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BIOTECHNOLOGY
INDUSTRY ORGANIZATION

July 19, 2011

BY ELECTRONIC DELIVERY (Opaorphan@hrsa.gov)

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

Re: Regulatory Information Number 0906-AA94 (Notice of Proposed Rulemaking: Exclusion of Orphan Drugs for Certain Covered Entities Under 340B Program)

Dear Commander Pedley:

The Biotechnology Industry Organization ("BIO") is pleased to submit the following comments on the Health Resources and Services Administration's ("HRSA") proposed rule with comment period, which was published in the Federal Register on May 20, 2011 (the "Proposed Rule"),[1] regarding the exclusion of orphan drugs under the 340B program for certain newly-designated covered entities. BIO is the largest trade organization to serve and represent the biotechnology industry in the United States and around the globe. BIO represents more than 1,100 biotechnology companies, academic institutions, state biotechnology centers, and related organizations in the United States. BIO members are involved in the research and development of health care, agricultural, industrial, and environmental biotechnology products.

As the representative of an industry that is devoted to improving health care through the discovery of new therapies, BIO understands the significance of the 340B drug pricing program, which requires manufacturers of covered outpatient drugs to charge no more than a defined ceiling price to certain specified safety net providers, defined by statute.[2] The 340B drug pricing program improves access to key drugs and therapies provided by those entities that often serve low-income or disadvantaged individuals.

[1] 76 Fed. Reg. 29183 (May 20, 2011).
[2] *See* 42 U.S.C. § 256b (describing the Public Health Service ("PHS") Drug Pricing Program).

As you are aware, the Patient Protection and Affordable Care Act of 2010, Pub. L. 111-148 ("ACA"),[3] added new types of entities to the list of covered entities that are eligible to receive 340B pricing. The ACA also directs that these new types of covered entities are ineligible for 340B pricing on drugs that have been designated by the Secretary as "orphan drugs," i.e., a drug that treats a rare disease or condition.[4] The new covered entity types that are ineligible for 340B pricing when purchasing orphan drugs are free-standing cancer hospitals, critical access hospitals, rural referral centers, and sole community hospitals.[5]

Taken together, these provisions clearly demonstrate that this unprecedented expansion of the 340B program, the first in its more than 17-year history, was based explicitly on the condition that the new covered entities not enjoy all of the same benefits as the existing entity types and, specifically, that the new covered entities be denied access to the 340B price for orphan drugs. Despite that explicit condition, HRSA has chosen to interpret the exclusion in a way that, effectively, allows the new covered entity types to participate in the 340B program on a more expansive footing with existing entity types. Like the pre-existing covered entity types, the new covered entities will be able to request the 340B price on orphan drugs, and manufacturers will be obligated to sell at that price with no questions asked. Covered entities are obligated to document compliance, but the Proposed Rule provides absolutely no details or specific requirements regarding those documentation obligations.

BIO has significant concerns with regard to HRSA's Proposed Rule implementing the orphan drug exclusion. BIO believes that the Proposed Rule is inconsistent with and impermissible under the language of ACA, and that HRSA's proposal, even if hypothetically permissible, is impractical and likely cannot be implemented in a manner that ensures covered entity compliance. Should HRSA move to finalize this proposal despite these significant concerns, HRSA should clarify that any indication-based implementation of the orphan drug exclusion applies on a prospective basis only.

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[3] As used in these comments, the abbreviation "ACA" shall refer collectively to the Patient Protection and Affordable Care Act of 2010, as amended by the Health Care and Education Reconciliation Act of 2010 ("HCERA"), The Medicare and Medicaid Extenders Act of 2010 ("MMEA"), and other subsequent legislation.

[4] In response to a request by a manufacturer or sponsor, the Secretary will designate a drug as an orphan drug pursuant to Section 526 of the Federal Food, Drug and Cosmetic Act, if it is designed to treat a disease or condition that affects fewer than 200,000 persons in the United States.

[5] As discussed below, children's hospitals previously were included in the list of entities to which the orphan drug exclusion applied, but subsequent legislation removed children's hospitals from that exclusion and reinstated their right to the ceiling price on orphan drugs retroactively to ACA's effective date. HCERA, Pub. L. 111-152, Section 2302, *amended by* MMEA, Pub. L. 111-309, Section 204(a)(1). Therefore, only free-standing cancer hospitals, critical access hospitals, rural referral centers, and sole community hospitals are referred to collectively herein as the "new covered entity types" or the "new covered entities" for purposes of the orphan drug exclusion.

I. The Proposed Rule Is Inconsistent with and Impermissible under the Clear Statutory Language of ACA

The language of the orphan drugs exclusion is clear. It applies to the orphan drug compound as a whole, and without exception. It reads:

> 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.[6]

While this language clearly applies the ceiling price exclusion to any "drug" subject to an orphan designation, HRSA proposes to limit the exclusion based on the drug's actual and ultimate use. Specifically, HRSA proposes to apply the ceiling price exclusion only to those purchases of an orphan drug where the drug ultimately is used for the rare disease or condition for which it received the orphan designation. The Proposed Rule specifies: "for these [newly-designated] covered entities, a covered outpatient drug *includes* designated orphan drugs that are transferred, prescribed, sold, or otherwise used for any indication other than treating the rare disease or condition for which the drug was designated" by the FDA.[7]

The Proposed Rule's indication-based interpretation is inconsistent with and impermissible under the plain language of the statute. As noted above, the statutory text of the orphan drug exclusion specifically applies to an orphan drug, not its intended use and without regard to whether all approved indications are designated as orphan indications. While a drug may receive an orphan designation because it can treat a rare disease or condition, the statutory language does not condition the exclusion on such usage. The statute instead uses the term "drug," which is a categorical definition under the Federal Food, Drug, and Cosmetic Act (FFDCA), which the Orphan Drug Act amends.[8] The definition is not limited by indication, but refers to the drug "article" as a whole. Had Congress intended the exclusion to apply more narrowly – to be dependent on the orphan *indication* of a drug rather than to the orphan-designated *drug as a*

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[6] *See* ACA, Pub. L. 111-148, Section 7101, *amended by* HCERA, Pub. L. 111-152, Section 2302 (emphasis added), *amended by* MMEA, Pub. L. 111-309, Section 204(a)(1).

[7] 76 Fed. Reg. at 29186 (emphasis added).

[8] Under FFDCA Section 201(g)(1), the term "drug" "means (A) articles recognized in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any article specified in clause (A), (B), or (C)." 21 U.S.C. §321(g)(1).

whole – Congress itself would have done so, as it did elsewhere in the very same legislation, when addressing another orphan drug exclusion.

A separate section of the ACA, Section 9008, creates a new branded prescription drug fee for manufacturers. This section specifically exempts orphan drugs from the branded prescription drug fee, but notes that the exemption expires "after the date on which such drug or biological product is approved by the Food and Drug Administration for marketing *any indication other than the treatment of the rare disease or condition*."[9] The branded prescription drug fee and the 340B amendments are included in the same legislation and both include an orphan drug exemption, but only the former defines the exception by reference to indication. And even as to the fee, Congress chose a bright-line test applicable to the drug as a whole (regardless of its intended use in any given patient) – that is, whether or not the drug has an approved non-orphan indication, not whether the drug is actually used for that non-orphan indication.

Congress has distinguished between orphan drugs and orphan indications in other legislation as well. Within the Social Security Act's discussion of the Prospective Payment System for Hospital Outpatient Departments, Congress has specified that an additional payment (commonly known as a "pass-through" payment) can be made for a drug or biological that has been designated as an orphan drug only where that drug or biological "*is used for a rare disease or condition* with respect to which the drug or biological has been designated as an orphan drug under section 526 of the Federal Food, Drug, and Cosmetic Act."[10] This provision specifically limits pass-through payments for orphan drugs to those uses that are for "a rare disease or condition."[11] This is precisely the type of qualifying language one would expect to see in the 340B orphan drug exclusion had Congress intended that exclusion to apply on the basis of the orphan indication only. Yet, as noted above, this type of qualifying language simply does not appear. Instead, the 340B exclusion applies to each orphan designated "drug," and HRSA is legally bound to implement the exclusion accordingly.

Given the plain language of the statute and the import of that language in light of Congress's use of indication-based language in the same and other legislation, BIO believes HRSA has no authority or discretion to implement an indication-based approach. "A regulation may not serve to amend a statute, nor add to the statute something which is not there."[12] Nor does HRSA's alleged "confusion in the marketplace" justify an override of an otherwise clear

[9] ACA, Pub. L. 111-148, Section 9008(e)(3) (emphasis added).
[10] 42 U.S.C. § 1395l(t)(6).
[11] *Id.*
[12] *California Cosmetology Coalition v. Riley*, 110 F.3d 1454, 1460 (9th Cir. 1997) (quotation marks and internal citations omitted).

statutory mandate.[13] An agency has discretion to choose among reasonable interpretations only when there is confusion in the statute itself,[14] and that plainly is not the case here.

Federal agencies must effect the unambiguously expressed intent of Congress as reflected in the actual language of the statute when interpreting a legislative enactment.[15] The Supreme Court has held that "an administrative agency's power to regulate in the public interest must always be grounded in a valid grant of authority from Congress."[16] Courts consistently have held, therefore, that the rulemaking authority of an agency may not extend beyond the plain language of a statute where Congress has left no ambiguity.[17] This constraint on agency rule making authority applies with equal force to any agency attempt, through rule making, to qualify the otherwise clear language of a statute.[18] Furthermore, courts have held that "[i]nterpretive regulations will not be followed where they conflict with the design of the statute or exceed the administrative authority granted."[19] HRSA's proposed attempt to limit and qualify the scope of the orphan drug exclusion conflicts with the plain language of the ACA and should not be finalized.

Isolated statements of Congressional intent that support HRSA's interpretation of the orphan drug exclusion have no relevance in the presence of otherwise clear statutory language. Statements of individual members of the legislature or language in committee reports or other legislative history are not entitled to the same weight as the plain language of the statutory text itself, and such statements are generally disregarded by courts when interpreting otherwise clear statutory language.[20] Indeed, courts consistently have held that a legislature's "intent" is not to be utilized in interpreting a statute where the statute speaks plainly to the question at issue.[21]

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[13] 76 Fed. Reg. at 29184.

[14] *See e.g. Federal Express Corp. v. Holowecki*, 552 U.S. 389, 403 (2008) (agency may only choose from among "reasonable alternatives" when interpreting a statute that has ambiguities).

[15] *Food and Drug. Admin. v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 125-26 (2000) *citing Chevron U.S.A., Inc. v. Natural Res. Def. Council, Inc.*, 467 U.S. 837, 842-43 (1984). *See also Griffin v. Oceanic Contractors, Inc.*, 458 U.S. 564, 571 (1982) ("There is, of course, no more persuasive evidence of the purpose of a statute than the words by which the legislature undertook to give expression to its wishes.").

[16] *Food & Drug Admin.*, 529 U.S. at 161.

[17] *Chevron U.S.A., Inc.*, 467 U.S. at 842 (courts are not called upon to defer to or consider an agency's interpretation of a statute where Congress has directly spoken to the precise question at issue).

[18] *See e.g., Koshland v. Helvering*, 298 U.S. 441, 447 (1936) ("the Secretary of the Treasury is without power by regulatory amendment to add a provision" to a statute that would qualify Congress' language).

[19] *See Usery v. Kennecott Copper Corp.*, 577 F.2d 1113 (10th Cir. 1977).

[20] *Southeastern Community College v. Davis*, 442 U.S. 397, 411 n.11 (1979). *See also NLRB v. Health Care & Retirement Corp.*, 511 U.S. 571, 582 (1994) ("It is the function of the courts and not the Legislature, much less a Committee of one House of the Legislature, to say what an enacted statute means.").

[21] *Alex v. City of Chicago*, 29 F.3d 1235, 1239 (7th Cir. 1994)(Where a statute is unambiguous, courts will not look to "the embellishments of secondary materials like legislative history, regulations or administrative rulings"). To the extent, therefore, that two Members of Congress are now expressing their personal opinion that HRSA's indication-based interpretation of the orphan drug exclusion comports with Congressional "intent," despite any contemporaneous evidence of such intent prior to passage, these opinions do not lend any

Given that courts would not rely upon such statements when determining the meaning of a clear Congressional pronouncement, HRSA likewise may not do so when implementing the orphan drug exclusion.

II. The Proposed Rule Faces Legal and Practical Barriers to Implementation

Under the Proposed Rule, a covered entity is permitted to access the ceiling price on orphan drugs so long as the covered entity does not use the drug for the rare disease or condition that is the basis for the orphan designation. The Proposed Rule also directs that "[m]anufacturers *must offer* covered entities covered outpatient drugs for purchase at or below the applicable 340B ceiling price if such drug is made available to any other purchaser."[22] Therefore, in effect, the Proposed Rule, requires that if a covered entity requests the ceiling price on an orphan drug, the manufacturer must assume the covered entity will only use that orphan drug (for a non-orphan use), and must offer the ceiling price upon request because of the new "must offer" requirement.[23] To support the assumption of covered entity compliance, HRSA directs the covered entities to maintain sufficient documentation to demonstrate use of any 340B-priced orphan drugs for non-orphan uses only.[24]

The Proposed Rule, therefore, can work as intended only if:

> (A) The "must offer' provision is now binding, and
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> (B) Covered entities, as a practical matter, have the capability to use existing medical and other record types to create the auditable records necessary to document compliance.

The first assumption is legally suspect, while the second one faces potentially insurmountable barriers. As discussed in more detail below, the "must offer" provision of ACA is not yet binding, despite multiple efforts by HRSA to assert that is the case. The second assumption overlooks the practical realities of tying drug purchases to indication-based uses, and thus places an administrative burden on covered entities to comply in an auditable manner. BIO strongly opposes the adoption of any Proposed Rule that is based on faulty legal positions and unrealistic assumptions of compliance, and that is very much the case here.

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legal support for HRSA's proposal. *See, e.g.*, Bread Political Action Comm. v. FEC, 455 U.S. 577, 582 n.3 (1982) (1977 litigation affidavit of a Senator and his aide as to intent in drafting a 1974 floor amendment cannot be given "probative weight" because such statements, made after enactment, represent only the "personal views" of the legislator).

[22] 76 Fed. Reg. at 29185 (emphasis added).

[23] 76 Fed. Reg. at 29185.

[24] *Id*. at 29186.

A. The Proposed Rule Impermissibly Assumes that ACA's "Must Offer" Provision Currently Is Binding

The "must offer" provision contained in ACA amended the 340B statute, at 42 U.S.C. § 256b(a). That language from ACA reads:

> Section 340B of the Public Health Service Act (42 U.S.C. § 256b(a)) is amended in subsection (a)(1), by adding at the end the following: "Each such agreement . . . shall require that the manufacturer 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."[25]

As BIO raised in previous comments to HRSA, submitted on November 19, 2010, this provision of ACA is not self-effectuating. Rather, it clearly requires the Secretary to amend the Pharmaceutical Pricing Agreement ("PPA") to include the "must offer" obligation.

The PPA is a contract. The Secretary is a party to that contract. As a contracting party, the government, through the Secretary, is subject to the normal rules governing contractual relationships. See, e.g., *United States v. Winstar Corp.*, 518 U.S. 839, 886 (1996) (applying standard contract principles to government contracting). The Secretary therefore cannot unilaterally change the terms of the contract and increase manufacturers' obligations.[26] When manufacturers entered into their PPAs, they promised to charge no more than the ceiling price to covered entities on any sales to those covered entities.[27] Manufacturers did not agree to sell to covered entities in all instances, with no discretion to decline the sale (for example, sales that would exceed an entity's proportional share within a reasonable limited distribution system), and the Secretary cannot amend the contract to that effect by fiat. As the PPA itself makes clear, "[e]xcept for changes of addresses, the Agreement will not be altered except by an amendment in writing signed by both parties."[28]

The Secretary has not yet updated or made any modification to the PPA for the 340B drug pricing program, and needless to say, the Secretary also has not required manufacturers to execute such an updated agreement. The Proposed Rule, therefore, cannot at this time invoke or rely upon ACA's "must offer" provision as a basis for HRSA's proposed interpretation and implementation of the orphan drug exclusion.

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[25] ACA, Pub. L. 111-148, Section 7102(b).

[26] *See id.* at 895 (noting that allowing the Government to alter contractual liability by passing a "regulatory statute" would flout the general principle that, "'[w]hen the United States enters into contract relations, its rights and duties therein are governed generally by the law applicable to contracts between private individuals'" (quoting *Lynch v. United States*, 292 U.S. 531, 579 (1934)).

[27] *See* PPA at § II(a).

[28] *See Id.* at § VII(h).

B. The Proposed Rule Fails to Ensure Compliance by Covered Entities

To support the assumption that covered entities can ensure orphan drugs purchased at the 340B price are used solely for non-orphan uses, the Proposed Rule requires covered entities to maintain separate purchasing accounts for orphan drugs: one for commercial prices for orphan uses, and one for 340B prices and non-orphan uses.[29] The Proposed Rule also directs covered entities to maintain auditable documentation of how 340B-priced orphan drugs are used.[30] *The ability of a covered entity to tie and document a particular orphan drug purchase to its ultimate use is, therefore, the cornerstone assumption of the Proposed Rule.*

Given the central role that such compliance documentation plays in the Proposed Rule, it is extremely concerning that HRSA refuses to specify the type or quality of documentation required. HRSA affirmatively has stated that it will not detail what the appropriate auditable documentation should include.[31] Instead, HRSA proposes to give the new covered entity types "flexibility" to comply with the recordkeeping requirements.[32]

HRSA's refusal to mandate particular documentation standards appears to be based on the assumption that covered entities will be readily able to tie and document the use of a particular unit of drug to the treatment of a particular disease or condition. Yet HRSA offers no basis for this critical assumption that covered entities can and will tie and document each 340B orphan drug unit to a non-orphan use, which is the foundation for HRSA's corresponding requirement that manufacturers sell the orphan drugs at the 340B price.

As discussed in detail below, BIO believes covered entities will face numerous, potentially insurmountable, challenges to tying and documenting 340B units to non-orphan uses. Given these very real obstacles to HRSA's central compliance assumption, BIO strongly urges HRSA to postpone finalization of any indication-based implementation until HRSA can (1) explore the available documentation options and, assuming traditionally available medical and other provider records are sufficient to tie a given 340B product to a particular use, then (2) propose and receive comment on specific standards of documentation. Any mandate on manufacturers to sell covered outpatient drugs at such a significant discount must be supported by clear evidence that covered entities will use the products only as directed. HRSA has provided no such basis, and practical realities suggest that such a basis may not exist. HRSA's

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[29] 76 Fed. Reg. at 29186. The term "commercial" as used in these comments is intended to denote non-340B pricing.

[30] *Id.* New covered entities that do not maintain appropriate auditable records sufficient to show compliance must purchase all orphan drugs outside of the 340B program. *Id.*

[31] *Id.* ("HHS does not currently mandate the method of demonstrating compliance [with the auditable records requirement] and allows flexibility of covered entities to do so.").

[32] *Id.*

Proposed Rule cannot be finalized in the absence of any effort to determine whether compliance by covered entities is even possible.

1. Significant Obstacles Exist to Covered Entities' Ability to Tie 340B Orphan Drugs to Non-Orphan Uses

As discussed in detail below, there are significant obstacles to the ability of covered entities to tie 340B orphan drug purchases to actual non-orphan uses in patients.

a. The Proposed Rule Unreasonably Assumes that Covered Entities Can Readily Identify a Patient's Disease or Condition

Covered entities participating in the 340B program purchase drugs like any other customer, and thus are not required to indicate for what use – orphan or non-orphan, on label or off label – the purchases are intended. The Proposed Rule recognizes this fact and, for that reason, requires the new covered entity types to document that any 340B-priced orphan drug is used only for a non-orphan use. Part of that documentation requirement is that the new covered entity types maintain separate purchasing accounts to differentiate between purchases made for orphan versus non-orphan uses. The Proposed Rule indicates that covered entities also must maintain auditable records to demonstrate compliance.

The Proposed Rule's requirement that such documentation be maintained assumes that such documentation can be readily created. BIO believes the opposite is the case – that the identification and documentation of the particular disease or condition for which a particular unit of an orphan drug is used will, instead, be cumbersome at best, if possible at all. BIO believes HRSA must actively consider and investigate the options available to covered entities to document orphan drug use, as that must form the basis of any judgment as to whether such documentation can reasonably be expected to be created and maintained in an auditable manner.

First and foremost, the covered entity must be able to identify the disease or condition for which a patient is being treated if it wishes to document that a given unit of a drug either was or was not used for the rare disease or condition for which the drug received its orphan designation. The most likely method for doing so is the ICD-9 code assigned to the patient's course of treatment. ICD-9 codes classify diseases and conditions by a code, up to six characters long. BIO believes this is the most likely approach because the ICD-9 code assigned to a patient encounter usually is available electronically in a patient's record and so is readily identifiable and retrievable. The difficulty, however, is that ICD-9 codes often do not provide the level of specificity needed to identify whether the patient's treated disease or condition is that which provided the basis for the relevant drug's orphan designation.

Where the ICD-9 code does not provide the detail necessary to identify whether or not the rare disease or condition is being treated, BIO expects that the covered entity would have to

resort to the written medical record to identify the actual disease or condition treated. Additionally, for those orphan drugs dispensed in a retail pharmacy setting (*e.g.*, self-administered or oral formulations of an orphan drug) ICD-9 codes are not captured or tracked. With the growth in use of contract pharmacies, this could be a particular problem, because the contract pharmacy would require systems be in place to track the drug to the disease/condition, which is neither on the prescription nor the claim form. Even if this information were available, the contract pharmacy would have to have a way of tracking that disease information back to the invoice, which goes to the covered entity rather than the contract pharmacy.

Such a system would present several substantial challenges for the newly-eligible covered entities. Implementation of new inventory systems and computer systems would create financial and administrative burdens for the covered entities; further, the series of steps that would be needed to tie inventory items to orphan/non-orphan indications would still be unreliable, despite its costs. Specifically, covered entities would need: 1) a data crosswalk between each NDC and orphan designations; and 2) a data crosswalk between orphan designations and ICD-9 codes. We are not aware that either type of crosswalk exists.

While it is theoretically possible to create a crosswalk between NDCs and orphan designations, it would be necessary to update it on an ongoing, real-time basis in order to reflect new FDA designations. Additionally, such a crosswalk would need to distinguish between those NDCs granted orphan designation versus those without orphan designation. For example, cancer of the ovary, described by ICD-9 code 183.X, is treated with both orphan and non-orphan drugs. The crosswalk would need to distinguish between bevacizumab, (a drug granted orphan designation) versus cisplatin, carboplatin, and paclitaxel (non-orphan drugs). Each newly-eligible entity would have to implement these software updates immediately in order to assure that it could make appropriate real-time decisions on whether to purchase at the 340B or non-340B price. Any such software system would have to be accompanied by implementation of quality control procedures and be subject to external audits in order to make it usable and to demonstrate to manufacturers, and the covered entity, that proper pricing occurred.

We do not believe it is even theoretically possible to develop a crosswalk between orphan designations and ICD-9 codes. As a preliminary matter, the only information available to hospitals, manufacturers and the Government related to the disease for which a drug is used is the ICD-9 code on a claim form (and in the future an ICD-10 diagnosis code). With respect to the utility of ICD-9 codes, CMS has stated that the ICD-9 coding system "does not provide the necessary detail for patients' medical conditions …"[33] and "is 30 years old, has outdated and obsolete terminology, uses outdated codes that produce inaccurate and limited data, and is inconsistent with current medical practice. It cannot accurately describe the diagnoses and

[33] *See* "CMS ICD-10-CM PCS: An Introduction", dated April 2010, at http://www.cms.gov/ICD10/Downloads/ICD-10Overview.pdf

inpatient procedures of care delivered in the 21st century."[34] The ICD-9 system also cannot accurately describe diagnoses for patients treated in outpatient departments, due to its lack of specificity. Lack of granularity in ICD-9 codes is particularly problematic with respect to rare diseases, because ICD-9 "is not detailed enough to specifically identify many rare diseases."[35] This is important because, if the ICD-9 code does not provide the information to determine whether the patient was treated for the rare disease for which the drug was designated, then these determinations cannot be automated and, instead, covered entity staff would need to review the patient's medical record to make that determination. Not only would this effort be time-consuming and burdensome for the covered entity's staff, but it is likely to be doomed to failure unless the medical record for the date of drug administration clearly demonstrates the reason for use of the drug. Even then, if there is no ICD-9 code that properly identifies the rare disease for which the drug was used, it would be impossible to communicate that information to a manufacturer without use of patient identifiable information that is protected under HIPAA. In short, for covered entities to accurately identify and document the purpose for which a drug is used in an auditable manner would be extremely burdensome and could divert resources from other patient-centered responsibilities. Even if covered entities could perform the necessary activities, many coding decisions would likely be subjective and susceptible to disputes with manufacturers (the resolution of which would consume additional hospital resources).

Commonly there is not a one-to-one relationship between ICD-9 codes and rare diseases. As one example, the keynote speaker at a recent rare disease forum cited ICD-9 code 270.3, *Disturbances of branched chain amino-acid metabolism*, which subsumes six separate rare diseases (hypervalinemia; leucinosis; maple syrup urine disease; disturbances of metabolism of leucine, isoleucine, and valine; intermittent branched-chain ketonuria; and leucine-induced hypoglycemia).[36] This ICD-9 code is not specific enough to distinguish between these various diseases. Rare cancers are among the orphan diseases that may not line up well with ICD-9 codes, because the indications for a cancer drug are generally more detailed than non-cancer ICD-9 codes. In this regard, cancer drugs have indications that frequently depend on factors such as whether the cancer is metastatic (whether it has spread from its original site), previous therapies the patient has tried and failed (whether the drug is a first-line treatment, second-line, etc.), the stage of the cancer, or the specific type of cell from which the cancer is derived (e.g., glioblostama). ICD-9 codes identify cancers by site, but do not differentiate cancers by stage, by cell type or by prior treatment failures. Thus, an ICD-9 code generally will not be adequate to determine whether an orphan drug for a rare cancer has been used for its designated indication or for another indication.[37] Moreover, these problems will persist even after providers switch to the

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[34] *See* "CMS ICD-10-CM PCS: An Introduction." Dated April 2010. Available at http://www.cms.gov/ICD10/Downloads/ICD-10Overview.pdf

[35] *See* "The Contribution of Large Healthcare Systems to Improving Treatment for Patients with Rare Diseases," pg. 20, Keynote Address at Uniting Rare Diseases Forum delivered by Dr. Joe Selby, Kaiser Permanente Northern California on January 12, 2010. Available at: http://rarediseases.info.nih.gov/files/Selby.pdf

[36] *Id.* at 21.

[37] We have included a listing of the ICD-9 codes for certain types of cancer as Appendix A to these comments.

ICD-10 system in 2013, because many rare diseases have no specific ICD-10 code.[38] As noted in a 2008 conference on rare diseases, 400 rare diseases have no specific ICD-10 code.[39] As noted earlier, the only solution in cases where a drug's orphan indication(s) do not correspond to an ICD-9 code is a manual review of the medical record to determine whether the drug was used for its orphan indication – a highly inefficient and inexact process that would likely lead to inaccuracies and would be difficult to audit effectively or to communicate in a HIPAA compliant way to a manufacturer. Such a system would, therefore, place the newly-eligible covered entities at risk of non-compliance, even if they expended significant resources in an attempt to make correct determinations.

Another issue that would frustrate any effort to determine whether an orphan drug is "transferred, prescribed, sold, or otherwise used for the rare condition or disease for which that orphan drug was designated"[40] is that hospital outpatient department claims may list up to nine ICD-9 codes,[41] some of which may correspond to the drug's orphan designation(s), and some of which may not. When a patient has more than one illness, ICD-9 codes for two or more illnesses may be on the claim and it could be very difficult to determine which illness (or indication) accounted for a drug's administration. A common example is when a patient has two types of cancer, the administered drug is indicated for both of them, and one is an orphan indication. In such a case, it may not be possible, even with chart review, to determine whether the drug was administered for its orphan indication.

The above examples assume that the entire contents of a single vial are used for one patient. However, Medicare instructions allow hospitals to use a single vial, even a single use vial, on two or more patients if that is consistent with the standard of care. When that happens, and part of the vial is administered to a patient for an orphan indication while another part is administered to a second patient for a non-orphan indication, it will never be possible to tie the purchase of a single vial to a single indication – even with medical record review.

Thus, the Proposed Rule makes two faulty assumptions – first, that it is always possible to tie drug purchase and use to a specific indication, and second, that covered entities can and will implement the sort of complex and labor-intensive review and documentation process necessary to do so where it can theoretically be done. The Rule further assumes that covered entities will do so as a matter of course, despite these challenges and despite the lack of any clear direction or requirements from HRSA. These assumptions make the Proposed Rule untenable.

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[38] *See* "Proposal of a Priority List of Rare Diseases Needing a Specific ICD Code," (pg. 10), delivered by Dr. Ana Rath in February 2008. Available at: http://www.orpha.net/testor/doc/RDTF_anna/WG/CodingandClassification/meetings/Feb62008/presentations/aNACodingandclassificationfeb08-PlistAna.pdf

[39] *Id.* at 6.

[40] 42 C.F.R. § 10.21(a), 76 Fed. Reg. at 29189.

[41] Medicare Claims Processing Manual, Chapter 25 § 75.5.

b. The Proposed Rule Unreasonably Assumes that Covered Entities Can Tie a Patient's Disease/Condition to a Particular Unit of Drug, either at the Time of Purchase or under a Split Billing/Replenishment Model

Second, even assuming that covered entities can identify the actual disease or condition treated by a particular unit of a drug, covered entities also will need to be able to tie the identified disease or condition to the unit of drug in their purchasing systems. The Proposed Rule appears to assume that a covered entity will be able to identify the intended use for the orphan drug at the time of purchase, but provides no support for this assumption or its reasonableness, and BIO believes that any such assumption is unfounded. Health care providers rarely know the intended use for a drug at the time of sale. It is the exception rather than the rule that drugs are purchased on a patient-specific basis or for immediate use in a facility. The more common situation is for product to be purchased in advance and held in general inventory and pulled from stock as needed.[42]

Covered entities may attempt to address this second concern by using an "inventory replenishment" or "split billing" approach similar to what HRSA has stated may be acceptable under the 340B program more generally for those covered entities, usually hospitals, that do not want to maintain separate physical inventories of 340B (outpatient) and non-340B (inpatient) product.[43] While HRSA has never issued formal guidance regarding inventory replenishment, BIO understands that it most typically involves a hospital covered entity's purchase of all product at commercial prices, identification and quantification of those commercial units used on the outpatient side, and then purchase of "replacement" product of the same NDC at the 340B price. Covered entities may believe they can use this same model to purchase all orphan drugs at commercial prices and then seek to replenish inventories at the 340B price for product that is not used for the rare disease or condition that generated the orphan designation. The Proposed Rule does not even address the possibility that covered entities would rely on this approach, and thus, needless to say, also fails to discuss whether such a model would be reasonable and sufficient to address the covered entity's compliance obligations.

BIO strongly opposes any compliance model that permits the inventory replenishment approach, for two reasons: (1) as noted above, BIO believes significant obstacles exist to covered entities' ability to identify the disease or condition treated by a given unit of a drug, which is a necessary prerequisite to this approach, and (2) BIO believes that HRSA already has failed to appropriately oversee and regulate covered entities' current use of the inventory replenishment

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[42] As noted above, where an orphan drug is sold in multiple use containers and a covered entity requests the 340B price, HRSA should clarify that the covered entity would be obligated to document that all uses of the container's contents would be for the treatment of patients for a disease or condition other than that which is the subject of the orphan designation.

[43] *See* http://answers.hrsa.gov/app/answers/detail/a_id/97/kw/inventory%20replenishment/session/L3RpbWUvMTMwODU5MjE3OS9zaWQvbkVRZDlfd2s%3D

model.[44] Given these two concerns, this approach should not be extended into a new area where documentation standards are even more challenging.

Multiple consulting and software firms currently promote inventory replenishment models, with no known oversight by HRSA. Those programs depend on the covered entity's ability to identify the hospital department in which a given drug is used, so that the covered entity can identify whether the drug is used in the inpatient or outpatient setting. "Mixed use" settings of a hospital, such as a radiology department, where both inpatients and outpatients are treated, already present particular obstacles under this approach because in such settings the hospital cannot determine as a categorical matter whether the patient at issue is an inpatient or outpatient. HRSA appears to leave covered entities to figure this out on their own, with the assumption that the covered entity will do so reasonably and in a compliant way.[45] The Proposed Rule, by leaving the particular method of compliance implementation to the discretion of the covered entity, would unreasonably permit covered entities to push this model into an even more complex area of patient identification – to whether the patient is or is not being treated for a particular rare disease or condition.

At bottom, HRSA has issued a Proposed Rule that ignores significant and complex operational obstacles to compliant implementation by covered entities. Assuming that covered entities either will readily overcome such obstacles, or otherwise opt out and purchase only at commercial prices, is an unreasonable and insufficient basis for mandating significant manufacturer discounts. That nevertheless is the approach adopted by HRSA with the Proposed Rule and is the reason why BIO strongly opposes the Proposed Rule's finalization in this form. BIO instead urges HRSA to explore these operational difficulties itself and propose specific implementation and documentation standards to address them, subject to further notice and comment, before finalizing any indication-based rule.

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[44] For example, BIO understands that disproportionate share hospital (DSH) covered entities may believe it permissible to purchase through a group purchasing organization (GPO) the initial commercial product used in the outpatient setting that later is replenished with 340B product. BIO believes this practice clearly violates the GPO prohibition, which prohibits DSH entities from purchasing *any* outpatient drugs through GPOs, *see* 42 U.S.C. § 256b(a)(4)(L)(iii), but HRSA has not addressed this practice. But HRSA has not provided any informal guidance on this.

[45] *See* HRSA FAQ, DSH Outpatient Settings and 340B, found at http://answers.hrsa.gov/app/answers/detail/a_id/418/kw/mixed%20use/session/L3RpbWUvMTMwODY5MDEyOS9zaWQvVWdsUjc1eGs%3D (noting that covered entities that operate in a mixed-use environment must "develop a tracking system to ensure that drugs purchased through the 340B program are not used for hospital inpatients"); *see also* 340B Prime Vendor Program FAQ, found at https://www.340bpvp.com/public/faq/faq_dsh.asp#Q4.

2. Any Implementation of an Indication-Based Rule without HRSA-Specified Documentation Standards Must Include a Requirement that the Covered Entity File Its Compliance Plan with HRSA

HRSA's proposed implementation of the orphan drug exclusion cannot function without appropriate compliance, and documentation of compliance, on the part of the new covered entities. Given the likely and significant obstacles to such documentation efforts, compliance by covered entities cannot be presumed. BIO believes covered entities should be required to submit written compliance documentation plans prior to seeking 340B prices for non-orphan uses of orphan drugs. At a minimum, BIO believes such compliance plans should address how the covered entities will implement alternative purchasing accounts for 340B versus non-340B prices, ensure that drugs are used only for 340B or non-340B purposes as applicable, and account for and document this process. These compliance plans should also be made available to manufacturers upon request.

If covered entities believe they can comply with the Proposed Rule's documentation requirements, then those same covered entities should be willing to document how they plan to do so and submit those plans to HRSA. HRSA itself will learn through this process and gain needed insight into the operational challenges posed by the Proposed Rule. Manufacturers also will gain needed reassurance of the integrity of covered entities' purchasing and compliance systems.

3. Manufacturer Audit Rights Are an Insufficient Remedy to Address Covered Entity Non-Compliance

The Proposed Rule indicates that manufacturers can conduct an audit under current HRSA guidelines should the manufacturer suspect a covered entity is not complying with the provisions of the Proposed Rule.[46] While BIO appreciates HRSA's re-affirmation of the audit process in this context, BIO believes this option does not provide a meaningful remedy to manufacturers and that the Proposed Rule cannot be finalized until such a remedy is created.

First and foremost, the existing audit guidelines, which were finalized and published in the Federal Register on December 12, 1996,[47] confer audit rights on manufacturers only in relation to covered entity violations of Sections 256b(a)(5)(A)-(B), which prohibit duplicate discounts and patient-based diversions of drugs. *See* 42 U.S.C. § 256b(a)(5)(C). The audit guidelines by their own terms do not apply to violations of Section 256b(e), and therefore the new covered entity types could refuse to comply with any audit request relating to a potential violation of the orphan drug exclusion. As the existing audit guidelines were finalized through a notice and comment process in the Federal Register, BIO assumes that that same process would

[46] 76 Fed. Reg. at 29186.
[47] 61 Fed. Reg. 65406.

need to be followed to amend those guidelines to permit audits in relation to covered entity compliance with Section 256b(e).[48]

Second, as addressed in our previous comments dated November 19, 2010, BIO believes the current audit process itself is overly burdensome and unworkable. It does not provide an accessible remedy for manufacturers, because manufacturers must submit an audit work plan for the Department's review and then hire an independent public accountant to perform the audit.[49] This process is cumbersome and cost prohibitive. Moreover, the requirement that manufacturers use independent auditors is unnecessary, considering that manufacturers' internal auditors may audit a covered entity at significantly less expense and with more efficiency.

As noted in our prior BIO comments, BIO suggests that, using the existing reasonable cause standard, manufacturers should be required only to submit an audit plan to HRSA, giving HRSA 30 days to raise an objection to the plan. If no objection is raised, BIO believes the manufacturer should be able to conduct the audit spelled out in the audit plan either itself or through a third-party firm identified in the audit plan, and submit the resulting audit report to HRSA.

C. The Proposed Rule Should Be Implemented on a Prospective Basis Only

BIO strongly believes that the Proposed Rule should be implemented on a prospective basis only. First, as a legal matter, the Proposed Rule should not be applied on a retroactive basis. Retroactivity is not favored in the law, and a "grant of legislative rulemaking authority will not . . . be understood to encompass the power to promulgate retroactive rules unless that power is conveyed by Congress in express terms."[50] The Proposed Rule departs significantly from the clear language of the statutory exception, and manufacturers have relied upon that language in good faith in implementing the exclusion to date. Second, even if covered entities are able to tie and document drug purchases on a prospective basis through the creation of the processes and documentation necessary under the Proposed Rule to do so, it is extremely unlikely that such processes and documentation would have been in place for earlier periods. The retroactive application of an indication-based approach would seemingly require covered entities to at least attempt to create such complex documentation on a retroactive basis, and will almost certainly lead to significant disputes. Thus, should HRSA move forward with an indication-based interpretation of the orphan drug exclusion, despite the significant legal and operational concerns discussed above, BIO urges HRSA to make clear that such a final rule applies prospectively only.

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[48] Notice of the proposed rule making for the existing audit procedure was originally filed in the Federal Register on June 10, 1994, with comments due on July 11, 1994. *See* 59 Fed. Reg. 30021. The Final Notice with respect to the audit mechanism was filed on December 12, 1996. *See* 61 Fed. Reg. 65406.

[49] 61 Fed. Reg. at 65406, 65408.

[50] *See e.g., Bowen v. Georgetown Univ. Hosp.*, 488 U.S. 204, 208 (1988).

III. Additional Issues

The Proposed Rule raises a number of additional issues not specifically related to the legal authority for HRSA's proposed approach or the practical obstacles to covered entity compliance. These additional issues are addressed below.

A. Manufacturers Should Not Be Required to Provide 340B Prices on Drugs for which the only Approved Indication(s) is an Orphan Condition.

The Proposed Rule would *require* manufacturers to sell orphan drugs at the ceiling price upon request, based on the assumption that the requesting covered entity would use the orphan drug only for a non-orphan use.[51] In many cases, a drug that is designated and approved by the Secretary to treat a rare disease or condition may have only that single approved indication. When a covered entity requests the 340B price on such a product, the covered entity necessarily is representing to the manufacturer that it will be using the orphan drug for an off-label use. HRSA should clarify that manufacturers are not required to sell orphan-designated drugs at 340B prices where the only non-orphan use is necessarily off-label. While the sale of drugs for off-label use is legal and permissible, absent such a clarification, and given HRSA's position that the "must offer" provision is currently binding, the Proposed Rule would effectively mandate off-label sales, at significant discounts that carry the risk of enforcement scrutiny. Because of the intense scrutiny that FDA, the HHS Office of Inspector General, and the Justice Department give to activity that surrounds off-label uses of drugs, the application of the ceiling price requirement to a manufacturer's knowing sale for off-label use could cause significant unintended consequences for that manufacturer. We urge HRSA to address this issue by removing the requirement that manufacturers sell for non-orphan use at the 340B price where the only approved indication is an orphan one.

B. HRSA Should Delay Implementation until CMS Confirms that Sales for Non-Orphan Uses at the 340B Price Are Exempt from Best Price

Under the Medicaid Drug Rebate Program, prices charged by manufacturers to covered entities are exempt from Best Price calculations *in general*.[52] That statutory exception was created before ACA, however, and CMS has not yet provided guidance on whether sales of orphan drugs at the 340B price fall within that exception. As discussed above, the Proposed Rule would require manufacturers sell orphan drugs at the 340B price in certain circumstances. Given that the Proposed Rule mandates such sales at the 340B price, and that such prices will almost certainly set Best Price if not excludable from that price determination, BIO believes that CMS must first confirm that such sales are exempt from Best Price before HRSA can require manufacturers to extend such deeply discounted pricing on orphan drugs to newly-covered

[51] 76 Fed. Reg. at 29185.
[52] 42 U.S.C. § 1396r-8(c)(1)(C)(i)(I); 42 C.F.R. § 447.505(d)(1).

entities. BIO requests that HRSA postpone any implementation of this requirement until CMS has issued such guidance.

Moreover, as provided under section 340B(a)(10) of the Public Health Service Act, the law does not prohibit manufacturers from charging a price for a drug that is lower than the maximum price that may be charged under section 340B(a)(1). CMS has delegated the responsibility for regulating the Medicaid Best Price exemption, and HRSA is working with CMS to develop policy on the treatment of orphan drugs to covered entities under 340B(a)(4)(M) (other than a children's hospital described in subparagraph (M)), (N), and (O) with respect to Medicaid Best Price. Until HRSA and CMS issues this policy, which will be prospective in its effect, manufacturers are permitted to make reasonable assumptions regarding the Medicaid Best Price calculations, including exclusions applicable to those calculations.

C. Covered Entity Registration Must Remain Limited to One Classification per Covered Entity and Only for the Period during which the Covered Entity Satisfies Eligibility Requirements

HRSA has proposed that "[w]here safety-net organizations meet more than one eligibility criteria as covered entities," such covered entities are limited to participating in the 340B program as only one covered entity type.[53] BIO supports this limitation and believes it is important to ensure transparency and accountability in the 340B program. BIO recommends that HRSA finalize this aspect of the Proposed Rule.

In validating covered entity eligibility, BIO recommends that HRSA not permit those entities that no longer meet the statutory definition of a "covered entity" to continue receiving discounts under the 340B program while they work towards eligibility under the same or a different covered entity category during that period. The 340B statute simply does not give HRSA the authority to create this sort of grace period. A covered entity is entitled to the 340B price only when it satisfies the statutory requirements for eligibility. Once it no longer does so, then access to the discounts must cease as well.

BIO also recommends that HRSA address whether its system for verifying covered entity eligibility includes checking the registration information provided by the covered entity to ensure that such information is accurate. Without this type of process, certain covered entity organizations may impermissibly stretch the limits of the 340B program, thereby committing fraud on the program. If HRSA itself does not have the resources for such verification efforts, such information should be made available to manufacturers upon request so that manufacturers can review that eligibility information themselves.

[53] 76 Fed. Reg. at 29189.

D. The 340B Statute Does Not Permit Cancer Hospitals to Opt-Out of the 340B Program as to Orphan Drugs as a Category in Order to Use GPOs for All Orphan Drug Purchases

Of the new covered entity types created by ACA, only free-standing cancer hospitals are subject to the group purchasing organization ("GPO") prohibition found in Section 256b(a)(4)(L)(iii). The Proposed Rule provides that cancer hospitals can purchase orphan drugs for orphan uses through a GPO, provided the entity maintains the documentation required as to 340B-price product used for non-orphan diseases and conditions. It does so on the theory that such drugs do not constitute "covered outpatient drugs" and the GPO prohibition applies only to covered outpatient drugs.[54] This approach is justifiable only to the extent that HRSA's indication-based interpretation of the Proposed Rule is permissible, which as discussed in detail above is not.

In the alternative, the Proposed Rule provides that cancer hospitals can simply elect to purchase all orphan drugs outside of the 340B program, even when used for the rare diseases or conditions that were the source of the orphan designation, in which case the cancer hospital can use a GPO for all orphan drug purchases.[55] The Proposed Rule provides absolutely no explanation for how or why this proposal is permitted under the 340B statute or the program's existing guidance on the GPO prohibition. This option is simply added on at the end of the Notice's discussion of covered entity compliance obligations.

BIO believes this latter option is impermissible under the statute as well as the terms of the Proposed Rule itself, and opposes its inclusion in any final rule. The GPO prohibition applies to covered outpatient drugs as a category. If a cancer hospital opts to participate in the 340B program, then it is subject to that prohibition across all covered outpatient drug purchases. Nothing in the statute or HRSA's prior guidance on the GPO prohibition provide for an opt-out of the 340B program as to certain categories of products. A covered entity is either in or out of the program, and if that covered entity is in the program, then it must comply with all conditions of participation as to all of its outpatient drug purchases, including the GPO prohibition. Indeed, in this same Proposed Rule, as discussed above, HRSA specifies that a covered entity that participates in the 340B Program must live with any restrictions imposed on the covered entity category through which the covered entity enrolls under the program. This opt-out option is completely contrary to that provision in the Proposed Rule.

Congress added cancer hospitals to the 340B Program as part of ACA, and in doing so specifically crafted that legislation to have the GPO prohibition apply uniquely to cancer hospitals and not to the other new covered entity types. Congress did so in the same legislation that created the orphan drug exception, and Congress did not carve-out such products from the

[54] *Id.* at 29186. HRSA previously has issued guidance stating that this same rationale permits DSH-covered entities to purchase inpatient drugs through a group purchasing arrangement. *See* 59 Fed. Reg. 25110, 25113.
[55] *Id.*

GPO prohibition. The statutory framework could not be clearer. HRSA has no statutory authority to create this exception here.

F. Use of "Transferred, Prescribed, Sold, or Otherwise Used" Language

Throughout the Proposed Rule, HRSA discusses orphan drugs with the language of whether the drug is "transferred, prescribed, sold, or otherwise used" for an orphan or non-orphan use.[56] These are new terms to HRSA's discussion of compliance under the 340B program, but the Proposed Rule does not explain what they mean or elaborate on how these terms fit in to HRSA's overall guidance and compliance requirements.

BIO assumes that this new language relates to whether a covered entity is complying with the statutory prohibition against reselling or transferring 340B product to a person who is not a patient.[57] BIO understands that HRSA is in the process of developing new guidance regarding the patient definition, but that guidance has not yet been released. Until HRSA issues further guidance regarding the import of these new terms, and provides opportunity for stakeholder comment, BIO is concerned that HRSA's use of this new language, and in particular the term "transferred," will cause confusion among manufacturers and covered entities alike. BIO urges HRSA to disclose the purpose of these new terms and provide opportunity for stakeholder comment prior to including these terms in any final rule.

G. Identification of Orphan Drugs

HRSA has indicated that it is the FDA's responsibility to make orphan designations under Section 526 of the FFDCA.[58] BIO agrees that the most appropriate method for manufacturers and covered entities to determine whether a drug is designated as an orphan drug by the FDA is by reference to the listing of orphan drugs on the FDA's website.[59]

H. Technical Correction to Section 10.2 Language

Finally, as a point of technical clarification, the definition of 340B price is discussed inconsistently and incorrectly in the Proposed Rule. Specifically, the proposed regulatory text for Section 10.2 incorrectly defines the 340B ceiling price as "the *price paid for the drug under title XIX* of the Social Security Act reduced by a rebate percentage."[60] The italicized language is incorrect, and should instead refer to "the *average manufacturer price* for the drug under title XIX . . . " in accordance with Section 340B(a)(1) of the statute.

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[56] 76 Fed. Reg. at 29189.
[57] *See* 42 U.S.C. § 256b(a)(5)(B).
[58] 76 Fed. Reg. at 29186.
[59] As HRSA notes in the Proposed Rule, the FDA's listing can be accessed by the public at http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm.
[60] 76 Fed. Reg. at 29189 (emphasis added)

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BIO thanks HRSA for this opportunity to comment on the orphan drug exclusion Proposed Rule. We look forward to continuing to work with the agency to ensure that qualified safety net providers receive access to covered outpatient drugs for the benefit of patients in a way that is both practical and reflects the statutory directive of Congress.

Please contact Laurel Todd at (202)-962-9200 if you have any questions regarding our comments. Thank you for your attention to this very important matter and for your consideration of BIO's views.

Respectfully submitted,

/s/

Laurel Todd
Managing Director
Reimbursement and Health Policy

	Malignant					
	Primary	Secondary	Ca in situ	Benign	Uncertain Behavior	Unspecified
Neoplasm *(Continued)*						
brachial plexus	171.2	198.89	—	215.2	238.1	239.2
brain NEC	191.9	198.3	—	225.0	237.5	239.6
basal ganglia	191.0	198.3	—	225.0	237.5	239.6
cerebellopontine angle	191.6	198.3	—	225.0	237.5	239.6
cerebellum NOS	191.6	198.3	—	225.0	237.5	239.6
cerebrum	191.0	198.3	—	225.0	237.5	239.6
choroid plexus	191.5	198.3	—	225.0	237.5	239.6
contiguous sites	191.8	—	—	—	—	—
corpus callosum	191.8	198.3	—	225.0	237.5	239.6
corpus striatum	191.0	198.3	—	225.0	237.5	239.6
cortex (cerebral)	191.0	198.3	—	225.0	237.5	239.6
frontal lobe	191.1	198.3	—	225.0	237.5	239.6
globus pallidus	191.0	198.3	—	225.0	237.5	239.6
hippocampus	191.2	198.3	—	225.0	237.5	239.6
hypothalamus	191.0	198.3	—	225.0	237.5	239.6
internal capsule	191.0	198.3	—	225.0	237.5	239.6
medulla oblongata	191.7	198.3	—	225.0	237.5	239.6
meninges	192.1	198.4	—	225.2	237.6	239.7
midbrain	191.7	198.3	—	225.0	237.5	239.6
occipital labe	191.4	198.3	—	225.0	237.5	239.6
parietal lobe	191.3	198.3	—	225.0	237.5	239.6
peduncle	191.7	198.3	—	225.0	237.5	239.6
pons	191.7	198.3	—	225.0	237.5	239.6
stem	191.7	198.3	—	225.0	237.5	239.6
tapetum	191.8	198.3	—	225.0	237.5	239.6
temporal lobe	191.2	198.3	—	225.0	237.5	239.6
thalamus	191.0	198.3	—	225.0	237.5	239.6
uncus	191.2	198.3	—	225.0	237.5	239.6
ventricle (floor)	191.5	198.3	—	225.0	237.5	239.6
branchial (cleft) (vestiges)	146.8	198.89	230.0	210.6	235.1	239.0
breast (connective tissue) (female) (glandular tissue) (soft parts)	174.9	198.81	233.0	217	238.3	239.3
areola	174.0	198.81	233.0	217	238.3	239.3
male	175.0	198.81	233.0	217	238.3	239.3
axillary tail	174.6	198.81	233.0	217	238.3	239.3
central portion	174.1	198.81	233.0	217	238.3	239.3
contiguous sites	174.8	—	—	—	—	—
ectopic sites	174.8	198.81	233.0	217	238.3	239.3
inner	174.8	198.81	233.0	217	238.3	239.3
lower	174.8	198.81	233.0	217	238.3	239.3
lower-inner quadrant	174.3	198.81	233.0	217	238.3	239.3

	Malignant					
	Primary	Secondary	Ca in situ	Benign	Uncertain Behavior	Unspecified
Neoplasm *(Continued)*						
breast *(Continued)*						
lower-outer quadrant	174.5	198.81	233.0	217	238.3	239.3
male	175.9	198.81	233.0	217	238.3	239.3
areola	175.0	198.81	233.0	217	238.3	239.3
ectopic tissue	175.9	198.81	233.0	217	238.3	239.3
nipple	175.0	198.81	233.0	217	238.3	239.3
mastectomy site (skin)	173.5	198.2	—	—	—	—
specified as breast tissue	174.8	198.81	—	—	—	—
midline	174.8	198.81	233.0	217	238.3	239.3
nipple	174.0	198.81	233.0	217	238.3	239.3
male	175.0	198.81	233.0	217	238.3	239.3
outer	174.8	198.81	233.0	217	238.3	239.3
skin	173.5	198.2	232.5	216.5	238.2	239.2
tail (axillary)	174.6	198.81	233.0	217	238.3	239.3
upper	174.8	198.81	233.0	217	238.3	239.3
upper-inner quadrant	174.2	198.81	233.0	217	238.3	239.3
upper-outer quadrant	174.4	198.81	233.0	217	238.3	239.3
broad ligament	183.3	198.82	233.39	221.0	236.3	239.5
bronchiogenic, bronchogenic (lung)	162.9	197.0	231.2	212.3	235.7	239.1
bronchiole	162.9	197.0	231.2	212.3	235.7	239.1
bronchus	162.9	197.0	231.2	212.3	235.7	239.1
carina	162.2	197.0	231.2	212.3	235.7	239.1
contiguous sites with lung or trachea	162.8	—	—	—	—	—
lower lobe of lung	162.5	197.0	231.2	212.3	235.7	239.1
main	162.2	197.0	231.2	212.3	235.7	239.1
middle lobe of lung	162.4	197.0	231.2	212.3	235.7	239.1
upper lobe of lung	162.3	197.0	231.2	212.3	235.7	239.1
brow	173.3	198.2	232.3	216.3	238.2	239.2
buccal (cavity)	145.9	198.89	230.0	210.4	235.1	239.0
commissure	145.0	198.89	230.0	210.4	235.1	239.0
groove (lower) (upper)	145.1	198.89	230.0	210.4	235.1	239.0
mucosa	145.0	198.89	230.0	210.4	235.1	239.0
sulcus (lower) (upper)	145.1	198.89	230.0	210.4	235.1	239.0
bulbourethral gland	189.3	198.1	233.9	223.81	236.99	239.5
bursa - *see* Neoplasm, connective tissue						
buttock NEC*	195.3	198.89	232.5	229.8	238.8	239.89
calf*	195.5	198.89	232.7	229.8	238.8	239.89
calvarium	170.0	198.5	—	213.0	238.0	239.2
calyx, renal	189.1	198.0	233.9	223.1	236.91	239.5

	Malignant					
	Primary	Secondary	Ca in situ	Benign	Uncertain Behavior	Unspecified
Neoplasm *(Continued)*						
lobe						
azygos	162.3	197.0	231.2	212.3	235.7	239.1
frontal	191.1	198.3	—	225.0	237.5	239.6
lower	162.5	197.0	231.2	212.3	235.7	239.1
middle	162.4	197.0	231.2	212.3	235.7	239.1
occipital	191.4	198.3	—	225.0	237.5	239.6
parietal	191.3	198.3	—	225.0	237.5	239.6
temporal	191.2	198.3	—	225.0	237.5	239.6
upper	162.3	197.0	231.2	212.3	235.7	239.1
lumbosacral plexus	171.6	198.4	—	215.6	238.1	239.2
lung	162.9	197.0	231.2	212.3	235.7	239.1
azygos lobe	162.3	197.0	231.2	212.3	235.7	239.1
carina	162.2	197.0	231.2	212.3	235.7	239.1
contiguous sites with bronchus or trachea	162.8	—	—	—	—	—
hilus	162.2	197.0	231.2	212.3	235.7	239.1
lingula	162.3	197.0	231.2	212.3	235.7	239.1
lobe NEC	162.9	197.0	231.2	212.3	235.7	239.1
lower lobe	162.5	197.0	231.2	212.3	235.7	239.1
main bronchus	162.2	197.0	231.2	212.3	235.7	239.1
middle lobe	162.4	197.0	231.2	212.3	235.7	239.1
upper lobe	162.3	197.0	231.2	212.3	235.7	239.1
lymph, lymphatic						
channel NEC (*see also* Neoplasm, connective tissue)	171.9	198.89	—	215.9	238.1	239.2
gland (secondary)	—	196.9	—	229.0	238.8	239.89
abdominal	—	196.2	—	229.0	238.8	239.89
aortic	—	196.2	—	229.0	238.8	239.89
arm	—	196.3	—	229.0	238.8	239.89
auricular (anterior) (posterior)	—	196.0	—	229.0	238.8	239.89
axilla, axillary	—	196.3	—	229.0	238.8	239.89
brachial	—	196.3	—	229.0	238.8	239.89
bronchial	—	196.1	—	229.0	238.8	239.89
bronchopulmonary	—	196.1	—	229.0	238.8	239.89
celiac	—	196.2	—	229.0	238.8	239.89
cervical	—	196.0	—	229.0	238.8	239.89
cervicofacial	—	196.0	—	229.0	238.8	239.89
Cloquet	—	196.5	—	229.0	238.8	239.89
colic	—	196.2	—	229.0	238.8	239.89
common duct	—	196.2	—	229.0	238.8	239.89
cubital	—	196.3	—	229.0	238.8	239.89
diaphragmatic	—	196.1	—	229.0	238.8	239.89

	Malignant					
	Primary	Secondary	Ca in situ	Benign	Uncertain Behavior	Unspecified
Neoplasm *(Continued)*						
sinus *(Continued)*						
contiguous sites with middle ear or nasal cavities	160.8	—	—	—	—	—
ethmoidal	160.3	197.3	231.8	212.0	235.9	239.1
frontal	160.4	197.3	231.8	212.0	235.9	239.1
maxillary	160.2	197.3	231.8	212.0	235.9	239.1
nasal, paranasal NEC	160.9	197.3	231.8	212.0	235.9	239.1
pyriform	148.1	198.89	230.0	210.8	235.1	239.0
sphenoidal	160.5	197.3	231.8	212.0	235.9	239.1
skeleton, skeletal NEC	170.9	198.5	—	213.9	238.0	239.2
Skene's gland	189.4	198.1	233.9	223.89	236.99	239.5
skin NEC	173.9	198.2	232.9	216.9	238.2	239.2
abdominal wall	173.5	198.2	232.5	216.5	238.2	239.2
ala nasi	173.3	198.2	232.3	216.3	238.2	239.2
ankle	173.7	198.2	232.7	216.7	238.2	239.2
antecubital space	173.6	198.2	232.6	216.6	238.2	239.2
anus	173.5	198.2	232.5	216.5	238.2	239.2
arm	173.6	198.2	232.6	216.6	238.2	239.2
auditory canal (external)	173.2	198.2	232.2	216.2	238.2	239.2
auricle (ear)	173.2	198.2	232.2	216.2	238.2	239.2
auricular canal (external)	173.2	198.2	232.2	216.2	238.2	239.2
axilla, axillary fold	173.5	198.2	232.5	216.5	238.2	239.2
back	173.5	198.2	232.5	216.5	238.2	239.2
breast	173.5	198.2	232.5	216.5	238.2	239.2
brow	173.3	198.2	232.3	216.3	238.2	239.2
buttock	173.5	198.2	232.5	216.5	238.2	239.2
calf	173.7	198.2	232.7	216.7	238.2	239.2
canthus (eye) (inner) (outer)	173.1	198.2	232.1	216.1	238.2	239.2
cervical region	173.4	198.2	232.4	216.4	238.2	239.2
cheek (external)	173.3	198.2	232.3	216.3	238.2	239.2
chest (wall)	173.5	198.2	232.5	216.5	238.2	239.2
chin	173.3	198.2	232.3	216.3	238.2	239.2
clavicular area	173.5	198.2	232.5	216.5	238.2	239.2
clitoris	184.3	198.82	233.32	221.2	236.3	239.5
columnella	173.3	198.2	232.3	216.3	238.2	239.2
concha	173.2	198.2	232.2	216.2	238.2	239.2
contiguous sites	173.8	—	—	—	—	—
ear (external)	173.2	198.2	232.2	216.2	238.2	239.2
elbow	173.6	198.2	232.6	216.6	238.2	239.2
eyebrow	173.3	198.2	232.3	216.3	238.2	239.2
eyelid	173.1	198.2	232.1	216.1	238.2	239.2

	Malignant					
	Primary	Secondary	Ca in situ	Benign	Uncertain Behavior	Unspecified
Neoplasm *(Continued)*						
skin NEC *(Continued)*						
face NEC	173.3	198.2	232.3	216.3	238.2	239.2
female genital organs (external)	184.4	198.82	233.30	221.2	236.3	239.5
clitoris	184.3	198.82	233.32	221.2	236.3	239.5
labium NEC	184.4	198.82	233.32	221.2	236.3	239.5
majus	184.1	198.82	233.32	221.2	236.3	239.5
minus	184.2	198.82	233.32	221.2	236.3	239.5
pudendum	184.4	198.82	233.32	221.2	236.3	239.5
vulva	184.4	198.82	233.32	221.2	236.3	239.5
finger	173.6	198.2	232.6	216.6	238.2	239.2
flank	173.5	198.2	232.5	216.5	238.2	239.2
foot	173.7	198.2	232.7	216.7	238.2	239.2
forearm	173.6	198.2	232.6	216.6	238.2	239.2
forehead	173.3	198.2	232.3	216.3	238.2	239.2
glabella	173.3	198.2	232.3	216.3	238.2	239.2
gluteal region	173.5	198.2	232.5	216.5	238.2	239.2
groin	173.5	198.2	232.5	216.5	238.2	239.2
hand	173.6	198.2	232.6	216.6	238.2	239.2
head NEC	173.4	198.2	232.4	216.4	238.2	239.2
heel	173.7	198.2	232.7	216.7	238.2	239.2
helix	173.2	198.2	232.2	216.2	238.2	239.2
hip	173.7	198.2	232.7	216.7	238.2	239.2
infraclavicular region	173.5	198.2	232.5	216.5	238.2	239.2
inguinal region	173.5	198.2	232.5	216.5	238.2	239.2
jaw	173.3	198.2	232.3	216.3	238.2	239.2
knee	173.7	198.2	232.7	216.7	238.2	239.2
labia						
majora	184.1	198.82	233.32	221.2	236.3	239.5
minora	184.2	198.82	233.32	221.2	236.3	239.5
leg	173.7	198.2	232.7	216.7	238.2	239.2
lid (lower) (upper)	173.1	198.2	232.1	216.1	238.2	239.2
limb NEC	173.9	198.2	232.9	216.9	238.2	239.5
lower	173.7	198.2	232.7	216.7	238.2	239.2
upper	173.6	198.2	232.6	216.6	238.2	239.2
lip (lower) (upper)	173.0	198.2	232.0	216.0	238.2	239.2
male genital organs	187.9	198.82	233.6	222.9	236.6	239.5
penis	187.4	198.82	233.5	222.1	236.6	239.5
prepuce	187.1	198.82	233.5	222.1	236.6	239.5
scrotum	187.7	198.82	233.6	222.4	236.6	239.5

	Malignant					
	Primary	Secondary	Ca in situ	Benign	Uncertain Behavior	Unspecified
Neoplasm *(Continued)*						
skin NEC *(Continued)*						
mastectomy site	173.5	198.2	—	—	—	—
specified as breast tissue	174.8	198.81	—	—	—	—
meatus, acoustic (external)	173.2	198.2	232.2	216.2	238.2	239.2
notes	173.5	198.2	232.5	216.5	238.2	239.2
neck	173.4	198.2	232.4	216.4	238.2	239.2
nose (external)	173.3	198.2	232.3	216.3	238.2	239.2
palm	173.6	198.2	232.6	216.6	238.2	239.2
palpebra	173.1	198.2	232.1	216.1	238.2	239.2
penis NEC	187.4	198.82	233.5	222.1	236.6	239.5
perianal	173.5	198.2	232.5	216.5	238.2	239.2
perineum	173.5	198.2	232.5	216.5	238.2	239.2
pinna	173.2	198.2	232.2	216.2	238.2	239.2
plantar	173.7	198.2	232.7	216.7	238.2	239.2
popliteal fossa or space	173.7	198.2	232.7	216.7	238.2	239.2
prepuce	187.1	198.82	233.5	222.1	236.6	239.5
pubes	173.5	198.2	232.5	216.5	238.2	239.2
sacrococcygeal region	173.5	198.2	232.5	216.5	238.2	239.2
scalp	173.4	198.2	232.4	216.4	238.2	239.2
scapular region	173.5	198.2	232.5	216.5	238.2	239.2
scrotum	187.7	198.82	233.6	222.4	236.6	239.5
shoulder	173.6	198.2	232.6	216.6	238.2	239.2
sole (foot)	173.7	198.2	232.7	216.7	238.2	239.2
specified sites NEC	173.8	198.2	232.8	216.8	238.2	239.2
submammary fold	173.5	198.2	232.5	216.5	238.2	239.2
supraclavicular region	173.4	198.2	232.4	216.4	238.2	239.2
temple	173.3	198.2	232.3	216.3	238.2	239.2
thigh	173.7	198.2	232.7	216.7	238.2	239.2
thoracic wall	173.5	198.2	232.5	216.5	238.2	239.2
thumb	173.6	198.2	232.6	216.6	238.2	239.2
toe	173.7	198.2	232.7	216.7	238.2	239.2
tragus	173.2	198.2	232.2	216.2	238.2	239.2
trunk	173.5	198.2	232.5	216.5	238.2	239.2
umbilicus	173.5	198.2	232.5	216.5	238.2	239.2
vulva	184.4	198.82	233.32	221.2	236.3	239.5
wrist	173.6	198.2	232.6	216.6	238.2	239.2
skull	170.0	198.5	—	213.0	238.0	239.2
soft parts or tissues - *see* Neoplasm, connective tissue						
specified site NEC	195.8	198.89	234.8	229.8	238.8	239.89

	Malignant					
	Primary	Secondary	Ca in situ	Benign	Uncertain Behavior	Unspecified
Neoplasm *(Continued)*						
spermatic cord	187.6	198.82	233.6	222.8	236.6	239.5
sphenoid	160.5	197.3	231.8	212.0	235.9	239.1
bone	170.0	198.5	—	213.0	238.0	239.2
sinus	160.5	197.3	231.8	212.0	235.9	239.1
sphincter						
anal	154.2	197.5	230.5	211.4	235.5	239.0
of Oddi	156.1	197.8	230.8	211.5	235.3	239.0
spine, spinal (column)	170.2	198.5	—	213.2	238.0	239.2
bulb	191.7	198.3	—	225.0	237.5	239.6
coccyx	170.6	198.5	—	213.6	238.0	239.2
cord (cervical) (lumbar) (sacral) (thoracic)	192.2	198.3	—	225.3	237.5	239.7
dura mater	192.3	198.4	—	225.4	237.6	239.7
lumbosacral	170.2	198.5	—	213.2	238.0	239.2
membrane	192.3	198.4	—	225.4	237.6	239.7
meninges	192.3	198.4	—	225.4	237.6	239.7
nerve (root)	171.9	198.89	—	215.9	238.1	239.2
pia mater	192.3	198.4	—	225.4	237.6	239.7
root	171.9	198.89	—	215.9	238.1	239.2
sacrum	170.6	198.5	—	213.6	238.0	239.2
spleen, splenic NEC	159.1	197.8	230.9	211.9	235.5	239.0
flexure (colon)	153.7	197.5	230.3	211.3	235.2	239.0
stem, brain	191.7	198.3	—	225.0	237.5	239.6
Stensen's duct	142.0	198.89	230.0	210.2	235.0	239.0
sternum	170.3	198.5	—	213.3	238.0	239.2
stomach	151.9	197.8	230.2	211.1	235.2	239.0
antrum (pyloric)	151.2	197.8	230.2	211.1	235.2	239.0
body	151.4	197.8	230.2	211.1	235.2	239.0
cardia	151.0	197.8	230.2	211.1	235.2	239.0
cardiac orifice	151.0	197.8	230.2	211.1	235.2	239.0
contiguous sites	151.8	—	—	—	—	—
corpus	151.4	197.8	230.2	211.1	235.2	239.0
fundus	151.3	197.8	230.2	211.1	235.2	239.0
greater curvature NEC	151.6	197.8	230.2	211.1	235.2	239.0
lesser curvature NEC	151.5	197.8	230.2	211.1	235.2	239.0
prepylorus	151.1	197.8	230.2	211.1	235.2	239.0
pylorus	151.1	197.8	230.2	211.1	235.2	239.0
wall NEC	151.9	197.8	230.2	211.1	235.2	239.0
anterior NEC	151.8	197.8	230.2	211.1	235.2	239.0
posterior NEC	151.8	197.8	230.2	211.1	235.2	239.0
stroma, endometrial	182.0	198.82	233.2	219.1	236.0	239.5