis by notifying HRSA.

Comment: One manufacturer requested that HRSA clarify that covered entities that lose their eligibility for the 340B Program are not permitted to participate while seeking to meet eligibility requirements.

Response: Once a covered entity is no longer eligible for the 340B Program and removed from the 340B public database, that entity is not eligible to purchase 340B drugs.

IV. Economic and Regulatory Impact

Executive Orders 13563 and 12866 direct agencies to assess all costs and benefits of available regulatory alternatives and, if regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, public health and safety effects, distributive impacts, and equity). Executive Order 13563 emphasizes the importance of quantifying both costs and benefits, or reducing costs, of harmonizing rules, and of promoting flexibility. This rule has been designated a ''significant action'' under section 3(f) of Executive Order 12866. The rule has been reviewed by the Office of Management and Budget.

Impact of the New Rule

Analysis of Impacts

HHS has examined the impact of this final 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). By way of background, the requirement that all covered entities maintain auditable records of 340B purchases is mandated by statute (340B(a)(5)(C) of the PHSA) and predates this rule. Therefore, this regulation does not increase the burden of tracking or making available auditable records of 340B drug purchases not impacted by the orphan drug exclusion.

This regulation does implement a revision to the preexisting statutory recordkeeping requirement by necessitating that newly covered entities listed in § 10.21(b) be responsible for ensuring that any orphan drugs purchased through the 340B Program are not transferred, prescribed, sold, or otherwise used for the rare condition or disease for which the orphan drugs are designated under section 526 of the FFDCA. A newly covered entity will be required to declare whether it will purchase orphan drugs under 340B in its initial application, annual recertification, or change request. Only when a newly covered entity can maintain and provide auditable records that track the indication for 340B purchases of orphan drugs, will the entity be in compliance with this regulation. Tracking the indication for orphan drugs may increase the administrative burden of utilizing orphan drugs under the 340B Program. HRSA has no data or experience to employ in projecting a burden estimate in these cases.

Our approach at implementation complies with statutory requirements while giving covered entities the flexibility to develop an alternative system of compliance (which must be approved by the Secretary) or decide not to use orphan drugs under the statute should they determine the burden to be excessive. Finally, none of the comments received provided a less burdensome alternative that meets the existing statutory requirements or provided information to quantify the burden under the Paperwork Reduction Act.

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.

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 promulgating any final 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 $139 million, using the most current (2011) Implicit Price Deflator for the Gross Domestic Product. HHS does not expect this final 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 either the costs or the benefits of the final rule. However, we expect the benefits to exceed the costs as explained below.

HHS has reviewed this final 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 requirements set forth in this final rule will 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, Benefits and Transfer Effects of the Regulation

1. Impact on Covered Entities

The final rule provides covered entities with clarity on the meaning of section 340B(e) of the PHSA and

provides flexibility in making purchasing decisions. Under the final rule, covered entities will have the choice to either purchase a drug with an orphan designation under the FFDCA outside of the 340B Program or to purchase such drugs under the 340B Program while maintaining auditable records required under section 340B(a)(5)(C) of the PHSA that show that such drugs are not used for an orphan drug indication. 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. However, as of April 1, 2013, 967 parent facilities and 2212 outpatient/child sites of the four types of affected entities are enrolled. Affected entities make up 10.3 percent of all covered entity types.

HHS has received anecdotal information suggesting that, absent this final rule, some manufacturers have refused to offer any orphan drugs for any indication under 340B to the newly-affected covered entities. By clarifying that such actions are inconsistent with drug manufacturers' participation agreements related to the 340B Program, the final rule is expected to increase affected covered entities' access to 340B price reductions on orphan drugs when those drugs are used for indications other than those for which the drug received an orphan drug designation. HHS does not have sufficient information to make a comprehensive assessment.

The total amount in reduced expenditures of drugs resulting from this rule depends on market activity absent this regulation, compared with market activity following promulgation of this final rule. 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 at $6 billion and make up an estimated 2 percent of the total prescription drug market. The only covered entities impacted by this final rule are the entities listed in 340B(e). In fiscal year 2012, these covered entities only made up an estimated 3.13 percent of total 340B sales for all covered entities. The purchase of orphan drugs would be a subset of these purchases.

The savings for entities purchasing under 340B varies considerably, with savings as high as 50 percent. HHS estimates that the final rule will help ensure sales at or below the 340B ceiling price in 50 to 75 percent of such sales to the newly-eligible entities where orphan designated drugs are used for an indication other than the rare disease or indication for which the orphan drug received its designation. Based upon these estimates, HHS projects that the final rule may result in a $6 to $9 million reduction in the cost to acquire drugs by the affected covered entities versus what these affected entities are paying to orphan drug manufacturers without the proposed rule for the purchase of these drugs for non-rare indications. HHS does not have sufficient data on the breakout of inpatient versus outpatient drug use. This cost reduction would be less if outpatient purchases by these covered entities were significantly less than inpatient purchases (*e.g.,* if outpatient drugs were 50 percent of orphan drug purchases, then the cost reduction would only be $10 to $15 million). While concrete estimates cannot be provided, HHS concludes that this rule will result in a net economic benefit to the affected covered entities. This conclusion is based upon the assumption that the final rule will result in greater access to 340B pricing on drugs that have an orphan designation and are being purchased for non-rare uses, than without the rule, 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, there would be continued uncertainty and variability with a general tendency among many manufacturers to broadly interpret the exclusion which would minimize or eliminate savings to the covered entities.

2. Impact on Participating Manufacturers

The final rule creates no new reporting or record-keeping requirements for manufacturers that have a 340B PPA with the Secretary. The final rule clarifies section 340B(e) to assist manufacturers in complying with their statutory responsibilities. As noted above, by definition, all 340B drugs must have marketing approval for at least one indication. There are approximately 390 drugs that have been approved by the FDA for rare diseases and conditions. 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 non-rare indications. Of those drugs, only those used for outpatients and for non-rare indications are eligible for purchase under the 340B Program. The pharmaceutical manufacturers of these orphan designated drugs with at least one marketing approval will be affected by this rule.

The impact of this final rule is narrowed by the fact that the orphan drug exclusion only applies to a subset of newly-eligible rural hospitals, critical access hospitals, and free-standing cancer hospitals which in fiscal year 2012, made up an estimated 3.13 percent of total 340B sales for all covered entities. 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 for non-rare indications, 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 occur when orphan designated drugs are purchased for their designated rare uses.

3. Impact on other Parties

HHS has concluded that this final 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 market place 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. Regulatory Flexibility Analysis

The final rule provides flexibility for the affected covered entities while supporting all statutory requirements. Alternative interpretations 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 less economically feasible for these entities to participate.

Paperwork Reduction Act

The final rule contains information-collection activities for certain covered entities that voluntarily choose to purchase designated orphan drugs by requiring them to establish internal data systems to ensure compliance with the statute. The information collection

requirements will assist covered entities in maintaining program integrity and compliance with the requirements in Section 340B of the PHSA. The existing 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 new statutory orphan drug requirements will necessitate an additional level of data to include the indication for which the orphan drug was prescribed or used.

In some cases the existing systems may include sufficient information to determine the indication for which the drug was used, in other cases new systems will need to be developed if the covered entity chooses to purchase orphan drugs under 340B. The administrative burden of making this change is difficult to estimate and no comments were received to assist us in doing so.

The final rule references statutory requirements to maintain auditable records sufficient to demonstrate program requirements. As required by the Paperwork Reduction Act of 1995 (PRA) (44 U.S.C. 3507(d)), a copy of this final rule was submitted to the Office of Management and Budget for its review of the collection of information.

Dated: May 20, 2013.

Mary K. Wakefield,

Administrator, Health Resources and Services Administration.

Approved: July 15, 2013.

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 adds 42 CFR part 10 to subchapter A to read as follows:

PART 10—340B DRUG PRICING PROGRAM

Sec.

Subpart A—General Provisions

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, as amended (21 U.S.C. 360bb); Sec. 701(a) of the Federal Food, Drug, and Cosmetic Act, as amended (21 U.S.C. 371(a)); Sec. 1927 of the Social Security Act, as amended (42 U.S.C. 1396r–8).

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 average manufacturer price for the drug under title XIX of the Social Security Act (SSA) reduced by a rebate percentage which is calculated as indicated in 340B(a)(1) and 340B(a)(2)(A). Manufacturers participating in the 340B Drug Pricing Program (340B Program) are required to provide these discounts on all covered outpatient drugs sold to participating 340B covered entities.

§ 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 in section 340B(a)(4) of the PHSA.

Covered outpatient drug has the meaning set forth in section 1927(k) of the SSA.

Group purchasing organization (GPO) is an entity that contracts with purchasers, such as hospitals, nursing homes, and home health agencies, to aggregate purchasing volume and negotiate final prices with manufacturers, distributors, and other vendors.

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

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.

Secretary means the Secretary of Health and Human Services and any other officer or employee of the Department of Health and Human Services to whom the authority involved has been delegated.

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.

Only organizations meeting the definition of a covered entity and listed on the 340B database are eligible to purchase covered outpatient drugs under the 340B Program. A covered entity remains responsible for complying with all other 340B requirements and applicable Federal, state, and local laws.

Subpart C—Drugs Eligible for Purchase Under 340B

§ 10.20 Drugs eligible for purchase under 340B.

The definition of a covered outpatient drug has the meaning given to such term in section 1927(k)(2) of the SSA except as provided in § 10.21 of this part.

§ 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 drugs that are designated under section 526 of the FFDCA when they 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 under section 526 of the FFDCA.

(b) *Covered entities to which the orphan drug exclusion applies.* (1) The exclusion of orphan drugs when used to treat the rare disease or condition for which the drug was designated under section 526 of the FFDCA from the definition of covered outpatient drugs described in paragraph (a) of this

section shall only apply to the following covered entities: free-standing cancer hospitals qualifying under section 340B(a)(4)(M) of the PHSA, critical access hospitals qualifying under section 340B(a)(4)(N) of the PHSA, and rural referral centers and sole community hospitals qualifying under section 340B(a)(4)(O) of the PHSA. The exclusion does not apply to the remaining covered entities that meet the 340B Program eligibility requirements.

(2) When an entity described in this paragraph (b) meets more than one eligibility criterion as a covered entity, the entity shall select its eligibility type and notify the Secretary. These eligible entities are limited to participating in the 340B Program under only one covered entity hospital type and shall abide by all applicable restrictions and requirements for that entity type. A covered entity subject to this provision may only change its participation type to another hospital entity type on a quarterly basis upon express written confirmation from the Secretary.

(c) *Covered entity responsibility to maintain records of compliance.* (1) A covered entity listed in paragraph (b) of this section is responsible for ensuring that any orphan drugs purchased through the 340B Program are not transferred, prescribed, sold, or otherwise used for the rare condition or disease for which the orphan drugs are designated under section 526 of the FFDCA. A covered entity listed in paragraph (b) of this section that purchases orphan drugs under the 340B Program is required to maintain and provide auditable records on request which document the covered entity's compliance with this requirement available for audit by the Federal Government or, with Federal Government approval, by the manufacturer.

(2) A covered entity may develop an alternative system by which it can prove compliance. Any alternate system must be approved by the Secretary prior to implementation. Each alternate system of compliance will be reviewed on a case-by-case basis.

(3) A covered entity listed in paragraph (b) of this section that cannot or does not wish to maintain auditable records sufficient to demonstrate compliance with this rule, must notify HRSA and purchase all orphan drugs outside of the 340B Program regardless of the indication for which the drug is used. Once a hospital is enrolled in 340B, it may change its decision to purchase all orphan drugs outside of the 340B Program on a quarterly basis by notifying HRSA.

This documentation will be made public. This information will also be verified during the annual recertification process.

(d) *Use of group purchasing organizations by a free-standing cancer hospital.* (1) A free-standing cancer hospital enrolled under section 340B(a)(4)(M) must also comply with the prohibition against using a GPO under section 340B(a)(4)(L)(iii) of the PHSA for the purchase of any covered outpatient drug.

(2) A covered entity that is a free-standing cancer hospital cannot use a GPO to purchase orphan drugs when they are transferred, prescribed, sold, or otherwise used for an indication other than the rare condition or disease for which that orphan drug was designated under section 526 of the FFDCA.

(3) A covered entity that is a free-standing cancer hospital may use a GPO for purchasing orphan drugs when orphan drugs are transferred, prescribed, sold, or otherwise used for the rare disease or condition for which it was designated under section 526 of the FFDCA.

(4) If a covered entity that is a free-standing cancer hospital chooses to use a GPO for purchasing an orphan drug used for a rare disease or condition for which it is designated, it is required to maintain auditable records that demonstrate full compliance with the orphan drug purchasing requirements and limitations. A free-standing cancer hospital covered entity that cannot or does not wish to maintain auditable records sufficient to demonstrate compliance, must notify HRSA and purchase all orphan drugs outside of the 340B Program, regardless of indication for which the drug is used, and is not permitted to use a GPO to purchase those drugs. Once a free-standing cancer hospital is enrolled in 340B, it may change its decision to purchase all orphan drugs outside of the 340B Program on a quarterly basis by notifying HRSA. This documentation will be made public. This information will also be verified during the annual recertification process.

(e) *Identification of orphan drugs.* Designations under section 526 of the FFDCA are the responsibility of and administered by the FDA. Only covered outpatient drugs that match the listing and sponsor of the orphan designation are considered orphan drugs for purposes of this section. HRSA will publish on its public Web site FDA's section 526 list of drugs that will govern the next quarter's purchases.

(f) *Failure to comply.* Failure to comply with this section shall be considered a violation of sections 340B(a)(5) and 340B(e) of the PHSA, as applicable.

[FR Doc. 2013–17547 Filed 7–22–13; 8:45 am]

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FEDERAL COMMUNICATIONS COMMISSION

47 CFR Part 1

[IB Docket No. 11–133; FCC 13–50]

Review of Foreign Ownership Policies for Common Carrier and Aeronautical Radio Licensees

AGENCY: Federal Communications Commission.

ACTION: Final rule; correction.

SUMMARY: The Federal Communications Commission (Commission) is correcting a final rule that appeared in the **Federal Register** of July 10, 2013 (78 FR 41314). The document issued final rules that apply to foreign ownership of common carrier, aeronautical en route and aeronautical fixed radio station licensees.

DATES: Effective on August 9, 2013.

FOR FURTHER INFORMATION CONTACT: Susan O'Connell or James Ball, Policy Division, International Bureau, FCC, (202) 418–1460 or via the Internet at *Susan.OConnell@fcc.gov* and *James.Ball@fcc.gov.*

SUPPLEMENTARY INFORMATION: In FR Doc. 2013–15314 appearing on page 41314 in the **Federal Register** of Wednesday, July 10, 2013, the following corrections are made:

Subpart F—Wireless Radio Services Applications and Proceedings [Corrected]

■ 1. On page 41321, in the third column, the heading of the table of contents for §§ 1.990 through 1.994, ''Foreign Ownership of U.S.-Organized Entities That Control Common Carrier, Aeronautical en Route, And Aeronautical Fixed Radio Station Licensees'' is corrected to read ''Foreign Ownership of Common Carrier, Aeronautical en Route, And Aeronautical Fixed Radio Station Licensees''.

■ 2. On page 41322, in the first column, the undesignated center heading for §§ 1.990 through 1.994, ''Foreign Ownership of U.S.-Organized Entities That Control Common Carrier, Aeronautical en Route, And Aeronautical Fixed Radio Station Licensees'' is corrected to read ''Foreign Ownership of Common Carrier, Aeronautical en Route, And