FDA U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM

To: NDA 206494, Avycaz (ceftazidime-avibactam) for injection, for intravenous use

From: CDER Exclusivity Board

Re: Eligibility of Avycaz for 5-Year NCE Exclusivity

Date: 12/21/2020

This memorandum documents the recommendation of the Exclusivity Board (Board) within the Center for Drug Evaluation and Research (CDER) regarding the eligibility of Avycaz (ceftazidime-avibactam) for injection, for intravenous use (Avycaz) (NDA 206494 held by Allergan, Inc. (Allergan))[1] for 5-year new chemical entity exclusivity (5-year NCE exclusivity) under section 505(c)(3)(E)(ii) and (j)(5)(F)(ii) of the Federal Food, Drug, and Cosmetic Act (FD&C Act).[2] Avycaz, a fixed-combination of ceftazidime, a third-generation cephalosporin antibacterial drug, and avibactam, a non-beta-lactam, betalactamase inhibitor (BLI), was approved on February 25, 2015, for the treatment of patients 18 years or older with two infections caused by designated susceptible microorganisms: complicated intra-abdominal infections (cIAI), and complicated urinary tract infections (cUTI), including pyelonephritis.[3] Ceftazidime is an "old antibiotic," an active ingredient and active moiety previously approved in a drug product under section 507 of FD&C Act, prior to enactment of the Food and Drug Administration Modernization Act of 1997 (FDAMA).[4] Avibactam is a new chemical entity, i.e., a drug that contains no active moiety that has been approved by FDA in any other application submitted under section 505(b) of the FD&C Act.[5] Avibactam protects ceftazidime from degradation by beta-lactamase enzymes, and maintains the antibacterial activity of ceftazidime against certain types of bacteria that express beta-lactamases.[6]

In the Exclusivity Summary for Avycaz, the reviewing division, the Division of Anti-Infective Products (DAIP or the "division") stated that Avycaz contains avibactam, a new chemical entity, in combination with ceftazidime, a previously approved active moiety, and that under the

---

[1] Allergan was acquired by AbbVie, Inc. on May 8, 2020.
[2] The "5-year NCE exclusivity statutory provisions."
[3] Avycaz has since been approved for two new indications: treatment of patients with hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia (HABP/VABP)(NDA 206494/S-004, approved on Feb. 1, 2018), and treatment of complicated urinary tract infections (cUTI) and complicated intra-abdominal infections (cIAI) to include patients 3 months to less than 18 years of age (NDA 206494/S-005 and -006, both approved on Mar. 14, 2019).
[4] Pub. L. No. 105-115 (Nov. 21, 1997).
[5] Such active moieties will be referred to as "new active moieties" in this memorandum.
[6] BLIs generally change both the spectrum of activity of the drug product, and expand the types of antimicrobial-related indications that can be treated.

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

Agency's post-October 2014 interpretation of 5-year NCE exclusivity described in FDA's final guidance entitled *New Chemical Entity Exclusivity Determinations for Certain Fixed-Combination Drug Products* (Oct. 2014) (Fixed-Combination NCE Guidance),[7] Avycaz is eligible for 5-year NCE exclusivity. The exclusivity summary makes no mention of the potential impact of section 505(v) of the FD&C Act, added as part of the QI Program Supplemental Funding Act of 2008[8] (QI Act), on this determination.

After the approval of Avycaz, a question arose within the Agency as to whether Avycaz was indeed eligible for 5-year NCE exclusivity because it contained in part an old antibiotic. The Agency questioned whether and how section 125 of FDAMA and section 505(v) of the FD&C Act added as part of the QI Act impacted the exclusivity analysis. The Agency determined that it would need to conduct this legal and regulatory analysis before including any exclusivity in the Orange Book for Avycaz. Therefore, in order to determine whether, Avycaz, a fixed-combination containing a new active moiety and an old antibiotic is eligible for 5-year NCE exclusivity, the Board considered the 5-year NCE exclusivity statutory provisions, the Fixed-Combination NCE Guidance, and the history of the regulation of antibiotics, including changes provided in FDAMA and the QI Act, among others. In particular, the Board evaluated whether section 505(v) of the FD&C Act poses any limitations on eligibility for 5-year NCE exclusivity.[9]

Upon review, the Board recommends that 5-year NCE exclusivity for Avycaz is proper under, among other things, the above legal and regulatory considerations, and in accordance with the Agency's policy objectives of incentivizing the development of antimicrobial[10] therapies that

---

[7] The guidance is available at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[8] Pub. L. No. 110-379 (Oct. 8, 2008).

[9] Although FDA has previously recognized 5-year NCE exclusivity plus the 5-year GAIN exclusivity extension for Zerbaxa (ceftolozane-tazobactam) (NDA 206829, approved on December 19, 2014), a fixed-combination containing a new active moiety and an old antibiotic in FDA's *Approved Drug Products With Therapeutic Equivalence Evaluations* (the Orange Book), available records indicate, however, that this conclusion was made only by considering the Fixed-Combination NCE Guidance, but without considering what, if any, impact section 505(v) of the FD&C Act would have on eligibility of Zerbaxa for 5-year NCE exclusivity.

[10] This document uses terms such as "antimicrobial", "antibacterial," "antibiotic," as well as "antimicrobial resistance," both in original text, and in citing to external references. The descriptions of these terms as understood for the purposes of this memo are provided below.

The term ***antimicrobial*** is generally used inclusively to refer to any agent (including an antibiotic) used to kill or inhibit the growth of microorganisms (bacteria, viruses, fungi, or parasites). See *A Public Health Action Plan to Combat Antimicrobial Resistance* (2012) Interagency Task Force on Antimicrobial Resistance, Co-Chaired by FDA, the Centers for Disease Control and Prevention (CDC), and the National Institutes of Health (NIH), at 3, available at https://www.cdc.gov/drugresistance/pdf/action-plan-2012.pdf.

The term ***antimicrobial resistance*** (AMR) is understood to mean "[t]he result of microorganisms changing in ways that reduce or eliminate the effectiveness of drugs, chemicals, or other agents used to cure or prevent infections." See CDC, Antibiotic Resistance Threats in the United States (2013), available at

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

include at least one novel active moiety. Specifically, the Board interprets the phrase "drug that . . . contains an antibiotic drug" in section 505(v)(1) to refer to a **drug product** that **contains wholly** an old antibiotic **drug substance or active moiety or combination of old antibiotic drug substances or active moieties**. Such an interpretation would remove from section 505(v) of the FD&C Act a fixed-combination drug product that contains a new active moiety in combination with an old antibiotic active moiety and would make such a fixed-combination eligible for 5-year NCE exclusivity.

The 5-year NCE exclusivity period for Avycaz expired on February 25, 2020. However, Avycaz has been designated by FDA as a qualified infectious disease product (QIDP) under the provisions of the Generating Antibiotic Incentives Now (GAIN) Act,[11] and thus qualifies for the exclusivity extension provided under section 505E(a) of the FD&C Act until February 25, 2025.

I. Factual Background

As noted above, Avycaz consists of the BLI avibactam, an NCE in fixed combination with ceftazidime, an old "beta-lactam" antibiotic. Beta-lactam/BLI fixed-combinations are a type of fixed-combination containing an antibiotic drug and another drug that enhances the effectiveness of the antibiotic drug by inhibiting or counteracting resistance.

Beta-lactam antibiotics, described as such because they contain a beta-lactam ring in their molecular structures, have since their discovery been a major component of the clinical armamentarium against increasingly prevalent multi-drug resistant (MDR) gram-negative bacteria that represent a significant threat to human health. Most beta-lactam antibiotics work by

---

www.cdc.gov/drugresistance/threat-report-2013/pdf/ar-threats-2013-508.pdf See also the WHO's description of antimicrobial resistance, available at https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance ("Antimicrobial resistance happens when microorganisms (such as bacteria, fungi, viruses, and parasites) change when they are exposed to antimicrobial drugs (such as antibiotics, antifungals, antivirals, antimalarials, and anthelmintics.)").

The term ***antibiotic*** is defined in section 201(jj) of the FD&C Act, which states that "[t]he term 'antibiotic drug' means any drug (except drugs for use in animals other than humans) composed wholly or partly of any kind of penicillin, streptomycin, chlortetracycline, chloramphenicol, bacitracin, or any other drug intended for human use containing any quantity of any chemical substance which is produced by a micro-organism and which has the capacity to inhibit or destroy micro-organisms in dilute solution (including a chemically synthesized equivalent of any such substance) or any derivative thereof." We note that CDER has generally ceased using the term ***antibiotic*** except when discussing specific provisions of the FD&C Act that rely on the definition in section 201(jj), such as section 505(v), the transition provisions of FDAMA, repealed section 507, and pre-FDAMA antibiotics. For purposes of this memorandum, the term ***antibiotic*** will be used when discussing these topics, whereas the term ***antibacterial drug*** will be used when discussing general policy considerations that apply to the development of drugs to treat or prevent bacterial infections.

[11] Title VIII of the Food and Drug Administration Safety and Innovation Act (FDASIA), Pub. L. No 112-144 (Jul. 9, 2012).

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

inhibiting cell wall biosynthesis in bacterial organisms. Beta-lactam antibiotics include penicillin derivatives (penams), cephalosporins (such as ceftazidime), monobactams, and carbapenems. Bacteria, however, often develop resistance to beta-lactam antibiotics by synthesizing beta-lactamases, enzymes that attack the beta-lactam ring. To overcome this resistance, restore the activity of the drug against certain beta-lactamase producing pathogens, and extend the spectrum of activity of the antibiotic to fight infections, beta-lactam antibiotics have recently been developed in fixed-combination with BLIs. BLIs alone may have little or no clinically relevant antibacterial activity at prescribed strengths when not combined with a beta lactam.

Ceftazidime, the old antibiotic in Avycaz, is a third generation cephalosporin beta-lactam antibiotic. A broad use antibiotic, it was first approved under section 507 by FDA in July 1985 (Fortaz, NDA 50578) for among other things, urinary tract infections, and intra-abdominal infections. Like with other beta-lactams, a mechanism of bacterial resistance to ceftazidime is hydrolysis by bacterial beta-lactamase enzymes that enzymatically cleave its beta-lactam ring. Avibactam, the new active moiety BLI, does not generally have any direct antibacterial activity, but protects ceftazidime from degradation by beta-lactamase enzymes, and maintains the antibacterial activity of ceftazidime against isolates of *Enterobacteriaceae and P. aeruginosa* that express several types of serine beta-lactamases.

II. Legal Background

A. Exclusivity under the FD&C Act

Section 505(b) through (d) of the FD&C Act establishes the approval requirements for new drug applications (NDAs). Stand-alone 505(b)(1) applications are supported entirely by investigations either conducted by the applicant or to which the applicant has a right of reference. The Drug Price Competition and Patent Term Restoration Act of 1984 (the Hatch-Waxman Amendments)[12] amended the FD&C Act and added section 505(b)(2) and (j) of the FD&C Act. Section 505(b)(2) provides an alternative pathway for approval of an NDA, under which some or all of the investigations relied on for approval were not conducted by or for the applicant and for which the applicant has not obtained a right of reference (a 505(b)(2) application). Section 505(j) establishes the abbreviated new drug application (ANDA) approval process, which provides a more streamlined route for generic drugs to be approved.
In addition to establishing the drug approval pathways in section 505(b)(2) and (j) of the FD&C Act, the Hatch-Waxman Amendments provide incentives for pharmaceutical innovation in the form of 5-year NCE exclusivity and 3-year exclusivity to protect qualified drugs submitted under section 505(b) from competition from certain 505(b)(2) applications and ANDAs for varying periods of time depending on the factual circumstances.

[12] Pub. L. No. 98-417 (1984).

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

1. 5-Year NCE Exclusivity

The FD&C Act provides for a 5-year period of exclusivity for a drug that contains a new (never previously approved) active moiety (known as a "new chemical entity") by barring the submission of ANDAs and 505(b)(2) applications that contain the new chemical entity. The 5-year exclusivity statutory provision provides:

> *If an application submitted under subsection (b) for a drug, no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under subsection (b), is approved after [September 24, 1984],* no application which refers to the drug for which the subsection (b) application was submitted and which [qualifies as a 505(b)(2) application] may be submitted under subsection (b) before the expiration of five years from the date of the approval of the application under subsection (b), except that such an application may be submitted under this subsection after the expiration of four years from the date of the approval of the subsection (b) application if it contains a certification of patent invalidity or noninfringement described in subclause (IV) of paragraph (2)(A)(vii). . . . [13]

In this provision, the first clause (italicized text) describes which "drugs" are new chemical entities (eligibility clause), and thus eligible for 5-year NCE exclusivity, while the second clause (plain text) describes the applications that are blocked by such exclusivity (bar clause). Under the eligibility clause, a drug is eligible for 5-year NCE exclusivity if it is "a *drug*, no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other [505(b)] application."

Once a drug has met the requirements of the eligibility clause, the bar clause prevents the submission of any ANDA or 505(b)(2) application that "refers to the *drug* for which the [505(b)] application was submitted." This bar on submission lasts for "five years from the date of the approval of the [505(b)] application,"[14] except that an ANDA or a 505(b)(2) application may be submitted after the expiration of 4 years from the date of approval if the ANDA or 505(b)(2) application contains a paragraph IV certification challenging a listed patent.[15] This bar (i.e., 5-year NCE exclusivity) does not block the submission, review, or approval of a stand-alone 505(b)(1) application.

---

[13] Section 505(c)(3)(E)(ii) of the FD&C Act (provision pertaining to 505(b)(2) applications) (emphasis added). See also Section 505(j)(5)(F)(ii) of the FD&C Act (provision pertaining to ANDAs). For purposes of this document, all references to exclusivity provisions will be references to 505(c) (which pertains to bars to submission or approval of NDAs). Any differences in how FDA interprets the parallel provisions in 505(j) are not relevant to this analysis and will not be separately discussed.

[14] Section 505(c)(3)(E)(ii) of the FD&C Act and 505(j)(5)(F)(ii).

[15] Id.

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

FDA's regulations implement the statutory 5-year NCE exclusivity provisions by taking an active moiety approach to the interpretation of 5-year NCE exclusivity. The regulations describe 5-year NCE exclusivity as follows:

> If a drug product that contains a *new chemical entity* was approved after September 24, 1984, in an NDA submitted under section 505(b) of the [FD&C Act], no person may submit a 505(b)(2) application or ANDA under section 505(j) of the [FD&C Act] for a drug product that contains the same *active moiety* as in the *new chemical entity* for a period of 5 years from the date of approval of the first approved NDA . . . .[16]

Thus, under 21 CFR 314.108(b)(2), if a drug product contains a *new chemical entity*, then a sponsor is generally barred from submitting any ANDA or 505(b)(2) application for a drug product that contains the same "*active moiety* as in the new chemical entity" until the 5-year NCE exclusivity period has expired.[17] FDA's regulations contain definitions that further help determine the applications that are eligible for 5-year NCE exclusivity.

- "New chemical entity" is defined as "a *drug* that contains no active moiety that has been approved by FDA in any other NDA submitted under section 505(b) of the [FD&C Act]."[18]

- "Active moiety" in turn is defined as "the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt . . . , or other noncovalent derivative . . . of the molecule, responsible for the physiological or pharmacological action of the drug substance."[19]

In defining these terms, the regulation interprets the statutory phrase "active ingredient" in the eligibility clause to refer to an "active moiety."[20] Other terms of art are defined in FDA's regulations:

- "Drug product," in part, means "a finished dosage form, e.g., tablet, capsule, or solution, that contains a drug substance. . . . "[21]

---

[16] 21 CFR 314.108(b)(2) (emphasis added).
[17] However, an ANDA or 505(b)(2) application may be submitted after 4 years from the date of approval of the NDA with NCE exclusivity if the application includes a certification of patent invalidity or noninfringement (i.e., a paragraph IV certification).
[18] 21 CFR 314.108(a) (emphasis added).
[19] 21 CFR 314.3(b).
[20] FDA Final Rule, *Abbreviated New Drug Applications; Patent and Exclusivity Provisions*, 59 FR 50338 at 50358 (Oct. 3, 1994) ("The agency has concluded that the term 'active ingredient,' as used in the phrase 'active ingredient (including any salt or ester of the active ingredient),' means active moiety.").
[21] 21 CFR 314.3(b).

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

- "Drug substance" is "an active ingredient that is intended to furnish pharmacological activity or other direct effect . . . but does not include intermediates used in the synthesis of such ingredient."[22]

- An "active ingredient" is "any component that is intended to furnish pharmacological activity or other direct effect . . . includ[ing] those components that may undergo chemical change in the manufacture of the drug product and be present in the drug product in a modified form intended to furnish the specified activity or effect."[23]

For a single-entity drug (i.e., where there is a single drug substance), if the drug contains an active moiety that the Agency has not previously approved, the drug will be eligible for 5-year NCE exclusivity.[24]

a. 5-Year NCE Exclusivity for Fixed-Combinations[25]

i. Pre-October 2014 FDA Interpretation

Prior to October 2014, FDA interpreted the word "drug" in the eligibility clause of the 5-year NCE exclusivity statutory and regulatory provisions to mean "drug product," not "drug substance." Under this interpretation of the statute and regulations, a "new chemical entity" referred to the entire drug product, which, in the case of a fixed-combination, included all of the active ingredients in that fixed-combination. Accordingly, in making the eligibility determination, FDA evaluated whether the *drug product* contained any previously approved active moiety. If the drug product as a whole contained at least one previously approved active moiety in combination with one or more active moieties that had not been previously approved, then that drug product was not eligible for 5-year NCE exclusivity. Therefore, a fixed-combination was not eligible for 5-year NCE exclusivity if the drug product contained any previously approved active moiety, even if the product also contained a "new active moiety" (i.e., an active moiety that the Agency had not previously approved).

---

[22] Id.

[23] Id.

[24] As explained in more detail below, prior to October 2014, FDA looked at whether the "drug product" contains a new active moiety in assessing eligibility for 5-year NCE exclusivity. After October 2014, pursuant to FDA's new interpretation of the statutory provisions, FDA looks individually at whether each "drug substance" contains a new active moiety. If any drug substance is one for which no active moiety has been previously approved, then the drug is eligible for 5-year NCE exclusivity. This change in interpretation generally did not affect 5-year NCE exclusivity determinations for single-entity drugs. Such products typically contain a single drug substance that contains a single active moiety. In such cases, where the single drug substance contains a previously approved active moiety, so does the drug product and, thus, the result is the same under either interpretation.

[25] A drug containing two or more active ingredients in a single dosage form will be referred to as a fixed-combination in this document, and a drug containing a single active ingredient will be referred to as a single-entity drug.

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

At the same time, the Agency interpreted the term "drug" in the bar clause of the 5-year NCE provision to mean "drug substance." FDA has explained that, after a drug product becomes eligible for 5-year NCE exclusivity, certain drug products subsequently developed that contain the same active moiety as the protected product would also benefit from the original product's 5-year NCE exclusivity until the exclusivity period for the original product has expired even if they would not, on their own, have qualified for an original 5-year NCE exclusivity.[26] Under this interpretation (known as the *umbrella policy*), 5-year NCE exclusivity does not attach only to the first approved drug product that was eligible for 5-year NCE exclusivity, but also protects other products containing the same active moiety approved during the 5-year exclusivity period, whether they are alone or in combination with a previously approved active moiety. FDA explained its reasoning for this interpretation as follows:

> [T]he agency interprets [5-year NCE exclusivity] to cover any subsequent approval of an application or supplemental application for a different ester, salt, or other noncovalent derivative, or a different dosage form, strength, route of administration, or new use of a drug with the same active moiety. Any modification to the product will be protected for the period of exclusivity remaining on the original application, unless the change occurs after or toward the end of the initial 5 years of exclusivity and independently qualifies for exclusivity under another exclusivity provision.[27]

Accordingly, under the umbrella policy, 5-year NCE exclusivity will apply not just to the first approved drug product containing no previously approved active moiety, but, with some exceptions, would also apply to any other drug product approved during the 5-year exclusivity period that contains the same new active moiety as in the first drug product, alone or in combination. Under the pre-October 2014 policy this meant that subsequently approved drug products that contained the protected active moiety alone or in a fixed-combination with another active moiety (regardless of whether the other moiety in the fixed-combination has been previously approved) would be protected for the balance of the exclusivity period even though fixed-combinations containing a previously approved active moiety in combination with a never previously approved active moiety would not have qualified on their own for an original period of 5-year NCE exclusivity. Under the pre-October 2014 approach, the order of approval mattered because in order to qualify for 5-year NCE exclusivity, the single entity had to be approved before the fixed-combination that contained the never previously approved active moiety in combination with one or more previously approved active moieties.

ii. Post-October 2014 FDA Interpretation

In October 2014, FDA adopted a new interpretation of the 5-year NCE statutory and regulatory provisions as applied to certain fixed-combinations. In light of the increasing public health

[26] FDA Proposed Rule, *Abbreviated New Drug Application Regulations*, 54 FR 28872 at 28898-28899 (July 10, 1989).
[27] Id.

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

importance of fixed-combinations to treat serious diseases and conditions, as well as the consideration of other factors, FDA reinterpreted the statutory language to allow fixed-combinations that contained a never previously approved active moiety in combination with one or more previously approved active moieties to qualify for an initial period of 5-year NCE exclusivity.

In October 2014, FDA issued a final guidance for industry entitled *New Chemical Entity Exclusivity Determinations for Certain Fixed-Combination Drug Products* (Oct. 2014) (Fixed-Combination NCE Guidance), which sets out FDA's new interpretation of the 5-year NCE exclusivity provisions as they apply to fixed-combination drugs.[28] FDA explained that under its current thinking, it would interpret the word "drug" in the statutory eligibility clause of the 5-year NCE provision to refer to the "drug substance," not the "drug product" as FDA had previously interpreted the statute. Consequently, FDA interpreted the word drug in the definitions of "new chemical entity" (which is defined as "a drug that contains no active moiety that has been approved by FDA in any other NDA submitted under section 505(b) of the [FD&C] Act") in the regulations to mean "drug substance" (i.e., active ingredient).[29] This meant that rather than analyze the entire drug product as a whole to determine initial eligibility for 5-year NCE exclusivity, FDA would analyze each drug substance (i.e., active ingredient) separately to determine whether it meets the definition of new chemical entity. Under this interpretation, a drug substance containing no previously approved active moiety would be eligible for 5-year NCE exclusivity even when such a drug substance is initially approved in a fixed-combination with another drug substance containing a previously approved active moiety. FDA explained that this is a permissible construction of the 5-year exclusivity statutory provisions and implementing regulations because of the inherent ambiguity in the term "drug" and noted that it serves the important public health goals of making additional incentives available for development of fixed combination drugs. FDA noted that it intended to apply the new interpretation prospectively from the date of the final guidance's publication (i.e., only to fixed-combinations approved *after* the issuance of the October 2014 final guidance) and that previously approved fixed-combination drugs would be subject to the pre-October 2014 interpretation (which, it noted, was also a permissible interpretation of the relevant statute and regulations).

iii. Ferring Lawsuit regarding Prepopik

On June 1, 2015, Ferring filed an action challenging the Agency's pre-October 2014 interpretation of the 5-year NCE exclusivity provision as applied to Prepopik, a fixed-combination approved in 2012.[30] Ferring argued that 1) FDA's prior interpretation was contrary

[28] The guidance is available at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.
[29] 21 CFR 314.3(b) (defining "drug substance" as an active ingredient).
[30] See Complaint for Declaratory, Injunctive, and Other Relief, *Ferring Pharm., Inc. v. Burwell*, No. CV 15-0802 (RC) (D.D.C. June 1, 2015).

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

to the plain meaning of the FD&C Act; 2) even if the relevant statutory provisions were ambiguous, FDA's prior interpretation was unreasonable; and 3) even if the prior interpretation was permissible, FDA's refusal to apply the October 2014 interpretation retroactively to Prepopik was arbitrary and capricious.

In a Memorandum Opinion and Order dated September 9, 2016, the U.S. District Court for the District of Columbia (*Ferring* court) concluded that FDA's pre-October 2014 interpretation of the word "drug" in the relevant statutory provisions governing 5-year NCE exclusivity was arbitrary and capricious in the context of certain fixed-combinations because the availability of 5-year NCE exclusivity under the pre-October 2014 interpretation arbitrarily turned on the order of approval.[31] The *Ferring* court appeared persuaded by examples that Ferring had provided showing that the temporal sequence of approval was outcome determinative under FDA's pre-October 2014 interpretation.[32] The court explained: "If a drug substance is sufficiently novel to warrant protection under a five-year exclusivity period—and sufficiently novel that other products containing that drug substance should also be protected through the umbrella policy—it is not apparent why timing, or the order in which the drugs were approved, should alter that assessment."[33] The *Ferring* court remanded the action to FDA for proceedings not inconsistent with the opinion.[34]

On remand, the Agency determined that Prepopik did not contain any drug substance with no previously approved active moiety so that even if the *Ferring* court's ruling were correct – that FDA's pre-October 2014 interpretation was irrational in that exclusivity availability turned on the order of approval – that ruling had no bearing on the eligibility of Prepopik for 5-year NCE exclusivity. All three drug substances in Prepopik–sodium picosulfate, magnesium oxide, and citric acid–contained previously approved active moieties. Therefore, FDA concluded that Prepopik was not eligible for 5-year NCE exclusivity under either the Agency's pre-October 2014 interpretation or the Agency's post-October 2014 interpretation.

2. 3-Year Exclusivity

For an application for a drug that is not eligible for 5-year NCE exclusivity because it does not contain an active moiety that has not been previously approved by FDA in an NDA submitted

[31] No. CV 15-0802 (RC), 2016 WL 4734333 (D.D.C. Sept. 9, 2016) (Sept. 2016 Ferring Opinion).
[32] The court explained: "The relevant point is that certain drug substances received a five-year period of marketing exclusivity—in which later fixed-combination drug products that included those drug substances were able to share, as a consequence of the umbrella policy—while others were denied the same marketing exclusivity period because a fixed-combination drug product was approved first." Sept. 2016 Ferring Opinion at 21-22.
[33] Id. at 22.
[34] The government filed a Notice of Appeal with the U.S. Court of Appeals for the District of Columbia Circuit on November 7, 2016. On March 14, 2017, the government filed an Unopposed Motion for Voluntary Dismissal of this appeal, and the order dismissing the appeal was issued on March 17, 2017.

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

under section 505(b), the Hatch-Waxman Amendments provide for a 3-year period of exclusivity under certain circumstances.[35] The 3-year exclusivity statutory provision provides:

> *If an application submitted under subsection (b) for a drug, which includes an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application approved under subsection (b), is approved after [September 24, 1984,] and if such application contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant*, the Secretary may not make the approval of an application submitted under subsection (b) for the conditions of approval of such drug in the approved subsection (b) application effective before the expiration of three years from the date of the approval of the application under subsection (b) if the investigations described in clause (A) of subsection (b)(1) and relied upon by the applicant for approval of the application were not conducted by or for the applicant and if the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted.[36]

The first clause (italicized) in section 505(c)(3)(E)(iii) of the FD&C Act, often referred to as the eligibility clause, describes the applications eligible for 3-year exclusivity. As in the 5-year NCE exclusivity provision, here FDA has interpreted the term "active ingredient" in the phrase "active ingredient (including any ester or salt of the active ingredient)" to mean active moiety. Under the eligibility clause in section 505(c)(3)(E)(iii), applications for single-entity drugs that are not eligible for 5-year NCE exclusivity (because their active moiety "has been approved in another application") are eligible for 3-year exclusivity if they include new clinical investigations (other than bioavailability studies), essential to approval of the application, that were conducted or sponsored by or on behalf of the applicant.[37]

The second clause in section 505(c)(3)(E)(iii) of the FD&C Act (plain text), often referred to as the bar clause, describes which 505(b)(2) applications or ANDAs will be blocked from approval by the 3-year exclusivity and thus describes the scope of 3-year exclusivity.[38] The Agency's interpretation of the bar clause and thus a determination of the scope of 3-year exclusivity vis a vis a subsequent 505(b)(2) NDA under section 505(c)(3)(E)(iii) of the FD&C Act involves two

---

[35] In general, given the structure of the statute, a particular drug can be eligible for 5-year NCE exclusivity (because it contains an active moiety that has not been previously approved) or 3-year exclusivity (because it does not contain an active moiety that has not been previously approved) but not both.

[36] Section 505(c)(3)(E)(iii) of the FD&C Act (emphasis added); see section 505(j)(5)(F)(iii) of the FD&C Act for the parallel provision for ANDAs. See also section 505(c)(3)(E)(iv) and section 505(j)(5)(F)(iv) of the FD&C Act (providing for 3-year exclusivity for supplements).

[37] FDA's implementing regulations at 21 CFR 314.108 interpret certain aspects of the statutory language regarding 3-year exclusivity.

[38] In contrast to the 5-year NCE exclusivity provision, which prevents *submission* of a 505(b)(2) application or ANDA during the exclusivity period, 3-year exclusivity is a bar on 505(b)(2) application or ANDA *approval* during the relevant period. Similar to the 5-year NCE exclusivity provision, 3-year exclusivity does not affect the approval of stand-alone 505(b)(1) applications.

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

steps. One step of the scope inquiry focuses on the drug at issue. The phrase "such drug in the approved subsection (b) application" in the bar clause refers to the earlier use of the term "drug" in the eligibility clause. The term "drug" in the eligibility clause refers to "a drug, which includes an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application," that is, in the case of a single entity drug, the drug product which includes a previously approved active moiety. Thus, for a single-entity 505(b)(2) drug to be potentially barred by 3-year exclusivity for another single-entity drug, the drug product must contain the same active moiety as the drug product with 3-year exclusivity.[39]

The second step of the scope inquiry focuses on the scope of the new clinical investigations essential to approval conducted or sponsored by the applicant. Under this aspect of the inquiry, the scope of the new clinical investigations essential to approval conducted or sponsored by the applicant determines the exclusivity-protected "conditions of approval" for which certain subsequent applications are barred. To interpret "conditions of approval" for the purpose of determining the scope of a product's exclusivity, FDA first asks what unique clinical question the new clinical investigations essential to approval answer for the first time about the safety and/or efficacy of the active moiety for the relevant use. The Agency makes this determination by evaluating the product at issue in comparison to previously approved drug products with the same active moiety and determining for which aspects of the drug product the clinical investigations were essential to approval. In many cases, the Agency also must consider whether the scope of the innovation is further defined by certain particular characteristics of the drug product, supported by the new clinical investigations essential to its approval, such that it would not bar approval of a subsequent product that does not share these same characteristics. The Agency makes this assessment by considering whether, in FDA's expert judgment, these characteristics would be clinically meaningful with respect to the use of the drug product that has exclusivity.

If a single-entity drug is eligible for 3-year exclusivity, the statute bars FDA from approving a 505(b)(2) application for such drug (i.e., another single-entity drug containing that active moiety) for the exclusivity-protected conditions of approval for a period of 3 years. This exclusivity, however, does not bar FDA from approving a 505(b)(2) application for a drug containing a different active moiety or a drug containing the same active moiety for different conditions of approval.

---

[39] See Letter from FDA to William H. Carson, M.D., President & CEO, Otsuka Pharmaceutical Development & Commercialization, Inc. and Ralph S. Tyler, Esq., Venable L.L.P. (Docket No. FDA-2015-P-2482) (Oct. 5, 2015), aff'd *Otsuka Pharmaceutical Co. v. Burwell*, Case No. 1:15-cv-01688-KBJ (D.D.C. July 28, 2016) (upholding FDA's conclusion that, for a single-entity drug to be potentially barred by 3-year exclusivity for another single-entity drug, the drug must contain the same active moiety as the drug with 3-year exclusivity), aff'd *Otsuka Pharmaceutical Co. v. Price*, No. 16-5229 (D.C. Cir. Aug. 29, 2017).

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

a. 3-Year Exclusivity for Fixed-Combinations

In analyzing eligibility for 3-year exclusivity for a fixed-combination, the Agency determines whether the fixed-combination (combination of active moieties) is supported by new clinical investigations (other than bioavailability studies) essential to approval of the application for the fixed-combination and were conducted or sponsored by the applicant.

505(b)(2) NDAs are barred from approval by 3-year exclusivity if they are seeking approval for "the conditions of approval of such drug." In the case of a fixed-combination, when determining which applications are seeking approval for "the conditions of approval of such drug" and thus have the potential to be blocked, FDA generally focuses its inquiry on applications that contain the same combination of active moieties as in the fixed-combination. This is because the clinical investigations that earn exclusivity must be submitted to the application for a product containing the combination, and necessarily support approval of the combination described in the application, but do not necessarily support approval of either of the individual components of which the drug product is comprised.[40] Thus, the conditions of approval of *such drug* necessarily encompass the conditions of approval of the *particular combination of active moieties* of the drug for which the application was submitted and for which new clinical investigations were essential.[41]

3. GAIN Exclusivity

In 2012, Congress enacted Title VIII of the Food and Drug Administration Safety and Innovation Act (FDASIA), titled *Generating Antibiotic Incentives Now* (GAIN).[42] The GAIN provisions, codified at section 505E of the FD&C Act, create incentives for the development of antibacterial and antifungal drug products that treat serious or life-threatening infections. The primary incentive is a 5-year exclusivity extension for certain applications for drug products that have been designated as a qualified infectious disease product (QIDP) and approved under section 505 of the FD&C Act.[43] This 5-year exclusivity extension is added to any 5-year NCE exclusivity, 3-year exclusivity, or 7-year orphan drug exclusivity and attaches on top of any 6-month pediatric exclusivity period for which the application otherwise qualifies.

---

[40] FDA regulations generally require that the combination as a whole be shown to be safe and effective and that each drug in the fixed-combination be shown to contribute to efficacy. It is not adequate for a sponsor to demonstrate only that the individual components are safe and effective. See 21 CFR 300.50.

[41] See CDER Exclusivity Board Memo re: Targiniq and Troxyca (Aug. 19, 2016) (determining that 3-year exclusivity for Targiniq (containing the combination of active moieties oxycodone and naloxone) did not block the approval of the 505(b)(2) application for Troxyca (containing the combination of active moieties oxycodone and naltrexone)).

[42] Pub. L. No. 112-144 (2012).

[43] Section 505E(a) of the FD&C Act.

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

B. FDA Regulation of Antibiotics

There is a long and complex history of FDA regulation of antibiotic drug products. "Among the more contentious aspects of this regulatory history have been questions about the applicability to antibiotic drugs of the patent listing, patent certification, and exclusivity provisions of sections 505(b), (c), and (j)."[44] In order to determine whether a fixed-combination containing a new active moiety and an old antibiotic is eligible for 5-year NCE exclusivity today, the Board must look at the history of the regulation of antibiotics, including changes provided in the Food and Drug Administration Modernization Act of 1997[45] (FDAMA) and the QI Program Supplemental Funding Act of 2008[46] (QI Act), among others, and must evaluate in particular whether section 505(v) of the FD&C Act (added as part of the QI Act) poses any limitations on eligibility for that exclusivity. A brief description of the history of FDA's regulation of antibiotics is set forth below.

1. Regulation of Antibiotics Under Section 507 of the FD&C Act

Prior to the enactment of FDAMA, FDA approved marketing applications for antibiotic drugs under section 507 of the FD&C Act, not under section 505. Among other distinctions, section 507 required the Agency to publish regulations (antibiotic monographs) that set forth standards of identity, strength, quality, and purity for each marketed antibiotic drug and required certification that each batch of an antibiotic drug met those standards.

At that time (as it does now) FDA approved marketing applications for non-antibiotic drugs under section 505 of the FD&C Act. The exclusivity, patent listing, patent certification, and 30-month stay provisions of the Hatch-Waxman Amendments (hereinafter referred to as Hatch-Waxman benefits) applied only to approvals under section 505 of the FD&C Act and did not apply to antibiotic drugs approved under section 507 of the FD&C Act.[47] Thus, 507 antibiotics could not list patents, were not eligible for exclusivities and were not subject to 30-month stays or other patent or exclusivity based delays in approval.

2. Regulation of Antibiotics After FDAMA

On November 21, 1997, Congress enacted FDAMA. FDAMA repealed section 507 of the FD&C Act and required that all future applications for antibiotic drugs be submitted under

---

[44] Letter from FDA to M. Labson, E. Jungman, T. Henteleff, et al. (Docket Nos. FDA-2009-P-0038; FDA-2009-P-0081; FDA-2009-P-0103; FDA-2009-P-0120) (Mar. 17, 2009) (2009 Petition Response).
[45] Pub. L. No. 105-115 (Nov. 21, 1997).
[46] Pub. L. No. 110-379 (Oct. 8, 2008).
[47] See *Glaxo, Inc. v. Heckler*, 623 F. Supp. 69 (E.D.N.C. 1985). The patent term extension provisions of the Hatch-Waxman Amendments did apply to antibiotics, thereby permitting the extension of the patent term for certain patents claiming antibiotic drugs (see 35 U.S.C. § 156(f)(4)(B) (1984) (making antibiotics regulated under section 507 products eligible for patent term extension)).

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

section 505 of the FD&C Act.[48] FDAMA included a transition provision declaring that an application approved under section 507 of the FD&C Act before enactment of FDAMA must be considered an application submitted, filed, and approved under section 505 of the FD&C Act.[49] Although FDAMA brought antibiotic approvals under section 505, Congress created an exception to this transition provision in section 125(d)(2) of FDAMA, which exempted certain applications for antibiotic drugs from those provisions of section 505 of the FD&C Act that provide Hatch-Waxman benefits. Section 125(d)(2) of FDAMA states:

> EXCEPTION.—The following subsections of section 505 (21 U.S.C. 355) shall not apply to any application for marketing in which the *drug* that is the subject of the application *contains* an *antibiotic drug* and the antibiotic drug was the subject of any application for marketing received by the Secretary of Health and Human Services under section 507 of such Act (21 U.S.C. 357) before the date of the enactment of this Act: [list of exclusivity, patent submission, patent certification, and 30-month stay provisions].[50]

In other words, section 125(d)(2) of FDAMA exempted an application from Hatch-Waxman benefits when "the drug that is the subject of the application contains an antibiotic drug and the antibiotic drug was the subject of any application for marketing received" by FDA under section 507 before November 21, 1997 (the date of enactment of FDAMA).[51]
Section 125(e) of FDAMA added the following definition of "antibiotic drug" to section 201 of the FD&C Act:

> The term 'antibiotic drug' means any drug (except drugs for use in animals other than humans) composed wholly or partly of any kind of penicillin, streptomycin, chlortetracycline, chloramphenicol, bacitracin, or any other drug intended for human use containing any quantity of any chemical substance which is produced by a micro-organism and which has the capacity to inhibit or destroy micro-organisms in dilute

---

[48] Section 125(b)(1) of FDAMA.
[49] Section 125(d)(1) of FDAMA.
[50] Section 125(d)(2) of FDAMA (emphasis added). The list of Hatch-Waxman provisions is as follows in section 125(d)(2) of FDAMA:

> (A)(i) Subsections (c)(2), (d)(6), (e)(4), (j)(2)(A)(vii), (j)(2)(A)(viii), (j)(2)(B), (j)(4)(B), and (j)(4)(D); and
> (ii) The third and fourth sentences of subsection (b)(1) (regarding the filing and publication of patent information); and
> (B) Subsections (b)(2)(A), (b)(2)(B), (b)(3), and (c)(3) if the investigations relied upon by the applicant for approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted.

Id. Subsection (j)(4)(D) and subsection (c)(3) pertained to the exclusivity provisions of the FD&C Act. Subsequently, section 505(j) was amended and what was previously section 505(j)(4)(D) is now section 505(j)(5)(F).
[51] Section 125(d)(2) of FDAMA. We note that Congress enacted FDAMA against the backdrop of FDA's pre-October 2014 interpretation of NCE exclusivity for fixed combination products.

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

> solution (including a chemically synthesized equivalent of any such substance) or any derivative thereof.[52]

Thus, Congress created a distinction between applications for antibiotic drugs for which the first application was received *after* FDAMA's effective date (November 21, 1997) and those for antibiotic drugs for which the first application was received *before* that date (old antibiotics). Under FDAMA, applications for the former were eligible for Hatch-Waxman benefits and those for the latter were not.

To provide transparency and assist in implementing the distinction between old antibiotic drugs and other antibiotic drugs, section 125(d)(3) of FDAMA authorized the Secretary to publish "the established name of each antibiotic drug" that was the subject of a marketing application received by FDA under section 507 prior to November 21, 1997 (i.e., each old antibiotic).[53]

The legislative history of FDAMA makes clear that Congress intended Hatch-Waxman benefits, like exclusivity, to be available to new antibacterial drugs developed to deal with drug-resistant strains but not for old antibiotics.[54]

After the enactment of FDAMA, FDA issued several documents that shed light on its interpretation of the FDAMA provisions related to antibiotics, especially section 125(d)(2) and the definition of "antibiotic drug."

a. 1998 Guidance on the Repeal of Section 507

In May 1998, FDA published guidance on the *Repeal of Section 507 of the Federal Food, Drug, and Cosmetic Act*. The Agency explained that "[n]ew applications (those received on or after November 21, 1997) under section 505(b) . . . for drugs that contain 'old' antibiotics . . . are not eligible for exclusivity."[55] In deciding whether an application is subject to the exception to exclusivity (as well as other Hatch-Waxman benefits) in section 125(d)(2) of FDAMA, FDA stated that factors to consider are that (1) the "drug that is the subject of the application must contain *(in whole or as part of a combination) an antibiotic drug*," and (2) the "antibiotic drug

---

[52] Section 201(jj) of the FD&C Act.
[53] Section 125(d)(3) of FDAMA.
[54] See, e.g., H.R. Rep. No. 105-310, at 77 (1997) ("the granting of market exclusivity [will] be limited to products that achieve the policy objective of increasing research toward the development of new antibiotics."); 143 Cong. Rec. H8479 (Oct. 7, 1997) (statement of Rep. Deutch) ("I think it is important that any additional exclusivity that we grant in terms of antibiotics, which would be the first time that there would be exclusivity for antibiotic drugs, that it be limited in scope very narrowly to the challenge we face in terms of resistant strains."); 143 Cong. Rec. S12243 (Nov. 9, 1997) (statement of Sen. Kennedy) (The legislation "provides incentives ... for development of new antibiotics to deal with emerging, drug-resistant strains of disease.").
[55] FDA guidance, *Repeal of Section 507 of the Federal Food, Drug, and Cosmetic Act* (May 1998), at 2.

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

that is contained in the application must have been the subject of a marketing application that was received by the Secretary on or before November 20, 1997."[56] FDA explained that "[o]ther factors, such as the extent to which derivatives of the active moiety of an old antibiotic are also considered to be old antibiotics, are beyond the scope of this administrative guidance and may be addressed as part of an Agency rulemaking proceeding."[57] This guidance suggests that, at that time, FDA was reading "drug that is the subject of the application contains an antibiotic drug and the antibiotic drug was the subject of any application" in section 125(d)(2) to mean "drug [**product**] that is the subject of the application **contains [in part]** an antibiotic drug [**active moiety**] and the antibiotic drug [**active moiety**] was the subject of any application." This reading looked at eligibility for 5-year NCE exclusivity and other Hatch-Waxman benefits on a product by product (rather than an active ingredient by active ingredient basis) and was consistent with how FDA was interpreting 5-year NCE exclusivity for combination drug products at that time. Under this reading, if a combination product consisted in whole or part of one or more old antibiotic active moieties it was considered ineligible for Hatch-Waxman benefits.

b. 2000 Proposed Rule

On January 24, 2000, FDA issued a proposed rule, titled *Marketing Exclusivity and Patent Provisions for Certain Antibiotic Drugs*, to implement section 125(d)(2) of FDAMA.[58] FDA explained that "[i]n applying section 125(d)(2) of [FDAMA], the agency must determine whether a drug that is the subject of an NDA or ANDA contains a pre-repeal antibiotic drug."[59] FDA explained its proposed interpretation that section 125(d)(2) – and therefore the exemption from Hatch-Waxman benefits – applies to a drug product that contains an *active moiety* that can be found in an antibiotic drug that was the subject of a marketing application received by FDA before November 21, 1997.[60]

---

[56] Id. at 3-4 (original emphasis omitted and emphasis added). In offering this guidance, FDA was regulating against the backdrop of the pre-October 2014 approach to 5-year NCE exclusivity for fixed combination drugs in which the first use of the term "drug" in the 5-year NCE exclusivity provision was interpreted to mean "drug product" and the term "active ingredient" was interpreted to mean active moiety such that a drug product containing a never previously approved active moiety in combination with a previously approved active moiety was not eligible for 5-year NCE exclusivity. As noted above, FDA has since changed its interpretation such that a never previously approved active moiety is eligible for 5-year NCE exclusivity even if its first approval is in a fixed combination drug that also includes a previously approved active moiety. However, FDA has not previously analyzed how this change might affect its approach to fixed combination drugs that contain a never previously approved active moiety and an old antibiotic in combination.

[57] Id. at 5.

[58] FDA Proposed Rule, *Marketing Exclusivity and Patent Provisions for Certain Antibiotic Drugs*, 65 FR 3623 (Jan. 24, 2000).

[59] Id. at 3624.

[60] Id.; see also proposed 21 CFR § 314.109(a) (stating that the "following [exclusivity and patent] provisions do not apply to any application or abbreviated application in which the drug that is the subject of the application or abbreviated application contains an antibiotic drug that has the same active moiety (as defined in § 314.108(a)) as an

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

To support this drug product/active moiety approach, FDA looked to the definition of "antibiotic drug" in section 201(jj) of the FD&C Act. FDA explained that "the term 'antibiotic drug' includes not only the 'chemical substance which is produced by a micro-organism,' and which 'has the capacity to inhibit or destroy micro-organisms,' but also '*any derivative' of any such substance*, such as a salt or ester of the substance."[61] Moreover, FDA explained that the Agency "has consistently looked at active moieties to determine if the exclusivity protection granted to a drug product would allow a subsequent ANDA or application described in section 505(b)(2) of the act to be submitted or approved."[62] Under this proposed drug product/active moiety approach, FDA noted that "NDA's for products that contain, for example, a salt of a pre-repeal antibiotic drug, or that propose such things as a new manufacturing process, new dosage form, or new use of a pre-repeal antibiotic drug, will be subject to the exceptions listed in section 125(d)(2) of [FDAMA]."[63] FDA included in the proposed regulation a list of the active moieties of antibiotic drugs that were subjects of marketing applications received by FDA before November 21, 1997.

FDA never finalized the rule but appears to have continued to take the drug product/active moiety approach although it had received comments opposing that approach. On December 12, 2008, FDA issued a Federal Register notice announcing the withdrawal of the 2000 proposed rule.[64] FDA explained that section 125(d) of FDAMA "was superseded by the enactment of Public Law 110–379 (S. 3560) on October 8, 2008, which included new provisions on marketing exclusivity and patent provisions for certain antibiotic drugs."[65]

c. 2003 Restasis Petition Response

In 2003, Allergan, the NDA holder for Restasis (cyclosporine) ophthalmic emulsion, submitted a citizen petition asserting that FDA should reclassify cyclosporine as a "non-antibiotic drug" and remove it from the list of old antibiotics, or, in the alternative, that FDA should determine that Restasis is not an antibiotic drug product that falls under section 125(d)(2) of FDAMA. Allergan made these requests because it wanted Restasis to be eligible for 3-year exclusivity and patent listing for which old antibiotics were ineligible. In its December 18, 2003, petition response, FDA denied Allergan's requests and provided its interpretation of the statutory definition of "antibiotic drug" and section 125(d)(2) of FDAMA.[66]

---

antibiotic drug that was the subject of a marketing application received by FDA under former section 507 of the act").

[61] Id. at 3624-25 (emphasis added).

[62] Id. at 3625.

[63] Id.

[64] FDA Notice, *Withdrawal of Certain Proposed Rules and Other Proposed Actions*, 73 FR 75625 (Dec. 12, 2008).

[65] Id. at 75626.

[66] Letter from FDA to T. Mahn, J. Mauk, W. Vicente, et al. (Docket No. 2003P-0275/CP1 & PSA1) (Dec. 18, 2003) (2003 Restasis Petition Response).

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

On the first issue, FDA determined that the "statutory definition of antibiotic drug turns on the nature of the *drug substance*; the definition does not reference a particular quantity of the drug substance, nor a particular indication."[67] FDA concluded that Restasis is an antibiotic drug (product) because it contains cyclosporine, which is an antibiotic drug substance.
FDA explained that it "need not resolve the question of whether to use the concept of *active moiety* in interpreting section 125(d)(2)," as FDA had proposed in the proposed rule[68] because "there appears to be no dispute that the drug substance in Restasis – cyclosporine – is the same drug substance that was present in cyclosporine drug products previously regulated by FDA under section 507 as antibiotic drugs."[69]

On the second issue, FDA determined that Restasis falls under section 125(d)(2) of FDAMA. Section 125(d)(2) applies to the following: "any application for marketing in which the *drug* that is the subject of the application *contains* an *antibiotic drug* and the *antibiotic drug* was the subject of any application for marketing received" by FDA under section 507. Allergan argued that "antibiotic drug" should refer to the drug product, and therefore because the Restasis drug product was not submitted in a marketing application under section 507, Restasis was not subject to the exemption in section 125(d)(2).

FDA rejected Allergan's interpretation and provided its interpretation of the terms "drug" and "antibiotic drug" used in section 125(d)(2). FDA noted that the use of "drug" in the first phrase "any application for marketing in which the drug that is the subject of the application" means the drug product, Restasis.[70] FDA determined that the use of "antibiotic drug" in the second phrase "contains an antibiotic drug and the antibiotic drug was the subject of any application" means the antibiotic drug substance, cyclosporine. In offering this interpretation of the relevant provision, the Agency focused on the meaning of the word "contains," explaining that "a drug product does not contain a drug product; rather, a drug product *contains* a drug substance."[71] FDA noted that its interpretation is dictated by the plain language of section 125(d)(2).

The Agency also noted that its interpretation is consistent with section 125(d)(3) which states that FDA is authorized to publish "the established name of each antibiotic drug" that was the subject of any application for marketing received by FDA under section 507. FDA explained

---

[67] Id. at 1 (emphasis added).
[68] Id. at 33 (emphasis added).
[69] Id. at 33. FDA added that it "does not need to reach the question of whether it is appropriate to use the concept of active moiety to interpret the phrase 'any derivative thereof'." Id.
[70] Id. at 37.
[71] Id. (emphasis in original). FDA further explained: "Under your reading, the statute (as applied to Restasis) would effectively mean that Hatch-Waxman benefits would not apply when – Restasis *contains* cyclosporine ophthalmic emulsion and cyclosporine ophthalmic emulsion was the subject of any application received by FDA under section 507 of the Act before the enactment of [FDAMA]. 'Restasis *contains* cyclosporine ophthalmic emulsion' does not make sense on its face. That is, drug products do not contain drug products; rather, drug products contain drug substances." Id. at 39 (emphasis in original).

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

that the "established name, for the purposes of section 125(d)(2), is the established name of the drug substance."[72]

FDA also explained that its interpretation of section 125(d)(2) of FDAMA is supported by the legislative history. FDA noted that the legislative history shows that "Congress' intent . . . was to provide incentives for significant science that would result in the development of *new antibiotic drug substances* to protect against new drug-resistant strains of diseases."[73]

Allergan filed a lawsuit against FDA over the classification of cyclosporine as an antibiotic, and the district court granted FDA's motion to dismiss.[74] The court determined that FDA's classification decision of cyclosporine as an antibiotic drug is supported by FDAMA and the administrative record. Specifically, the court noted that "It is clear that cyclosporine was the 'subject of an application for marketing' prior to FDAMA and that the FDA has determined that cyclosporine is an 'antibiotic.'"

d. 2007 Petition regarding Ziana

In April 2007, Medicis submitted a petition requesting that FDA reconsider and reverse its current policy that "any combination drug that has, as one of its active ingredients, a pre-1997 antibiotic ingredient is denied the incentives of market exclusivity and patent listing."[75] Medicis was the holder of the NDA for Ziana, a fixed-combination containing tretinoin, a non-antibiotic ingredient, and clindamycin, an old antibiotic. FDA approved Ziana in 2006, and FDA determined it was subject to the section 125(d)(2) FDAMA exemption from Hatch-Waxman benefits because the fixed-combination contained an old antibiotic drug substance. In the petition, Medicis made several public policy arguments, asserting that "an FDA decision to remove incentives for development of combinations of ingredients with pre-1997 antibiotic ingredients will undercut research and development for combinations that have the potential to defeat antibiotic resistance."[76] Medicis argued that FDA's policy "makes no sense," with a single-entity tretinoin product being eligible for exclusivity and patent listing, whereas a product containing both tretinoin and an old antibiotic is eligible for neither of these incentives.

As a legal matter, Medicis argued that the word "drug" in section 125(d)(2) of FDAMA should be interpreted as "drug product" and the word "contains" should be interpreted as "is." Under this reading of the statute, Hatch-Waxman benefits are not available where the drug product *is* an antibiotic drug product and that antibiotic drug product was the subject of a section 507 application.

---

[72] Id. at 38.
[73] Id. at 40 (emphasis in original).
[74] See *Allergan, Inc. v. Crawford*, 398 F. Supp. 2 13, 16 (D.D.C. 2005); see also *CollaGenex Pharms., Inc. v. Thompson*, No. 03-14-5, 2005 WL 256561 (D.D.C. Jan. 19, 2005) (granting FDA's motion to dismiss and upholding FDA's classification decision that Periostat (doxycycline hyclate) is an antibiotic drug).
[75] Letter from Don Beers, Arnold & Porter LLP to FDA, at 2 (Apr. 20, 2007).
[76] Id. at 5.

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

The Agency never substantively responded to the petition. In August 2011, after the enactment of the QI Act, Medicis withdrew the petition.

3. Regulation of Antibiotics Under the QI Act

On October 8, 2008, Congress enacted the QI Act. Section 4 of the QI Act, titled "Incentives for the Development of, and Access to, Certain Antibiotics," amended the FD&C Act to add section 505(v), titled "Antibiotic Drugs Submitted Before November 21, 1997." Section 505(v) of the FD&C Act created certain Hatch-Waxman benefits for drugs that contain old antibiotics, including 3-year exclusivity; however, the QI Act did not make applications for drugs that contain old antibiotics submitted after the date of enactment of the QI Act eligible for exclusivity to the same extent as other section 505 drugs.

"The legislative history of the QI Act indicates that Congress enacted the provision to encourage the development of truly novel antibiotics and novel uses of Old Antibiotics."[77] Congress sought to balance the desire to incentivize the development of new antibiotic drugs to combat antimicrobial resistance with the desire to ensure timely access to generic versions of antibiotic drugs. As Senator Burr stated, "Section 4 [of the QI Act], entitled 'Incentives for the Development of and Access to Certain Antibiotics,' is an important step forward to help spur research on new antibiotics and provide incentives for the creation of additional generic antibiotics."[78]

The QI Act created a distinction with respect to eligibility for exclusivity between (1) drugs that contain old antibiotics that were approved by FDA under section 507 before November 21, 1997 (i.e., approved old antibiotics) and (2) drugs that contain old antibiotics that were the subject of applications received under section 507 before November 21, 1997, but never approved (i.e., unapproved old antibiotics).
Section 505(v)(1), titled "Antibiotic Drugs Approved Before November 21, 1997," provides as follows:

> (A) IN GENERAL.—Notwithstanding any provision of the Food and Drug Administration Modernization Act of 1997 or any other provision of law, a sponsor of a drug that is the subject of an application described in subparagraph (B)(i) shall be eligible for, with respect to the drug, the 3-year exclusivity period referred to under clauses (iii)

[77] See Letter from FDA to ViroPharma, Inc., Docket No. FDA-2006-P-0007, at 69 (Apr. 9, 2012) (2012 Vancocin Petition Response).
[78] See 154 Cong. Rec. at S9638 (Sept. 26, 2008) (statement of Senator Burr); see also 153 Cong. Rec. at S5624 (May 7, 2007) (statement of Sen. Hatch when originally proposing bill in 2007) ("[t]he Hatch amendment is intended to be an initial step in the fight against the resistant strains of bacteria by increasing incentives and innovation"); 154 Cong. Rec. at H10171 (Sept. 27, 2008) (statement of Rep. Sullivan) ("[T]his bill provides an important correction in FDA policy regarding the development of antibiotics.").

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

and (iv) of subsection (c)(3)(E) and under clauses (iii) and (iv) of subsection (j)(5)(F), subject to the requirements of such clauses, as applicable.

(B) APPLICATION; ANTIBIOTIC DRUG DESCRIBED.—

(i) APPLICATION.—An application described in this clause is an application for marketing submitted under this section after the date of the enactment of this subsection in which the **drug** that is the subject of the application ***contains*** an **antibiotic drug** described in clause (ii).

(ii) ANTIBIOTIC DRUG.—An antibiotic drug described in this clause is an antibiotic drug that was the subject of an application approved by the Secretary under section 507 of this Act (as in effect before November 21, 1997).[79]

Under section 505(v)(1), an application submitted after enactment of the QI Act for a drug that contains an approved old antibiotic drug may be eligible for 3-year exclusivity. In defining when an application is subject to section 505(v)(1)(A) and therefore eligible for 3-year exclusivity, section 505(v)(1)(B)(i) uses the same language as that used in section 125(d)(2) of FDAMA. In particular, section 505(v)(1)(B)(i) applies to an application "in which the drug that is the subject of the application contains an antibiotic drug" that was the subject of an approved section 507 application, and section 125(d)(2) of FDAMA applied to an application "in which the drug that is the subject of the application contains an antibiotic drug" that was the subject of a section 507 application received by FDA.

Section 505(v)(2), titled "Antibiotic Drugs Submitted Before November 21, 1997, But Not Approved," provides as follows:

(A) IN GENERAL.—Notwithstanding any provision of the Food and Drug Administration Modernization Act of 1997 or any other provision of law, a sponsor of a drug that is the subject of an application described in subparagraph (B)(i) may elect to be eligible for, with respect to the drug—

(i)(I) the 3-year exclusivity period referred to under clauses (iii) and (iv) of subsection (c)(3)(E) and under clauses (iii) and (iv) of subsection (j)(5)(F), subject to the requirements of such clauses, as applicable; and

(II) the 5-year exclusivity period referred to under clause (ii) of subsection (c)(3)(E) and under clause (ii) of subsection (j)(5)(F), subject to the requirements of such clauses, as applicable; or

(ii) a patent term extension under section 156 of title 35, United States Code, subject to the requirements of such section.

(B) APPLICATION; ANTIBIOTIC DRUG DESCRIBED.—

(i) APPLICATION.—An application described in this clause is an application for marketing submitted under this section after the date of the enactment of this subsection in which the **drug** that is the subject of the application ***contains*** an **antibiotic drug** described in clause (ii).

(ii) ANTIBIOTIC DRUG.—An antibiotic drug described in this clause is an antibiotic drug that was the subject of 1 or more applications received by the

[79] Section 505(v)(1) of the FD&C Act (emphasis added).

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

> Secretary under section 507 of this Act (as in effect before November 21, 1997), none of which was approved by the Secretary under such section.

Under section 505(v)(2), if an application submitted after enactment of the QI Act is for a drug that contains an unapproved old antibiotic drug, then the sponsor may elect to be eligible for either: (1) the 3-year exclusivity and 5-year exclusivity periods, as applicable; or (2) a patent term extension under 35 U.S.C. § 156. In defining when an application is subject to 505(v)(2)(A), 505(v)(2)(B)(i) uses the same language as that used in section 125(d)(2) of FDAMA. Senator Burr noted that under the QI Act, "any antibiotic that was the subject of an application submitted to the FDA, but not approved before FDAMA, can get the 3 year and/or 5 year Hatch-Waxman exclusivity or a patent term extension. According to the FDA, approximately 10 antibiotics fit this category of submitted but not approved and about half of those could never be approved because of issues with the active ingredients."[80]
Section 505(v)(3) of the FD&C Act is a "limitations" provision with respect to the exclusivities and patent term extensions provided for under section 505(v)(1) and 505(v)(2). Section 505(v)(3) states as follows:

> (A) EXCLUSIVITIES AND EXTENSIONS.—Paragraphs (1)(A) and (2)(A) shall not be construed to entitle a drug that is the subject of an approved application described in subparagraphs (1)(B)(i) or (2)(B)(i), as applicable, to any market exclusivities or patent extensions other than those exclusivities or extensions described in paragraph (1)(A) or (2)(A).
> (B) CONDITIONS OF USE.—Paragraphs (1)(A) and (2)(A)(i) shall not apply to any condition of use for which the drug referred to in subparagraph (1)(B)(i) or (2)(B)(i), as applicable, was approved before the date of the enactment of this subsection.

Under section 505(v)(3)(A), section 505(v) does not entitle a drug that "contains" an old antibiotic drug to any new exclusivities or patent term extensions other than those provided for in section 505(v)(1) or section 505(v)(2). Section 505(v)(3)(B) provides a previously approved "condition of use" limitation on a drug's eligibility for 3-year exclusivity under section 505(v)(1) or section 505(v)(2).

Section 505(v)(4) addresses the general applicability of the Hatch-Waxman Amendments to old antibiotic drugs. Section 505(v)(4) provides as follows:

> (4) APPLICATION OF CERTAIN PROVISIONS.—Notwithstanding section 125, or any other provision, of the Food and Drug Administration Modernization Act of 1997, or any other provision of law, and subject to the limitations in paragraphs (1), (2), and (3), the provisions of the Drug Price Competition and Patent Term Restoration Act of 1984 shall apply to any drug subject to paragraph (1) or any drug with respect to which an election is made under paragraph (2)(A).

[80] See 154 Cong. Rec. at S9638 (Sept. 26, 2008) (statement of Senator Burr).

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

Section 505(v)(4) provides that, notwithstanding FDAMA's exclusion of old antibiotic drugs from Hatch-Waxman provisions and subject to the limitations on exclusivity in section 505(v)(1)-(3), the Hatch-Waxman provisions apply to any "drug" that contains an old antibiotic drug. These Hatch-Waxman provisions include, for example, provisions pertaining to patent submission, patent certification, 30-month stays, and eligibility of generic applicants for 180-day exclusivity. As noted, prior to enactment of the QI Act, the Hatch-Waxman provisions were not applicable to old antibiotic drugs. Specifically, in addition to being ineligible for Hatch-Waxman exclusivity protection, up until the enactment of the QI Act, a sponsor of an application for a drug that contains an old antibiotic drug was not eligible to list patents, and relatedly, an ANDA or 505(b)(2) applicant relying on that application could not submit a patent certification to any patents, as there were no patents listed in the Orange Book for such an application. Apart from the limitations noted in section 505(v)(1)-(3), after passage of the QI Act, the Hatch-Waxman provisions applied equally to old antibiotic drugs.

Section 4(b) of the QI Act set out "Transitional Rules" providing for patent listing, patent publication, patent certification deadlines, and 180-day exclusivity for certain old antibiotic drugs. Section 4(b)(1) provides that for patents issued on or before enactment of the QI Act, an NDA sponsor "of a drug to which subsection (v)(1) . . . applies" must submit the required patent information not later than 60 days after enactment of the QI Act. Section 4(b)(2) provides that FDA shall publish the patent information in the Orange Book not later than 90 days after enactment of the QI Act. Section 4(b)(3) provides for the eligibility of a pending ANDA applicant for 180-day exclusivity with respect to submitting a paragraph IV certification to a newly listed patent not later than 120 days after enactment of the QI Act.
After the enactment of the QI Act, FDA issued several documents that shed light on its interpretation of the QI Act provisions, particularly relating to the section 505(v) exclusivity provisions and the section 4(b) patent requirements.

a. 2008 Patent Submission Draft Guidance

In December 2008, FDA issued a draft guidance on *Submission of Patent Information for Certain Old Antibiotics*. The guidance provided FDA's interpretation of section 4(b)(1) of the QI Act, addressing which application holders of NDAs must submit patent information to the Agency under section 4(b)(1). FDA explained the following:

> ***Q2: Who must submit the patent information to FDA under section 4(b)(1) of the QI Act by December 5, 2008?***
> The sponsor of an NDA approved on or before October 7, 2008, *for a drug (including a combination drug) containing an antibiotic drug* that was the subject of an application approved under section 507 of the FD&C Act (as in effect before November 21, 1997) must submit this patent information.[81]

[81] FDA draft guidance, *Submission of Patent Information for Certain Old Antibiotics* (Dec. 2008), at 3 (emphasis added) (2008 Patent Submission draft guidance).

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

The Agency specifically stated that this draft guidance did "not address FDA's interpretation of the scope of, and procedural requirements associated with, new section 505(v) of the FD&C Act."[82] Despite this disclaimer, the above-referenced italicized language in the draft guidance provides some insight into FDA's interpretation of section 505(v)(1). Section 4(b)(1) applies to approved NDAs for drugs "to which subsection 505(v)(1) . . . applies." Section 505(v)(1) applies to a drug that contains an antibiotic drug that was the subject of an approved section 507 application. The use of the above-referenced italicized language in the draft guidance – "*for a drug (including a combination drug) containing an antibiotic drug*" – suggests that FDA is applying the same interpretation of "drug that … contains an antibiotic drug" that it applied in the FDAMA context to the QI Act. FDA appears to have been interpreting "drug" to mean "drug product," "contains" to mean "contains in whole or part," and "antibiotic drug" to mean "antibiotic drug substance or active moiety" such that a fixed-combination containing in part an old antibiotic drug substance or active moiety would be subject to section 4(b)(1) of the QI Act (and thus also section 505(v)(1)).[83]

b. 3-Year Exclusivity Precedent under Section 505(v)

Since the enactment of the QI Act, FDA has on several occasions analyzed the eligibility for 3-year exclusivity of a single-entity drug containing an old antibiotic. This exclusivity analysis has involved interpreting section 505(v)(1) and section 505(v)(3) of the FD&C Act.

In 2012, FDA determined that Vancocin (vancomycin hydrochloride) capsules was not eligible for 3-year exclusivity under section 505(j)(5)(F)(iv) of the FD&C Act because of the limitations on such exclusivity for certain old antibiotic drugs set forth in section 505(v) of the FD&C Act.[84] FDA first determined that Vancocin falls within the scope of section 505(v)(1)(A) of the FD&C Act because the supplemental NDA was submitted after October 8, 2008 and the drug product Vancocin "contains an antibiotic drug" that was the subject of an approved section 507 application. FDA noted that vancomycin, the active moiety of Vancocin, was on the list of old antibiotic active moieties in the 2000 proposed rule, and FDA also noted that the Agency approved the NDA for Vancocin capsules in 1986.[85]

FDA then determined that the Vancocin supplement was not eligible for 3-year exclusivity under the limitation in section 505(v)(3)(B) of the FD&C Act. Section 505(v)(3)(B) provides that 3-year exclusivity is not available for "any condition of use for which the drug . . . was approved

---

[82] Id. at 2.
[83] As noted above this was consistent with FDA's interpretation of the 5-year exclusivity provisions at that time.
[84] See 2012 Vancocin Petition Response at 70.
[85] See Federal Defendants' Memorandum in Opposition to Plaintiff's Motion for Temporary Restraining Order and/or Preliminary Injunction, Civ. Action No. 12-0584, at 19 (D.D.C. Apr. 17, 2012).

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

before the date of the enactment [of the QI Act]." FDA stated that, for section 505(v)(3)(B) not to be rendered superfluous, Congress must have intended to create a higher hurdle for 3-year exclusivity. FDA interpreted section 505(v)(3)(B) to permit 3-year exclusivity only for a *significant new use* for the drug, not for refinements in labeling related to previously approved uses.[86] To determine if a new use was significant, FDA examines whether it would result in a change in how, by whom or for what purpose the drug was used. Applying this interpretation of the statute to the facts at hand, FDA determined that the Vancocin supplement merely refined labeling regarding already approved conditions of use of the drug and therefore section 505(v)(3)(B) barred 3-year exclusivity for the supplement. The district court upheld FDA's decision denying 3-year exclusivity for Vancocin under section 505(v)(3)(B) of the FD&C Act.[87]

In 2015, FDA determined that Astragraf XL (tacrolimus) extended-release capsules qualified for 3-year exclusivity under section 505(c)(3)(E)(iii) and 505(v) of the FD&C Act.[88] FDA first determined that tacrolimus meets the statutory definition of "antibiotic drug" which turns on the nature of the "drug substance." FDA explained that "tacrolimus is an antibiotic drug substance that was the subject of an application for marketing received by FDA before November 21, 1997" and therefore is considered an "old antibiotic."[89] FDA concluded that Astagraf XL is subject to section 505(v)(1). FDA next analyzed whether Astragraf XL's exclusivity was subject to the limitation in section 505(v)(3)(B), and concluded that the new once-daily dosing regimen in de novo kidney transplant patients was a significant new condition of use and therefore Astragraf XL was eligible for 3-year exclusivity under section 505(v) despite the limitation in 505(v)(3)(B).[90] The district court upheld FDA's decision determining that Astagraf XL qualified for 3-year exclusivity.[91]

III. Policy Considerations

The Agency recognizes that there are important clinical and scientific reasons for certain old antibiotic active moieties to be in fixed-combination with certain new active moieties. In particular, some such fixed-combinations may provide invaluable therapies against the growing threat of antimicrobial resistance.

---

[86] 2012 Vancocin Petition Response at 70 (emphasis added).
[87] See *ViroPharma, Inc. v. Hamburg, et al.*, 898 F. Supp. 2d 1 (D.D.C. 2012); *ViroPharma, Inc. v. Hamburg, et al.*, 916 F. Supp. 2d 76 (D.D.C. 2013).
[88] See FDA General Advice Letter to Veloxis Pharms., NDA 206406 for Envarsus XR (Jan. 2015) (2015 Veloxis Letter).
[89] In a footnote, FDA noted that tacrolimus appears on the list of old antibiotic active moieties in the 2000 proposed rule. Id.
[90] FDA reached this conclusion by comparing Astagraf XL not to a previous approval of the same drug product but to Prograf (another tacrolimus product that had been previously approved with a twice daily dosing regimen). However, under the interpretation of section 505(v) described in this memo, we reach the same conclusion that Astagraf XL was eligible for 3-year exclusivity under section 505(v), although on a different ground.
[91] See *Veloxis Pharms., Inc. v. FDA*, 109 F. Supp. 3d 104 (D.D.C. 2015).

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

The Agency remains concerned that over the last several decades, for reasons both scientific and economic,[92] the number of new antibacterial drugs brought to market has fallen significantly from the peak approvals witnessed in the 1950s and 60s, increasing only slightly after 2011.[93] This trend has occurred against the backdrop of the emergence and spread of antimicrobial resistance, which jeopardizes the effectiveness of existing antibacterial drugs and leads to hospital and community-acquired infections for which few, or no therapeutic options exist.[94] In the United States alone, it has been estimated that over two million people are infected by drug-resistant bacteria each year.[95] Over the past decade, various branches of the federal government in recognizing antimicrobial resistance as a growing public health threat, have created programs to spur development and incentivize innovators to develop new and effective antimicrobial therapies. In particular, facilitating the development of new antibacterial and antifungal drugs is a policy priority for FDA in its efforts to specifically address antimicrobial resistance. Among other efforts undertaken by drug sponsors to address the threat of antimicrobial resistance is the development of fixed-combinations, including old antibiotic active moieties with new active moieties, such that the fixed-combination provides certain clinical benefits by restoring the activity of the older active moieties against certain resistant organisms.

In general, fixed-combinations provide additional clinical benefits, including the prevention of medication errors or incorrect dosing. For example, only one product needs to be administered by a healthcare provider/taken by a patient, rather than each product individually, to receive the benefits of both drugs in a fixed-combination. Thus, fixed-combination products play an important role in optimizing dosing regimens and improving patient outcomes. Such benefits are especially relevant in the context of antibacterial products because resistance is more likely to develop if there is non- adherence to the dose and

---

[92] As early as 2004, the Infectious Diseases Society of America (IDSA) reported that major pharmaceutical companies were losing interest in the antibiotics market because these drugs simply are not as profitable as drugs that treat chronic (long-term) conditions and lifestyle issues. *See* Interagency Task Force on Antimicrobial Resistance, *Action plan to combat antimicrobial resistance; part 1: domestic* (2001), available at: http://www.cdc.gov/drugresistance/actionplan/aractionplan.pdf; The Infectious Diseases Society of America (IDSA), Report: *Bad Bugs, No Drugs: As Antibiotic Discovery Stagnates, A Public Health Crisis Brews* (July 2004) ("IDSA 2004 Report"), available at: https://www.idsociety.org/uploadedFiles/IDSA/Policy_and_Advocacy/Current_Topics_and_Issues/Advancing_Product_Research_and_Development/Bad_Bugs_No_Drugs/Statements/As%20Antibiotic%20Discovery%20Stagnates%20A%20Public%20Health%20Crisis%20Brews.pdf.

[93] Ventola, C. L., The antibiotic resistance crisis: part 1: Causes and threats. *Pharmacy Ther.* 2015; 40:277–83; Malani, A., et al., Extending the cure: policy responses to the growing threat of antibiotic resistance, Washington DC: Resources for the Future; 2007.

[94] Antimicrobial resistance: global report on surveillance. Geneva: World Health Organization (WHO); 2014.

[95] CDC, Antibiotic Resistance Threats in the United States (2013), available at www.cdc.gov/drugresistance/threat-report-2013/pdf/ar-threats-2013-508.pdf

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

dosing schedule.[96] In addition, even in cases where antimicrobial resistance has developed, such resistance can be overcome when one or more antibacterial to which the organism is resistant can be used in combination with agents that restore the activity of the antibacterial against those resistant organisms thereby providing additional treatment options and improved patient outcomes. In particular, the benefits of two these types of drugs working together can be achieved when agents that restore the activity of an antibacterial are presented with existing antibacterial therapies in fixed-combination formats. Additional treatment options and improved patient outcomes become available in the context of old antibiotics because the activity of the old antibiotic can be restored such that the certain organisms are no longer resistant when the old antibiotic is used with drugs developed to target and overcome such resistance. For example, resistance to beta-lactams poses an exceptionally serious public health crisis because beta-lactams are among the most widely used classes of antibacterial drugs.[97] As noted above, resistance to beta-lactams primarily arises from bacterially produced beta-lactamases, enzymes that hydrolyze the beta-lactam ring, thereby diminishing the activity of the drug.[98] Adding a BLI to a beta-lactam antibacterial drug can restore the activity of the drug against certain beta-lactamase producing pathogens, depending on the spectrum of activity of the BLI. Some BLIs alone may have little or no clinically relevant antibacterial activity at prescribed strengths and some may have no direct antibacterial activity at any dose. In this way, beta-lactam/BLI fixed-combinations address the unmet need caused by growing resistance in Gram negative pathogens to currently available treatment options, which is recognized by the Centers for Disease Control and Prevention (CDC) as a public health threat.

The Agency believes that for effective patient care, it is preferable to have certain BLIs available as part of fixed-combinations. Administering beta-lactam/BLIs as fixed-combinations ensures that the components are given at the same time and in the appropriate ratios to provide effective therapy to patients. Administering beta-lactam/BLIs as fixed-combinations also prevents medication errors that would occur if a healthcare provider administers a beta-lactam or a BLI as monotherapy, which could result in patients receiving ineffective treatment for serious or life-threatening bacterial infections due to beta-lactam resistant organisms. These medication errors include the BLI being co-administered with an incorrect beta-lactam. Also, if the beta-lactam and BLI are given separately, there could be dosing errors based on the need for different dose adjustments for the beta-lactam and BLI, for example, in patients with renal impairment. Additionally, administering the beta-lactam and BLI separately, can be challenging in patients with limited intravenous access, as in critically ill patients. For these reasons, FDA has recommended to sponsors that they develop certain new BLIs and beta-lactams as part of a

---

[96] Nahid, P., et al. *Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis* (2016), available at https://www.idsociety.org/practice-guideline/treatment-of-drug-susceptible-tb/;

[97] Id. at 1. For instance, beta-lactams account for 65% of all prescriptions for injectable antibiotics in the United States, of which cephalosporins comprise nearly half of all such prescriptions.

[98] Beta-lactamases are now responsible for resistance to penicillins, extended-spectrum cephalosporins, monobactams, and carbapenems.

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

fixed-combination, as appropriate. A policy that then penalizes sponsors for developing these drugs in combination by denying 5-year NCE exclusivity to the fixed-combinations, when seeking approval for a new BLI or beta-lactam alone would guarantee such exclusivity, runs counter to important clinical and public health considerations. Given the benefits provided by such fixed-combinations, it would be in the interest of public health to encourage the development of such fixed-combinations through eligibility for 5-year NCE exclusivity. The Agency thus believes that there are important and compelling public policy reasons for the eligibility of fixed-combinations comprising an old antibiotic with a new active moiety for 5-year NCE exclusivity.

IV. Analysis and Discussion

Although FDA has opined on the applicability of section 505(v)(1) in the single moiety context, and has made a determination of eligibility for exclusivity for a fixed-combination that includes a new active moiety and an old antibiotic active moiety without apparent consideration of how section 505(v) affects that analysis, the Agency has not after enactment of the QI Act explicitly analyzed whether a fixed-combination containing in part an approved old antibiotic active moiety and in part a new active moiety (new chemical entity) is subject to section 505(v)(1) of the FD&C Act.

In light of (1) the strong policy reasons supporting eligibility for 5-year NCE exclusivity for a fixed-combination containing an old antibiotic active moiety and a new active moiety, (2) the post-October 2014 interpretation of 5-year NCE exclusivity, and (3) the *Ferring* court's determination that it would be arbitrary and capricious to make the availability of exclusivity turn on the order of approval, the Agency has undertaken an analysis of whether 5-year NCE exclusivity for a fixed-combination that includes a new (never previously approved) active moiety and an old antibiotic active moiety is supportable. This determination requires an analysis not only of the 5-year NCE exclusivity statutory provisions, but also the statutory provisions pertaining to old antibiotics, including section 505(v) of the FD&C Act. In particular, the key legal issue in this exclusivity analysis is whether a fixed-combination containing a new active moiety and an old antibiotic active moiety is subject to section 505(v)(1) of the FD&C Act.[99] The Board finds that although there are other potential readings of the relevant statutory provisions, we've decided that 5-year NCE exclusivity attaches and 505(v)(1) limitations on available exclusivity do not apply to a fixed-combination of a new active moiety and an old antibiotic active moiety. Under this interpretation, the word "contains" in the phrase "drug . . . contains an antibiotic drug" in 505(v) means "contains wholly" and therefore 505(v) does not

[99] The old antibiotic at issue in Avycaz is the subject of an *approved* application under section 507 of the FD&C Act. Therefore, the issue is whether Avycaz – a fixed-combination containing in part an approved old antibiotic – falls within the scope of section 505(v)(1) of the FD&C Act. Section 505(v)(2) of the FD&C Act concerns drugs that contain *unapproved* old antibiotics.

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

apply to a fixed-combination drug product that contains a new active moiety and an old antibiotic active moiety.[100]

A detailed written legal justification to analyze and justify this interpretation follows. Under this interpretation, if the word "drug" in the phrase "drug that is the subject of the application contains an antibiotic drug" in section 505(v)(1)(B)(i) means "drug product" (as FDA has previously argued in *Restasis*) and requires that FDA look at the fixed-combination as a whole when determining applicability of the exclusivity limitations in section 505(v), such a fixed-combination is subject to section 505(v)(1) unless FDA can determine that it is not a drug that "contains" an antibiotic drug. We make such a determination by interpreting the word "**contains**" in the phrase "drug that is the subject of the application contains an antibiotic drug" to mean "**consists of wholly**." Under this interpretation, 505(v) would not apply to such a combination (because it does not consist wholly of an old antibiotic drug or drugs) and, if section 505(v) does not apply, such a combination would be eligible for 5-year NCE exclusivity under our post-October 2014 interpretation of that provision.

More specifically, under section 505(c)(3)(E)(ii) and section 505(j)(5)(F)(ii) of the FD&C Act, a drug is eligible for 5-year NCE exclusivity if it is "a *drug*, no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other [505(b)] application." As explained above, in October 2014, in the Fixed-Combination NCE Guidance, FDA offered its new interpretation that the word "drug" in the eligibility clause of the 5-year NCE exclusivity provision refers to the "drug substance," and not the "drug product." This interpretation means that FDA will analyze each drug substance separately to determine if it meets the definition of new chemical entity and is therefore eligible for 5-year NCE exclusivity.

A drug substance containing no previously approved active moiety generally will be eligible for 5-year NCE exclusivity even when such a drug substance is approved in a fixed-combination with another drug substance containing a previously approved active moiety. Examining only section 505(c)(3)(E)(ii) and section 505(j)(5)(F)(ii) of the FD&C Act, under FDA's post-October 2014 interpretation of these provisions, a fixed-combination containing a new active moiety and an old antibiotic active moiety is eligible for 5-year NCE exclusivity because the non-antibiotic drug substance containing no previously approved active moiety is a new chemical entity. An extra layer of legal analysis is necessary, however, due to the statutory provisions relating to old antibiotics. As noted above, section 125(d) of FDAMA provided that subsections of section 505 concerning Hatch-Waxman benefits shall not apply to any application for marketing in

[100] FDA has received two letters from the NDA holder of Avycaz requesting that the Agency confirm that Avycaz is eligible for 5-year NCE exclusivity. See Letter from J. Czaban, Wiley Rein LLP, to Jay Sitlani, CDER Exclusivity Board (Mar. 16, 2016); Letter from K. Carver, Covington & Burling LLP, to Jay Sitlani, CDER Exclusivity Board (June 16, 2020). Among other things, these letters generally assert that FDA should interpret the word "drug" in the phrase "drug that . . . contains an antibiotic drug" in section 505(v)(1) to mean "drug substance," consistent with the Agency's interpretation of the 5-year exclusivity provisions in the Fixed-Combination NCE Guidance. For the reasons explained in this memo, the Board confirms that Avycaz is eligible for 5-year exclusivity.

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

which "the ***drug*** that is the subject of the application ***contains*** an ***antibiotic drug*** and the antibiotic drug was the subject of any application for marketing"[101] under section 507 before the date of the enactment of FDAMA.

As also noted above, the QI Act, which added section 505(v) of the FD&C Act, used the same language as in section 125 of FDAMA to describe the drugs to which it applied but created certain exclusivity incentives for applications for drugs that contain old antibiotics submitted after the date of enactment of the QI Act. Section 505(v)(1) applies to applications submitted after enactment of the QI Act "in which the **drug** that is the subject of the application ***contains*** an **antibiotic drug**" that was the subject of an approved application under section 507.[102] However, the QI Act did not make such applications eligible for exclusivity to the same extent as other section 505 drugs.

Under section 505(v)(1) of the FD&C Act, if a drug "contains" an old antibiotic drug that has been previously approved, then the sponsor may be eligible for, at most, 3-year exclusivity. If available at all, the eligibility for 3-year exclusivity is limited by the "conditions of use" provision in section 505(v)(3)(B). Section 505(v)(3)(B) provides that the 3-year exclusivity period is not available for "any condition of use for which the drug referred to in subparagraph (1)(B)(i) . . . was approved before the date of the enactment of [the QI Act]." FDA interprets section 505(v)(3)(B) to permit 3-year exclusivity "only for a significant new use" of the drug.[103] Section 505(v)(3)(A) states that a drug subject to section 505(v)(1)(B) is not entitled to any exclusivities other than that described in section 505(v)(1)(A). In other words, if a drug "contains" an old antibiotic drug such that 505(v)(1) applies, then that drug is only eligible for 3-year exclusivity where the requirements are met. Such a drug would not be eligible for 5-year NCE exclusivity.

As noted above, the quoted language in section 505(v)(1) is essentially identical to language in section 125(d)(2) of FDAMA.[104] With respect to this same language in section 125(d)(2) of FDAMA, FDA previously interpreted this language to mean the following: "in which the **drug [product]** that is the subject of the application ***contains [in whole or part]*** an **antibiotic drug [substance or active moiety]**" and the antibiotic drug substance or active moiety was the subject of an application received by FDA under section 507.[105] Under this interpretation, fixed-combinations containing an old antibiotic drug substance as well as a non-old antibiotic drug substance were subject to the exemption from Hatch-Waxman benefits in section 125(d)(2) of

---

[101] Pub. L. No. 105-115, 111 Stat. 2295, 2326-2327 (1997) (emphasis added).
[102] Section 505(v)(1)(B)(i), (ii) of the FD&C Act (emphasis added).
[103] See 2012 Vancocin Petition Response at 70.
[104] Section 125(d)(2) of FDAMA ("in which the **drug** that is the subject of the application ***contains*** an **antibiotic drug**") (emphasis added).
[105] 2003 Restasis Petition Response at 37.

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

FDAMA (see, for example, Ziana mentioned above). This interpretation was consistent with FDA's pre-October 2014 interpretation of 5-year exclusivity for fixed-combination products. If FDA were to apply its interpretation of the FDAMA language to the same language in section 505(v)(1),[106] a fixed-combination containing an old antibiotic active moiety and a new active moiety, such as Avycaz, would fall within the bounds of section 505(v)(1). Under this interpretation, even if the fixed-combination contains a drug substance that is a new active moiety (new chemical entity) as well as an old antibiotic drug substance, the fixed-combination would not be entitled to 5-year NCE exclusivity but would instead only be eligible for 3-year exclusivity in certain circumstances. This outcome would not advance FDA's public policy and public health goal to incentivize and encourage the development of novel fixed-combinations to address the growing threat of antimicrobial resistance. Nor does it align with FDA's current policy for NCE exclusivity for fixed-combination products under which 5-year NCE exclusivity attaches where any drug substance in a fixed-combination does not contain any active moiety that has previously been approved. In addition, if 505(v) were to apply to such a fixed-combination, it would make availability of exclusivity for the new moiety in the fixed-combination turn on the order of approval – if it is approved first in a fixed-combination it will be ineligible for 5-year NCE exclusivity but if it is approved first in a single-entity drug product, it will maintain eligibility for 5-year NCE exclusivity.

In the 2003 Restasis Petition Response, where the Agency set out its interpretation of the language in section 125(d)(2) of FDAMA as it applied to cyclosporine ophthalmic emulsion, FDA noted that the plain language of the statute dictated the Agency's interpretation.[107] The court in *Allergan* considered FDA's interpretation and did not explicitly rule on whether "drug" meant drug substance or drug product but concurred with FDA, holding, "[i]t is clear that cyclosporine was the 'subject of an application for marketing' prior to FDAMA and that the FDA has determined that cyclosporine is an 'antibiotic.'"[108] While FDA's interpretation of the statutory language in *Allergan* was reasonable, it can be argued that, upon further reflection, it is not the only reasonable interpretation of the statutory language. The phrase "drug that . . . contains an antibiotic drug" in section 125(d)(2) of FDAMA and in section 505(v) of the FD&C Act is susceptible to more than one plausible interpretation and therefore this language is ambiguous.[109]

Specifically, the operative words in this statutory provision – "drug," "contains," and "antibiotic drug" – have multiple potential meanings. The FD&C Act defines the term "drug" broadly and delegates to FDA the task of determining how to apply the definition in particular statutory

---

[106] The language in the 2008 Patent Submission draft guidance – "for a drug (including a combination drug) containing an antibiotic drug" – suggests that FDA applied the same interpretation of "drug that . . . contains an antibiotic drug" in the FDAMA context to the language in the QI Act.
[107] 2003 Restasis Petition Response at 37.
[108] See *Allergan, Inc. v. Crawford*, 398 F. Supp. 2d 13, 23-16 (D.D.C. 2005).
[109] See, e.g., *Otsuka Pharm. v. Burwell*, 302 F. Supp. 3d 375, 394 (2016).

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

provisions.[110] "Drug" can mean a finished drug product ("articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man" or "intended to affect the structure or function of the body of man")[111] or the components of a finished drug product ("articles intended for use as a [drug] component").[112] Therefore, FDA has recognized, and courts have accepted, that "drug" can be interpreted, among other possible meanings, to mean either drug product or drug substance.[113]

As described above, "antibiotic drug" is defined to mean "any *drug* . . . composed wholly or partly of any kind of penicillin, streptomycin, chlortetracycline, chloramphenicol, bacitracin, or any other drug intended for human use containing any quantity of any chemical substance which is produced by a micro-organism and which has the capacity to inhibit or destroy micro-organisms in dilute solution (including a chemically synthesized equivalent of any such substance) or *any derivative thereof*."[114] The use of the word "drug" in this definition of antibiotic drug in particular does not resolve the statutory ambiguity, as this word in this context can plausibly be interpreted to include a finished drug product, or a component of a drug product, as described above. Moreover, the use of the phrase "any derivative thereof" in the statutory definition of "antibiotic drug" provides further ambiguity about the meaning of the term "antibiotic drug" because it is common to talk of derivatives of active moieties, not of drug products or drug substances.

The word "contains" is also open-ended and is susceptible to more than one meaning. The general purpose dictionary defines "contain" to mean "to consist of wholly or in part: comprise; include."[115] Under this definition of "contains," it is reasonable to interpret "contains" to have two distinct meanings: (1) to consist of wholly; or (2) to consist of in part. Because a fixed-combination drug product contains in part an antibiotic drug substance and an antibiotic drug substance contains wholly an antibiotic active moiety, the use of the word "contains" does not resolve the ambiguity of whether "drug" means "drug product" or "drug substance" in the key definitional phrase.

---

[110] Section 201(g) of the FD&C Act. See, e.g., *Pharmanex v. Shalala*, 221 F.3d 1151, 1156 (10th Cir. 2000) ("[T]he term 'drug' is defined in [section 201(g) of the FD&C Act (21 U.S.C. 321(g))] to include both finished drug products as well as individual constituents. Thus, the definition of 'new drug' is largely colored by the ambiguity that attends the broad term 'drug.'"). See also *United States v. Sullivan*, 332 U.S. 689, 694 (1948) ("[FDA] is given rather broad discretion [in administering the FD&C Act].").

[111] Section 201(g)(1)(B) and (C) of the FD&C Act.

[112] Section 201(g)(1)(D) of the FD&C Act.

[113] See, e.g., *United States v. Generix Drug Corp.*, 460 U.S. 453, 459 (1983) (holding that section 201(g)(1) of the FD&C Act is "plainly broad enough to include" both "active ingredient" and "drug product"); *Pfizer, Inc. v. FDA*, 753 F. Supp. 171, 176 (D. Md. 1990) (stating that the definition of drug "covers both a finished 'drug product' and its active and inactive ingredient or ingredients.").

[114] Section 201(jj) of the FD&C Act (emphasis added).

[115] Webster's Third New International Dictionary.

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

Given the ambiguity in the statutory language, FDA has the discretion to interpret this statutory language in a reasonable manner based on its expertise and experience in administering complex statutory exclusivity provisions,[116] and in a way that advances its important policy and public health goals. As described above, the operative language in section 505(v)(1) is as follows: "in which the **drug** that is the subject of the application ***contains*** an **antibiotic drug**" that was the subject of an approved application under section 507.[117] The Board has decided that the interpretation that is consistent with the statute and best meets the important policy goals of incentivizing the development of fixed-combination products to address concerns related to antimicrobial resistance is: "in which the **drug [product]** that is the subject of the application ***contains [wholly]*** an **antibiotic drug [substance or active moiety or combination of antibiotic drug substances or active moieties]**."

This proposed interpretation of section 505(v)(1) is very similar to FDA's interpretation of the same language in section 125(d)(2) of FDAMA with one key exception. Under FDA's interpretation of section 125(d)(2), FDA interpreted "contains" to mean "consists of in part." Where a fixed-combination contained two drug substances and one drug substance was an old antibiotic [drug substance or active moiety], FDA determined that the drug product contained – in part – an old antibiotic drug substance or active moiety and therefore was exempt from Hatch-Waxman benefits under FDAMA. While this interpretation was reasonable, FDA can also reasonably depart from this interpretation, consistent with its departure from its prior interpretation of section 505(c)(3)(E)(ii) for fixed-combination products and adopt the alternative definition of "contains" to accomplish its public health goals. Specifically, FDA reasonably can choose to interpret "contains" in section 505(v) to mean "consists of *wholly*" or "comprises" to incentivize development of products that combine an old antibiotic active moiety with a new active moiety. Such combinations have the potential to improve the efficacy, safety, or ease of use (and therefore compliance with dosing) of the old antibiotic – important public health goals.

Under this interpretation of the key language in section 505(v)(1), for single-entity drug products, FDA would analyze whether the single-entity drug product contains an antibiotic drug substance or active moiety that was the subject of an approved section 507 application and would interpret the language in section 505(v)(1) for single-entity drugs as follows: "in which the **drug [product]** that is the subject of the application ***contains [wholly]*** an **antibiotic drug [substance or active moiety]**" that was the subject of an approved section 507 application.

It should be noted that FDA's 3-year exclusivity precedent with respect to section 505(v)(1) of the FD&C Act is consistent with this interpretation. In 2012, FDA determined that Vancocin was a single-entity drug product that contained [wholly] an approved old antibiotic drug active moiety – vancomycin – and therefore fell within the bounds of section 505(v)(1). Similarly, in 2015, FDA determined that Astagraf XL was a single-entity drug product that contained [wholly]

[116] Deference is especially appropriate when the statutory and regulatory regimes implemented by the agency are complex. See *Actavis Elizabeth LLC v. FDA*, 625 F.3d 760, 766 (D.C. Cir. 2010).
[117] Section 505(v)(1)(B)(i), (ii) (emphasis added).

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

an approved old antibiotic drug active moiety – tacrolimus – and therefore was subject to section 505(v)(1).

The legislative history of the QI Act supports FDA's interpretation that a fixed-combination containing a new active moiety and an old antibiotic active moiety does not fall within the bounds of section 505(v)(1). Congress enacted the QI Act to encourage the development of truly novel antibiotics and novel uses of old antibiotic drug products to fight against drug-resistant bacterial infections.[118] Congress sought to incentivize the development of novel uses of old antibiotic drug products by providing for the availability of 3-year exclusivity in certain limited circumstances. FDA's interpretation of the key language in section 505(v)(1) gives meaning to the Congressional intent to encourage the development of truly novel antimicrobial products and new uses for old antibiotic drug products. FDA's interpretation makes it possible for a fixed-combination containing a new active moiety and an old antibiotic active moiety to be eligible for 5-year NCE exclusivity, which is important for incentivizing the research and development of new antibacterial drug products to fight antimicrobial resistance.

Denying NCE exclusivity to a fixed-combination containing a new active moiety and an old antibiotic active moiety does not appear to be fully consistent with the Congressional intent. Such a fixed-combination is arguably more innovative and may make a greater contribution to public health than a new use of an old antibiotic drug product; it contains in part an active moiety that has never before been approved in an NDA and arguably, should be eligible for the NCE exclusivity that Congress intended for such a never previously approved moiety.

This construction of section 505(v)(1) also serves important public policy goals. Under FDA's interpretation, a drug sponsor can choose to develop the fixed-combination first or the single-entity drug first, and still receive 5-year NCE exclusivity in either circumstance. If FDA were to conclude that a fixed-combination containing a new active moiety and an old antibiotic active moiety was only eligible for 3-year exclusivity under section 505(v)(1), one could argue, based on the reasoning in the *Ferring* decision, that the Agency's policy is arbitrary and capricious because the timing and sequence in which the drugs are approved determines whether a drug is eligible for 5-year NCE exclusivity.[119] There is a strong possibility that a court, like the *Ferring* court, would be persuaded by that argument. In addition, it would not be optimal to adopt an interpretation in which a drug sponsor would have to develop the single-entity drug (with the new active moiety alone) first, in order to be eligible for 5-year NCE exclusivity. As explained above, in many instances, there would be more clinical value – especially in the fight against antimicrobial resistance – in developing the fixed-combination containing the new active moiety and old antibiotic from the outset, especially in the case of BL/BLI combinations where the

[118] See, e.g., 154 Cong. Rec. S9638 (Sept. 26, 2008) (statement of Sen. Burr).
[119] Sept. 2016 Ferring Opinion at 22 ("If a drug substance is sufficiently novel to warrant protection under a five-year exclusivity period—and sufficiently novel that other products containing that drug substance should also be protected through the umbrella policy—it is not apparent why timing, or the order in which the drugs were approved, should alter that assessment.").

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

activity of the new active moiety is only significant when the new active moiety is used in combination with the old antibiotic active moiety.

Thus, this interpretation of section 505(v)(1) also serves the important public health goal of facilitating the development of new antibacterial drug products. As explained above, such development is a policy priority for FDA in its efforts to address antimicrobial resistance. New antibacterial fixed-combinations also provide certain clinical benefits, including the prospect of increased patient compliance with a more simplified dosing regime and the prevention of medication errors or incorrect dosing, and it is in the interest of the public health for 5-year NCE exclusivity to be available to incentivize the development of these products.

V. Conclusion

For the reasons stated above the Board recommends that the Agency recognize 5-year NCE exclusivity for Avycaz.

Sanjay Sitlani -S

Digitally signed by Sanjay Sitlani -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Sanjay Sitlani -S, 0.9.2342.19200300.100.1.1=2000359378
Date: 2020.12.21 12:50:43 -05'00'

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CARMEN L DEBELLAS
12/21/2020 03:14:19 PM