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December 10, 2019

Congressional Research Service
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R46110

CRS REPORT
Prepared for Members and
Committees of Congress

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SUMMARY

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Defining Active Ingredient: The U.S. Food and Drug Administration's Legal Interpretation of Regulatory Exclusivities

Whether many provisions of the Federal Food, Drug, and Cosmetic Act (FD&C Act) apply to a particular drug product turns in part on the novelty of the "active ingredient" of the drug in question. In particular, the Food and Drug Administration (FDA) must assess the novelty of the active ingredient in a new drug, comparing it to a previously approved drug's active ingredient to determine whether the new drug qualifies for the five-year "new chemical entity" (NCE) exclusivity. FDA generally cannot accept new drug applications that refer to a drug with NCE exclusivity (i.e., rely on its clinical data and FDA's approval of the drug) for five years. Companies that receive approval for drugs with new active ingredients generally enjoy a competitive advantage in the market while the exclusivity is in effect—and after, depending how long it takes for generic versions to receive approval once applications can be submitted.

Comparing active ingredients can be technically quite complicated. For instance, compounds in a final drug product may convert to other compounds through chemical reactions inside the body before arriving at the site of the therapeutic effect. In addition, related but distinct drug molecules may be clinically indistinguishable or convert into the same pharmacologically or physiologically active component inside the body. Alternatively, two drug molecules with the same core compound may have different compounds appended to them by either covalent or noncovalent bonds. For example, replacing a hydrogen atom in an acid molecule with "a metal or its equivalent" forms a salt, while replacing the hydrogen atom with "an organic radical" forms an ester. These derivatives may or may not vary from each other in clinically significant ways. This raises the question of *which* derivative(s), if any, should be considered to be the same active ingredient as the core or base molecule. Generally, a more expansive interpretation of phrase "active ingredient," that is, one that considers more types of derivatives to be the same active ingredient, reduces the number of drugs eligible for NCE regulatory exclusivity by expanding the drug ingredients considered previously approved, which allows for earlier introduction of generic versions of those drugs.

Historically, for the exclusivity provisions, FDA has interpreted "active ingredient" to mean "active moiety," as defined by FDA regulations. FDA generally defines active moiety as the core molecule or ion of a drug (i.e., the drug molecule without certain appendages) that is "responsible for the physiological or pharmacological action of a drug substance." FDA's interpretation has generated disputes between FDA and pharmaceutical companies, as FDA's approach tends to exclude some drugs from being afforded five-year NCE exclusivity under the FD&C Act. In 2015, a federal district court rejected FDA's interpretation as inconsistent with the statutory language, though it did not explicitly invalidate FDA's regulations.

In the 116th Congress, legislation has been introduced that would generally codify FDA's current approach to evaluating NCE exclusivity and extend that approach to certain other provisions under the FD&C Act. This proposed legislation would moot questions about the validity of FDA's interpretation and clarify when chemical entities are sufficiently similar to be considered identical for purposes of drug approval and exclusivity.

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Introduction

Whether many provisions of the Federal Food, Drug, and Cosmetic Act (FD&C Act) apply to a particular drug product turns in part on the novelty of the "active ingredient" of the drug in question. In particular, the Food and Drug Administration (FDA) must assess the novelty of the active ingredient in a new drug, comparing it to a previously approved drug's active ingredient to determine whether the new drug qualifies for the five-year "new chemical entity" (NCE) exclusivity.[1] FDA generally cannot accept new drug applications or abbreviated new drug applications that refer to a drug with NCE exclusivity (i.e., rely on its clinical data and FDA's approval of the drug) for five years.[2] Companies that receive approval for drugs with new active ingredients generally enjoy a competitive advantage in the market while the exclusivity is in effect until generic drugs enter the market.[3] Given how expensive it can be to bring a new drug to market,[4] when Congress passed the Hatch-Waxman Amendments in 1984 to allow an abbreviated pathway for approval of generic drugs, it also created NCE exclusivity to reward innovators of new pharmaceutical products with an opportunity to recoup their investment.[5]

To determine whether FD&C Act provisions that depend in part on the drug's "active ingredient" apply, FDA must evaluate the "active ingredient(s)" of both the drug under review and any previously approved drug that may contain the same active ingredient.[6] This process can be technically quite complicated. For instance, compounds in a final drug product may convert to other compounds through chemical reactions inside the body before arriving at the site of the therapeutic effect, and related but distinct drug molecules may be clinically indistinguishable or convert into the same pharmacologically or physiologically active component inside the body.[7] This phenomenon raises the question of which molecule—the one existing before or after ingestion—should be the relevant molecule for purposes of determining active ingredient.[8]

Alternatively, two drug molecules with the same core compound may have different compounds appended to them by either covalent (i.e., shared electrons) or noncovalent (i.e., no shared electrons) bonds.[9] For example, replacing a hydrogen atom in an acid molecule with "a metal or its equivalent" forms a salt, whereas replacing the hydrogen atom with "an organic radical" forms

[1] 21 U.S.C. §§ 355(j)(5)(F)(ii) & 355(c)(3)(E)(ii).

[2] *Id.* Abbreviated new drug applications that challenge nonexpired listed patents may be submitted after four years. *Id.*

[3] *Generic Competition and Drug Prices*, FOOD & DRUG ADMIN. (Nov. 28, 2017), https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/generic-competition-and-drug-prices (finding association between generic competition and lower drug prices).

[4] *See generally* Joseph A. Di Masi, Henry G. Grabowski, & Ronald W. Hansen, *Innovation in the Pharmaceutical Industry: New Estimates of R&D Costs*, 47 J. HEALTH ECON. 20 (2016).

[5] *See, e.g.*, King Drug Co. of Florence, Inc. v. Smithkline Beecham Corp., 791 F.3d 388, 394 (3d Cir. 2015) ("Congress attempted to balance the goal of 'mak[ing] available more low cost generic drugs, H.R. Rep. No. 98-857, pt. 1, at 14-15 (1984), *reprinted in* 1984 U.S.C.C.A.N. 2647, 2647-48, with the value of patent monopolies in incentivizing beneficial pharmaceutical advancement, *see* H.R. Rep. No. 98-857, pt. 2, at 30 (1984), *reprinted in* 1984 U.S.C.C.A.N. 2686, 2714."); Yaniv Heled, *Patents v. Statutory Exclusivities in Biological Pharmaceuticals—Do We Really Need Both?*, 18 MICH. TELECOMM. & TECH. L. REV. 419, 427-30, 434-36 (2012).

[6] *See, e.g.*, 21 U.S.C. § 355(c)(3)(E).

[7] *See, e.g.*, Actavis Elizabeth LLC v. FDA, 625 F.3d 760, 762-63, 766 (D.C. Cir. 2010); Abbott Laboratories v. Young, 920 F.2d 984, 986 (D.C. Cir. 1990).

[8] *See infra* "FDA's Definition of Active Moiety."

[9] *Actavis Elizabeth LLC*, 625 F.3d at 765-66.

an ester.[10] These derivatives may or may not vary from each other in clinically significant ways,[11] raising the question of *which* derivative(s), if any, should be considered as the same active ingredient as the core or base molecule.[12] Generally, a more expansive interpretation of the phrase "active ingredient," that is, one that considers more types of derivatives to be the same active ingredient, reduces the number of drugs eligible for NCE regulatory exclusivity by expanding the drug ingredients considered previously approved, which, in turn, allows for earlier introduction of generic versions of those drugs.

As discussed in more detail below, historically, for purposes of the exclusivity provisions, FDA has interpreted "active ingredient," as the term appears in statute, to mean "active moiety," as defined by FDA regulations.[13] FDA generally defines active moiety as the core molecule or ion of a drug (i.e., the drug molecule without certain appendages) that is "responsible for the physiological or pharmacological action of a drug substance."[14] FDA's interpretation has generated disputes between FDA and pharmaceutical companies, as FDA's approach tends to exclude some drugs from being afforded five-year NCE exclusivity under the FD&C Act.[15] In 2015, a federal district court rejected FDA's interpretation as inconsistent with the statutory language, though it did not explicitly invalidate FDA's regulations.[16]

This report discusses FDA's interpretation of the FD&C Act as referring to active moieties, judicial review of FDA's interpretation, and how FDA's rationale has changed over time. In the 116th Congress, legislation has been introduced that would generally codify FDA's current approach to evaluating NCE exclusivity and extend that approach to other provisions under the FD&C Act that include the phrase "active ingredient (including any ester or salt of the active ingredient)."[17]

FDA Interpretation of Active Ingredient

Multiple provisions of the FD&C Act use the phrase "active ingredient (including any ester or salt of the active ingredient)."[18] Among them are a provision for five-year exclusivity to drugs approved under a new drug application (NDA) with active ingredients that FDA has not previously approved,[19] a provision for three-year exclusivity for drugs with the same active ingredient as previously approved drugs that required additional clinical studies for approval due to other changes,[20] and provisions authorizing priority review vouchers for certain types of

[10] Amarin Pharm. Ireland Ltd. v. FDA, 106 F. Supp. 3d 196, 199 n.1 (D.D.C. 2015).

[11] *Actavis Elizabeth LLC*, 625 F.3d at 765-66.

[12] *See infra* "FDA's Definition of Active Moiety."

[13] *See* 21 C.F.R. § 314.3; 59 Fed. Reg. 50,338, 50,357-58, 50,368-69 (Oct. 3 1994).

[14] 21 C.F.R. § 314.3(b).

[15] *See generally*, Actavis Elizabeth LLC v. FDA, 625 F.3d 760 (D.C. Cir. 2010); Abbott Labs. v. Young, 920 F.2d 984 (D.C. Cir. 1990); Otsuka Pharm. Co. v. Burwell, 302 F. Supp. 3d 375 (D.D.C. 2016); Ferring Pharm., Inc. v. Burwell, 169 F. Supp. 3d 199 (D.D.C. 2016).

[16] Amarin Pharm. Ireland Ltd. v. FDA, 106 F. Supp. 3d 196, 217-19 (D.D.C. 2015).

[17] S. 1636, 116th Cong. (2019); S. 1895, 116th Cong. § 208 (2019).

[18] 21 U.S.C. § 355(c)(3)(E)(i),(ii), (iii) & (v); *id.* § 355(j)(5)(F)(i), (ii), (iii) & (v); *id.* § 355(l)(2)(A)(i); *id.* § 355(s); *id.* § 355(u)(1); *id.* § 360b(c)(2)(F)(i), (ii), and (v); *id.* § 360n(a)(4)(C); *id.* § 360ff(a)(4)(A)(ii); & *id.* § 360bbb-4a(a)(4)(D).

[19] 21 U.S.C. § 355(c)(3)(E)(ii) & (j)(5)(F)(ii).

[20] *Id.* § 355(c)(3)(E)(iii) & (j)(5)(F)(iii).

drugs.[21] In the context of the five-year-exclusivity, which FDA has coined "new chemical entity" or NCE exclusivity,[22] FDA interprets the term "active ingredient" to mean "active moiety."[23] FDA reasons that this definition, which allows a wider range of molecules to be considered previously approved, is warranted in the new drug context to encourage innovation by ensuring that a new drug is truly innovative.[24] This interpretation of "active ingredient" in the NCE exclusivity context has been the subject of a decades-long debate.

The statutory provision on NCE exclusivity states, in relevant part,

> If an application submitted under subsection (b) of this section 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) of this section, is approved . . . no application may be submitted under this subsection which refers to the drug for which the subsection (b) application was submitted before the expiration of five years from the date of approval of the application under subsection (b) of this section . . . .[25]

Disputes over how FDA should interpret this provision have centered on the meaning of the phrase "active ingredient (including any ester or salt of the active ingredient)."[26] The FD&C Act does not define the term "active ingredient."[27] Rather than define "active ingredient" for purposes of the exclusivity provisions, FDA examines the relevant drugs' active moieties.[28] Specifically, FDA defines NCE exclusivity in its regulations as "a drug that contains no *active moiety* that has been approved by FDA in any other application submitted under section 505(b) of the act."[29] The various other exclusivity regulations also refer to active moieties.[30]

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[21] *Id.* §§ 360ff(a)(4)(A)(ii), 360n(a)(4)(C), 360bbb-4a(a)(4)(D).

[22] *Id.* § 355(j)(5)(F)(ii); 21 C.F.R. § 314.108. *See also* 21 U.S.C. § 355(c)(3)(E)(ii) & (iii), 355(j)(5)(F)(iii). The three-year exclusivity for drugs with previously approved active ingredients that require additional clinical studies to be approved (e.g., for new indications or methods of use) includes similar statutory language and has been similarly interpreted by FDA to refer to active moieties. *See* 21 U.S.C. § 355(j)(5)(F)(iii) & (iv); 21 C.F.R. § 314.108.

[23] 21 C.F.R. § 314.108.

[24] Abbreviated New Drug Application Requirements; Patent and Exclusivity Provisions, 59 Fed. Reg. 50,338, 50,358 (Oct. 3, 1994).

[25] 21 U.S.C. § 355(j)(5)(F)(ii) (emphasis added). *See also id.* § 355(c)(3)(E)(ii).

[26] *See, e.g.*, Amarin Pharm. Ireland Ltd. v. FDA, 106 F. Supp. 3d 196, 206-07 (D.D.C. 2015); Actavis Elizabeth LLC v. FDA, 625 F.3d 760, 761-62 (D.C. Cir. 2010); Abbott Labs. v. Young, 920 F.2d 984, 985-86 (D.C. Cir. 1990). "Esters and salts are molecules that form in chemical reactions when the hydrogen atom of an acid molecule is replaced by another substance." *Amarin Pharm. Ireland Ltd.*, 106 F. Supp. 3d at 199.

[27] FDA did not define "active ingredient" when it originally enacted regulations to implement the Hatch-Waxman Amendments. *See generally* 59 Fed. Reg. 50,338. However, it did define the term outside of the exclusivity context in 2016 when implementing the Medicare Prescription Drug, Improvement, and Modernization Act of 2003. *See* 81 Fed. Reg. 69,580, 69,580, 69,637 (Oct. 6, 2016). FDA regulations now define "active ingredient" as

> [A]ny component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals[,] 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.

21 C.F.R. § 314.3. However, FDA has not changed its approach to NCE exclusivity, as the agency continues to examine the active moiety of the relevant drugs. *See id*. § 314.108.

[28] *See, e.g.*, 54 Fed. Reg. 28,872, 28,896-98 (July 10, 1989); 59 Fed. Reg. 50,338, 50357-58, 50,368-69 (Oct. 3 1994); *New Chemical Entity Exclusivity Determinations for Certain Fixed-Combination Drug Products: Guidance for Industry*, U.S. DEP'T OF HEALTH AND HUMAN SERV., FOOD & DRUG ADMIN. (2014).

[29] 21 C.F.R. § 314.108(a) (emphasis added).

[30] *Id.* § 314.108(b)(2) & (4).

FDA defines "active moiety" in its regulations as follows:

> Active moiety is the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance.[31]

Key Terms

Ester. An organic compound formed by reaction between alcohols and acids.

Salt. A chemical compound formed by reaction of an acid with a base, in which the hydrogen of the acid has been replaced by metal or other positive ions.

Covalent bond. A chemical bond created by sharing electrons.

Noncovalent bond. A chemical bond that does not entail sharing electrons.

Source: Rennie, R., & Law, J. (Eds.), A Dictionary of Chemistry. Oxford University Press.

As one court put it, "[f]or salts, esters, and noncovalent derivatives, a molecule's 'active moiety' can be thought of as its core; salt, ester and noncovalent derivative versions of the same basic molecule have different appendages, but they share the same active moiety."[32] Put another way, because these specified derivatives would be considered to have the same "active moiety," if FDA approves a drug containing any one of the specified derivatives as the active ingredient, a later approved drug containing another form of a specified derivative or even the core molecule would not be entitled to NCE exclusivity. For instance, if Drug A contains as its active ingredient a *salt*, *ester*, or *other noncovalent derivative* of a molecule that FDA previously approved as part of Drug B, Drug A would not be entitled to NCE exclusivity because FDA had previously approved that active moiety.[33] Similarly, if Drug B contains as its active ingredient a salt derivative of a molecule, and Drug A contains that same molecule or an ester derivative of that molecule and is approved after Drug B, Drug A would not be entitled to NCE exclusivity.[34] In contrast, if Drug A contained as its active ingredient a non-ester *covalent* derivative of a molecule that FDA previously approved in Drug B, Drug A could be considered to have a new active moiety and be eligible for NCE exclusivity if other relevant conditions are met. If a drug molecule is converted to a different but related compound after ingestion, the relevant molecule for determining active moiety is the compound in the final drug product before the drug is ingested.

Challenges to FDA's Approach

In the NCE exclusivity context, FDA's interpretation of "active ingredient" as "active moiety," as well as its definition of "active moiety," have both been subject to dispute. Challenges to FDA's approach to NCE exclusivity have generally addressed two questions:

[31] *Id.* § 314.3.

[32] Amarin Pharm. Ireland Ltd. v. FDA, 106 F. Supp. 3d 196, 199-200 (D.D.C. 2015).

[33] 21 U.S.C. §§ 355(c)(3)(E)(ii) & (iii), 355(j)(5)(F)(iii).

[34] 21 C.F.R. § 314.108.

1. Whether FDA may permissibly interpret the phrase "no active ingredient (including any ester or salt of the active ingredient) of which has been approved" as "a drug that contains no active moiety that has been approved."[35]
2. Whether FDA has correctly defined "active moiety," including whether FDA may permissibly deny exclusivity for—in addition to "salts and esters," which appear in the statute—other noncovalent derivatives of the underlying drug molecule.[36]

FDA's Interpretation of the Exclusivity Provision

Proposed Rule. In 1989, in its implementing regulations for the Hatch-Waxman Amendments, FDA first interpreted the FD&C Act's exclusivity provisions to distinguish between NCEs, which are entitled to a five-year term of regulatory exclusivity, and previously approved active ingredients, which are entitled to three years of regulatory exclusivity, based on active moieties.[37] To support its interpretation in the proposed rule, the agency relied on the statutory text, FDA's preexisting classification scheme for drugs that included a "new molecular entity" class based on active moieties, and the legislative history of the Hatch-Waxman Amendments.[38] FDA reasoned that "Congress was aware of FDA's classification scheme" when it passed the Hatch-Waxman Amendments, including FDA's "longstanding interpretation of the term 'new molecular entity' [as] a compound containing an entirely new active moiety."[39] In support of its definition of active moiety, which includes other noncovalent derivatives of a drug molecule in addition to the drug molecule itself and its salt and esters, FDA reasoned that Congress "did not intend to confer significant periods of exclusivity on minor variations of previously approved chemical compounds."[40] FDA did not specifically identify which part of the statutory phrase "an active ingredient (including any ester or salt of the active ingredient)" it had determined to be ambiguous when adopting the interpretation of "active moiety."[41]

Initial Litigation Rejecting FDA Approach. Between FDA's proposed rule in 1989 and its final rule in 1994 implementing the exclusivity regulations, two cases addressed the agency's interpretation of the phrase "active ingredient (including any ester or salt of the active ingredient)" to mean active moiety. In *Abbott Laboratories v. Young*, the U.S. Court of Appeals for the D.C. Circuit (D.C. Circuit) considered FDA's denial of 10-year exclusivity[42] for Depakote, an anticonvulsant seizure medication that used divalproex sodium as its active

[35] Related to this question is what language FDA has determined to be ambiguous to allow it room for its interpretation.

[36] Related to this question is whether the term active moiety must include other covalent derivatives that convert into the same compound to achieve the therapeutic effect.

[37] *See, e.g.*, 54 Fed. Reg. at 28,896-98; 59 Fed. Reg. at 50357-58, 50,368-69.

[38] 54 Fed. Reg. at 28,897-98.

[39] *Id.*

[40] *Id.* at 28,898.

[41] Under the *Chevron* doctrine, established by the Supreme Court in *Chevron U.S.A. v. Natural Resources Defense Council*, when reviewing agency interpretations of statutes, the court first asks "whether Congress has directly spoken to the precise question at issue." 467 U.S. 837, 842 (1984). "If so, the court must 'give effect to the unambiguously expressed intent of Congress.'" *Amarin Pharm. Ireland Ltd.*, 106 F. Supp. 3d at 205 (quoting *Chevron U.S.A.*, 467 U.S. at 843). Only if the court "concludes that Congress has left an ambiguity or 'gap' to fill on the 'precise question at issue'" does the court proceed to ask "whether the agency's construction of the statute is a 'permissible' one," in which case the court defers to the agency. *Id.* at 206. Finding ambiguity in the statutory provision accordingly allows the court to consider FDA's interpretation.

[42] For drugs approved between January 1, 1982, and September 24, 1984 (before the Hatch-Waxman Amendments was passed), Congress provided a 10-year period of exclusivity for drugs with new chemical entities and a 2-year period of exclusivity for all other drugs. 21 U.S.C. § 355(j)(5)(F).

ingredient.[43] FDA based its decision on findings that (1) divalproex sodium is a salt of valproic acid that converts into valproic acid in the body, and (2) the agency previously approved valproic acid as the active ingredient in Depakene.[44] The court determined that the FD&C Act's use of the phrase "*the* active ingredient" is ambiguous, as it could refer to the active ingredient in the original approved drug or in the later approved drug.[45] However, the D.C. Circuit rejected FDA's reliance on the term "including" to justify using its definition of active moiety, which extends beyond salts and esters of the active ingredient to other noncovalent derivative molecules, as "*linguistically* infeasible."[46] Specially, the court concluded that Congress used the term "including" in the provision at issue not to provide examples of molecular derivatives undeserving of regulatory exclusivity but to extend the covered active ingredients to the two particular derivatives—esters and salts.[47] Upon concluding that the statute is ambiguous and that FDA failed to provide a reasonable construction, the D.C. Circuit remanded the case to FDA for further actions.[48]

Around the same time, the U.S. Court of Appeals for the Federal Circuit (Federal Circuit) considered the U.S. Patent and Trademark Office's (USPTO's) denial of Glaxo's request for a patent-term extension for its patent claiming cefuroxime axetil, the active ingredient in Ceftin tablets.[49] The Hatch-Waxman Amendments require the USPTO to extend the terms of a patent claiming a product or a method of using or manufacturing a product when (1) the product is "subject to a regulatory review period" (e.g., the FDA drug approval process) and (2) the permission to market the product following the regulatory review (e.g., FDA approval of the drug) is the "first permitted commercial marketing or use of the *product*."[50] In turn, the statute defines "product" to mean "the active ingredient of a new drug . . . including any ester or salt of the active ingredient."[51] Interpreting the product as the active moiety, the USPTO found that cefuroxime (an acid) rather than cefuroxime axetil (an ester of cefuroxime) was the active moiety in Ceftin.[52] Because FDA had previously approved two drugs with cefuroxime *salts* as active ingredients,[53] the USPTO determined that FDA's approval of Ceftin was not the "first permitted commercial marketing or use of the product" and denied the patent-term extension.[54]

The Federal Circuit held that the USPTO's denial of the patent term extension was contrary to law, affirming the district court's judgment.[55] In contrast to the D.C. Circuit, which viewed the relevant statutory language as ambiguous, the Federal Circuit held that the terms in the phrase "active ingredient of a new drug . . . including any ester or salt of the active ingredient" all have a plain meaning.[56] The court determined—without discussing its reasoning in any detail—that the

[43] 920 F.2d 984, 986 (D.C. Cir. 1990).

[44] *Id.*

[45] *Id.* at 987-88.

[46] *Id.* at 988.

[47] *Id.*

[48] *Id.* at 989-90.

[49] Glaxo Operations UK Ltd. v. Quigg, 894 F.2d 392, 393-94 (Fed. Cir. 1990).

[50] 35 U.S.C. § 156(a) & (f).

[51] *Id.* § 156(f)(2).

[52] Glaxo Operations UK Ltd., 894 F.2d at 394.

[53] Glaxo Operations UK Ltd. v. Quigg, 706 F. Supp. 1224, 1225-26 (E.D. Va. 1989).

[54] Glaxo Operations UK Ltd., 894 F.2d at 394.

[55] *Id.* at 399-400.

[56] *Id.* at 395.

USPTO's interpretation was inconsistent with the plain meaning of these terms.[57] While acknowledging that legislative history can reveal "a *clearly expressed* legislative intention contrary to the statutory language," it identified no such support for the USPTO's interpretation here.[58] Because the court found there was no clear legislative intent that the phrase be interpreted to refer to variations on the approved active ingredients beyond that product's ester or salt, an extension of the term for the patent claiming cefuroxime axetil was warranted because FDA had not approved that drug product or an ester or salt of it.[59] While the appellate court did not elaborate on how it arrived at its interpretation, the district court had included more detail on the plain meaning of the operative statutory phrase, concluding that cefuroxime—the acid from which cefuroxime axetil is derived—could not be an "active ingredient" of Ceftin because it was not an *ingredient*, as that term is commonly understood because it did not appear in the Ceftin tablets in that form.[60]

Final Rule. In the wake of these rulings, public comments to FDA's proposed rule contended that *Abbott Laboratories* and *Glaxo Operations* rejected the agency's proposed interpretation of the NCE exclusivity provision, particularly its reliance on the phrase active moieties.[61] Nonetheless, when FDA finalized its NCE exclusivity regulations in 1994, the agency included its proposed definition of "active moiety," but modified its justification.[62] Rather than interpreting the *parenthetical phrase* (i.e., "(including any ester or salt of the active ingredient)") "broadly to include all active ingredients that are different but contain the same active moiety," which the D.C. Circuit in *Abbott Laboratories* had rejected as "linguistically impermissible," the agency concluded that the *term "*active ingredient," as used in the relevant provision, means active moiety.[63] FDA did not, however, directly address the Federal Circuit's opinion.

FDA also disagreed with comments objecting to its inclusion of other noncovalent derivatives in the definition of "active moiety," meaning that such derivatives would not receive NCE exclusivity. The agency reaffirmed that it "does not believe that providing exclusivity for . . . noncovalent derivatives of a previously approved active moiety would be consistent with the statutory intent" because such derivatives "generally do[] not affect the active moiety of a drug product."[64] FDA accordingly enacted the definition of active moiety as proposed.

D.C. Circuit Upholds FDA Use of Pre-Ingestion Rather than Post-Ingestion to Interpret Active Ingredient. In 2010, in *Actavis Elizabeth LLC v. FDA*, the D.C. Circuit revisited FDA's interpretation of "active ingredient," nearly two decades after the agency finalized its regulations in 1994.[65] That opinion focused specifically on the term "active ingredient" in the context of whether the relevant molecule should be considered prior to its ingestion in the human body (i.e., the compound in the final drug product pre-ingestion) or after ingestion where the compound may convert to another related compound (e.g., from an ester to an acid) that is responsible for the drug's therapeutic effects (i.e., post-ingestion).[66] A generic manufacturer challenged FDA's award

[57] *Id.*

[58] *Id.* at 395-400.

[59] *Id.* at 395-99.

[60] Glaxo Operations UK Ltd. v. Quigg, 706 F. Supp. 1224, 1227-28 (E.D. Va. 1989).

[61] 59 Fed. Reg. 50,338, 50,357-58 (Oct. 3, 1994).

[62] *Id.*

[63] *Id.*

[64] *Id.* at 50,358.

[65] Actavis Elizabeth LLC v. FDA, 625 F.3d 760, 764-66 (D.C. Cir. 2010).

[66] *Id.* Note that the court in *Abbott Laboratories v. Young* had explained the distinction between active ingredient and

of NCE exclusivity for Vyvanse, a drug that treats attention deficit hyperactivity disorder.[67] Vyvanse's active ingredient is lisdexamfetamine dimesylate, a salt of lisdexamfetamine, meaning that lisdexamfetamine is the active moiety under FDA regulations.[68] Lisdexamfetamine uses an amide bond (a type of covalent bond involving nitrogen) to connect a portion of lysine, a common amino acid, with dextroamphetamine.[69] Once in the body, a chemical reaction converts lisdexamfetamine to dextroamphetamine.[70] FDA had approved drugs with dextroamphetamine but had not yet approved drugs with lisdexamfetamine.[71]

Actavis, a generic manufacturer seeking to market a generic version of Vyvanse, alleged that because dextroamphetamine is responsible for the therapeutic effect inside the body and FDA had previously approved drugs with dextroamphetamine, Vyvanse had no right to NCE exclusivity.[72] Focusing on the term "active," Actavis contended that "active ingredient" necessarily must refer to "the drug molecule that reaches the 'site' of the drug's action" because that is the part of the drug responsible for its "activity," which Activis argued meant the therapeutic effect.[73]

The court rejected Actavis's arguments. First, the court observed that the FD&C Act does not define the term "active ingredient" and that the statute's legislative history "is silent on what determines novelty" for NCE exclusivity.[74] The court also concluded that the statute's structure and purpose did not preclude FDA's interpretation.[75] Accordingly, the court held that (1) "active ingredient" is ambiguous as to whether it referred to the pre-ingestion or post-ingestion molecule, and (2) FDA's interpretation of "active ingredient" to refer to the pre-ingestion molecule is reasonable.[76]

The court further affirmed FDA's choice of a bright-line distinction between noncovalent derivatives (which do not receive NCE exclusivity) and non-ester covalent derivatives (which can receive NCE exclusivity and was at issue for Vyvance). While the D.C. Circuit acknowledged that some noncovalent bonds might alter a drug's properties and some covalent bonds might not,[77] the court deferred to FDA's explanation that "its policy is based in part on the 'difficulty in determining precisely which molecule, or portion of a molecule, is responsible for a drug's effects.'"[78] The court did not, however, directly address FDA's use of the term "active moiety," its inclusion of the other noncovalent derivatives in the definition, or the interaction between FDA's definition of active moiety and the statutory parenthetical.

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active moiety as the former being "the substance prior to introduction into the human body" and the latter being "the substance that creates the actual therapeutic effect within the body." 920 F.2d 984, 986 (D.C. Cir. 1990). While this distinction may be accurate for some drugs if the active ingredient converts to the active moiety inside the body, this explanation is not fully consistent with FDA's regulatory definition of "active moiety" or with FDA's analysis in practice. *See, e.g.*, Actavis Elizabeth LLC v. FDA, 625 F.3d 760, 764-66 (D.C. Cir. 2010).

[67] *Actavis Elizabeth LLC*, 625 F.3d at 762.

[68] *Id.* at 762-63.

[69] *Id.* at 763.

[70] *Id.*

[71] *Id.*

[72] *Id.* at 762.

[73] *Id.*

[74] *Id.*

[75] *Id.*

[76] *Id.* at 765-66.

[77] *Id.* at 766.

[78] *Id.*

District Court Rejects FDA Interpretation of Active Ingredient as Active Moiety. Five years later, in *Amarin Pharmaceuticals Ireland Ltd. v. FDA*, a federal district court in the District of Columbia expressly considered FDA's interpretation of "active ingredient" to mean "active moiety," as defined in its regulations.[79] Amarin had obtained FDA approval for Vascepa**,** whose active ingredient is icosapent ethyl, the ethyl ester of eicosapentaenoic acid (EPA), a type of omega-3 fatty acid.[80] But FDA denied Amarin's request for NCE exclusivity for Vascepa because it had previously approved Lovaza, a drug whose active ingredient is "a mixture that is primarily composed of seven kinds of omega-3 fatty acid ethyl esters" including the ester of EPA.[81] When FDA approved Lovaza, it considered the mixture as a whole the "active ingredient," and it later denied a petition from Lovaza's sponsor requesting FDA to recharacterize Lovaza as having multiple active ingredients on the grounds that "the Lovaza mixture has not been 'fully characterized.'"[82] In other words, in approving Lovaza, FDA did not specifically approve an ester of EPA (or any other component omega-3 fatty acid ethyl esters) as an active ingredient. But when evaluating Vascepa's eligibility for NCE exclusivity, FDA relied on new studies to find that EPA was an active moiety of Lovaza and that, accordingly, FDA had previously approved Vascepa's active moiety.[83]

Rather than recognize multiple active ingredients in Vascepa, FDA provided a new interpretation framework for certain mixtures to treat them as having one *active ingredient* but multiple *active moieties*. In its decision letter to Amarin, FDA acknowledged that the agency had previously taken an inconsistent approach to identifying the active ingredients and active moieties for naturally derived mixtures, such as Lovaza, when evaluating NCE exclusivity.[84] FDA "explained that, although they are often conflated, it is important to distinguish between the meaning of the terms active ingredient and active moiety."[85] And that while "the distinction between active moiety and active ingredient[] generally is negligible" for "drugs that are composed of a single, well-characterized molecule," "the distinction between active ingredient and active moiety . . . becomes crucial" "[f]or naturally derived mixtures comprising multiple molecules."[86]

Critically, the agency distinguished between (1) "poorly characterized" and (2) "well-characterized mixtures" based on how difficult it is "'to determine with any certainty . . . which molecules in the mixture are consistently present or potentially are responsible for the physiological or pharmacological activity of the drug.'"[87] For *poorly characterized* mixtures, FDA stated that it had "of necessity" treated the whole mixture as both the active ingredient and the active moiety.[88] However, for *well-characterized* mixtures, FDA outlined "a three-part 'framework' 'for identifying the active moiety or moieties of such mixtures.'"[89] FDA would consider component parts of well-characterized mixtures to be previously approved active moieties if

[79] 106 F. Supp. 3d 196, 208 (D.D.C. 2015).

[80] *Id.* at 202.

[81] *Id.* at 201.

[82] *Id.*

[83] *Id.* at 203-04.

[84] *Id.* at 203.

[85] *Id.* at 204 (internal quotations omitted) (referencing FDA decision letter).

[86] *Id.* (internal quotations omitted).

[87] *Id.*

[88] *Id.*

[89] *Id.*

1. specific molecules in the mixture have been identified;
2. those specific molecules are "consistently present in the mixture"; and
3. those molecules are "responsible at least in part for the physiological or pharmacological action of the mixture, based on a finding that they make a meaningful contribution to the activity of the mixture."[90]

In effect, for single-molecule and poorly characterized drugs, FDA would apply a one-to-one approach between the active ingredient and active moiety, but for well-characterized mixtures, it would apply a one-to-many approach: one active ingredient with multiple active moieties.[91]

The district court set aside FDA's decision denying NCE exclusivity for Vascepa based on its interpretation of "active ingredient" to mean "active moiety".[92] The court first relied on the canon against surplusage, finding that FDA's interpretation of the term "active ingredient" "would render the parenthetical clause in the exclusivity provisions either redundant or incomprehensible."[93] By defining active moiety to *exclude* "those appended portions of the molecule that cause the drug to be an ester, salt . . . or other noncovalent derivative,"[94] the court concluded that FDA rendered the statutory parenthetical "(including any ester or salt of the active ingredient)" either unnecessary or incomprehensible.[95] The court reasoned that FDA in effect read the parenthetical out of the statute by inserting "active moiety" in place of "active ingredient," violating the canon against surplusage that assumes Congress does not include unnecessary language in a statute.[96]

The court then used the presumption of consistent usage to reject FDA's view of active ingredient as synonymous with active moiety.[97] Significantly, FDA only interpreted active ingredient to mean active moiety with respect to the FD&C Act's *exclusivity provisions*, relying on alternative interpretations of "active ingredient" elsewhere in the statute, such as, perhaps most notably, the provision allowing sponsors to submit abbreviated NDAs for generic drugs with the same active ingredient as an approved drug.[98] FDA argued that it was justified in adopting different interpretations of the same phrase in different parts of the statute because the provisions had different statutory purposes.[99] The agency contended that because the abbreviated NDA process focuses on safety and efficacy, a narrower range of molecules should be considered identical to previously approved drugs to ensure that FDA conducts a full review for safety and efficacy of any drugs that may clinically differ from previously approved drugs.[100] In contrast, FDA argued that the exclusivity provisions aim to encourage innovation, requiring a wider range of molecules

[90] *Id.*

[91] *Id.* at 204-205.

[92] *Id.* at 217-19.

[93] *Id.* at 209.

[94] 21 C.F.R. § 314.3.

[95] Amarin Pharm. Ireland Ltd. v. FDA, 106 F. Supp. 3d 196, 209 (D.D.C. 2015).

[96] *Id.* FDA offered an alternative interpretation that active moiety replaced the entire phrase "an active ingredient (including any ester or salt of the active ingredient)" rather than simply "active ingredient." *Id.* at 215-16. The court rejected this interpretation as well. *Id.* First, the court found that FDA had not relied on this interpretation in either its final rule or its decision letter. *Id.* Second, the court determined that this interpretation raises the same issues identified by the D.C. Circuit in *Abbott Laboratories v. Young*. *Id.*

[97] *Id.* at 210.

[98] *Id.*

[99] *Id.* at 210-11.

[100] *Id.*

to be considered previously approved to ensure the new drug is truly innovative.[101] While acknowledging that "the presumption of consistent usage is not unrebuttable," the court considered FDA's justifications for the differing interpretations of active ingredient unpersuasive.[102] The court observed that Congress passed both provisions at the same time in the same part of the same statute, that the abbreviated NDA provisions and exclusivity provisions were two sides of the same coin intended to balance competition and innovation, and that Congress included the parenthetical "including any ester or salt of the active ingredient" in the exclusivity provision but *not* the abbreviated NDA provision, thus already distinguishing between the two provisions.[103]

Finally, the court determined that FDA's use of active moiety was inconsistent with the statutory requirement that the active ingredient "has been approved."[104] It noted that FDA approves active ingredients, not active moieties, and that under FDA's proposed framework it would not even determine the relevant active moiety under another drug applied for exclusivity.[105] Accordingly, an active moiety would never have previously been approved.[106]

Rejecting each of FDA's arguments and concluding FDA's interpretation invalid on multiple grounds, the court set aside the specific administrative decision being challenged in that case—that is, FDA's exclusivity determination for Vascepa—and remanded to FDA.[107] The court did not, however, explicitly invalidate or set aside FDA's implementing regulations.[108] FDA regulations therefore remain in place, but with questions looming as to their validity and defensibility.[109]

FDA's Definition of Active Moiety

Beyond whether FDA can interpret the phrase "active ingredient" in the FD&C Act's exclusivity provisions to mean active moiety, how FDA has defined "active moiety" has also been the subject of legal challenges. The statutory parenthetical includes esters and salts of an active ingredient as the same active ingredient for determining exclusivity, meaning that an ester and salt of an active ingredient is ineligible for exclusivity.[110] FDA's definition of active moiety extends beyond those two derivatives, however, to also include molecules with *other noncovalent appendages*.[111] At the same time, the agency *excludes* from its definition of active moiety molecules with appendages

[101] *Id.*

[102] *Id.* at 211-12.

[103] *Id.*

[104] *Id.* at 213.

[105] *Id.* at 214.

[106] *Id.*

[107] *Id.* at 219. On remand, FDA determined that Vascepa was eligible for NCE exclusivity. Letter from Janet Woodcock, Director, Center for Drug Evaluation and Research, Food & Drug Admin, to Robert A. Dormer, Hyman, Phelps & McNamara, P.C. (Counsel for Amarin Pharmaceuticals Ireland Ltd.) (May 31, 2016) http://www.fdalawblog.net/wp-content/uploads/archives/docs/VASCEPA%20-%20Exclusivity%20Determination%20on%20Remand.pdf (conveying decision on exclusivity for Vascepa (icosapent ethyl) capsules (NDA 202057)).

[108] *See* Letter from Janet Woodcock to Robert A. Dormer, *supra* note 107, at 13.

[109] Watson Laboratories filed an appeal, but the D.C. Circuit dismissed the appeal on the grounds that the district court order remanding the decision to FDA was not a final appealable order. Amarin Pharm. Ireland Ltd. v. FDA, No. 15-5214, 2015 WL 9997417 (D.C. Cir. 2015).

[110] 21 U.S.C. §§ 355(c)(3)(E)(ii), 355(j)(5)(F)(ii).

[111] 21 C.F.R. § 314.3.

attached through *non-ester covalent* bonds, meaning that drug molecules that differ from previously approved drugs based on such appendages would be eligible for NCE exclusivity.[112] Brand name manufacturers have challenged including other noncovalent derivatives, which limits the availability of NCE exclusivity, while generic manufacturers have challenged excluding non-ester covalent derivatives, which expands the availability of NCE exclusivity.

Other Derivatives with Noncovalent Bonds. As discussed above, *Abbott Laboratories v. Young* also addressed FDA's inclusion of other noncovalent derivative forms of the molecule in addition to salts and esters, which the statute explicitly includes.[113] At the time, FDA relied on a broad interpretation of the word "including" to justify examining the base molecule without salts, esters, or any other component connected by noncovalent bonds.[114] The agency viewed the term "including" as providing *examples* of molecules that would be considered minor modifications that do not merit five-year NCE exclusivity, rather than an exhaustive list.[115] While the *Abbott Laboratories* court considered FDA's approach defensible on policy grounds, it considered the agency's approach "linguistically infeasible."[116] It stated that it "cannot agree with [FDA's] unconvincing attempts to employ the 'including' clause to cover all possible permutations of active ingredient," distinguishing the NCE exclusivity "including" clause "from instances where an 'including' clause is designed to merely illustrate a few examples of the general category."[117] Rather than provide its own interpretation, however, the court remanded the decision to FDA.[118]

FDA subsequently modified its interpretation of the statutory language in its 1994 final regulations. Rather than interpret the parenthetical phrase, the agency concluded that the term "active ingredient" means "active moiety," as defined in its regulations.[119] In so doing, FDA reaffirmed its view that allowing NCE exclusivity for other noncovalent derivatives would be inconsistent with statutory intent.[120]

In 2015, as explained above, *Amarin Pharmaceuticals Ireland Ltd. v. FDA* rejected FDA's revised interpretation.[121] However, because the court only set aside the challenged agency action at issue in that case without invalidating FDA regulations, FDA regulations remain in force with its original definition of "active moiety."[122]

Derivatives with Non-Ester Covalent Bonds. As discussed above, in *Actavis Elizabeth LLC v. FDA*, the D.C. Circuit upheld FDA's decision to exclude derivatives with different *covalent* bonds from its definition of active moiety.[123] Unlike noncovalent bonds, covalent bonds entail the sharing of electrons between molecules, which tends to create a stronger bond.[124] The court held that FDA's policy was reasonably "based on its view that drug derivatives containing non-ester

[112] *Id.*

[113] 920 F.2d 984, 988 (D.C. Cir. 1990).

[114] *Id.* at 987.

[115] *Id.* at 987-88.

[116] *Id.* at 988.

[117] *Id.*

[118] *Id.* at 989-90.

[119] 59 Fed. Reg. 50,338, 50,358.

[120] *Id.*

[121] Amarin Pharm. Ireland Ltd. v. FDA, 106 F. Supp. 3d 196, 217-19 (D.D.C. 2015).

[122] *Id.* at 219.

[123] 625 F.3d 760, 765-66 (D.C. Cir. 2010).

[124] HARVEY LODISH ET AL., MOLECULAR CELL BIOLOGY §§ 2.1 & 2.2 (4th ed. 2000).

covalent bonds are, on the whole, distinct from other types of derivative drugs such that the former are uniquely deserving of 'new chemical entity' status and the resulting five-year exclusivity."[125] In particular, the court pointed to a 1989 response letter from FDA to a citizen petition. In that letter, the agency explained that "even minor covalent structure changes are capable of producing not only major changes in the activity of the drug but changes that are not readily predicted." Nonetheless, FDA observed that "the formation of a salt . . . or of an ester, is not intended to, and generally cannot, alter the basic pharmacologic or toxicologic properties of the molecule."[126] Accordingly, without holding directly on whether FDA reasonably *included* other noncovalent derivatives in its active moiety definition, the court held that FDA's *exclusion* of non-ester *covalent* derivatives was reasonable.[127]

Legislative Proposals in the 116th Congress

Against this backdrop of decades of complex litigation over FDA's interpretation of active ingredient, three bills have been introduced in the 116th Congress that address this issue. [128] Each proposed legislation would generally (1) codify FDA's interpretation that eligibility for NCE exclusivity should be based on the drug's active moiety and (2) incorporate FDA's definition of active moiety by reference.[129] Specifically, the proposed legislation would do so by replacing the entire phrase "active ingredient (including any ester or salt of the active ingredient)" with "active moiety (as defined by the Secretary in section 314.3 of title 21, Code of Federal Regulations (or any successor regulations))" wherever it is found, except for a few provisions that expired in 1984.[130] This change would be made to several FD&C Act provisions, including the NCE exclusivity provision, three-year exclusivity for other changes, and provisions providing priority review vouchers for tropical disease treatments, rare pediatric disease treatments, and countermeasures for agents that threaten national security. [131]

Adopting this interpretation would resolve certain legal uncertainties under current case law. In *Amarin Pharmaceuticals v. FDA*, the court rejected FDA's interpretation but did not explicitly invalidate FDA's regulations.[132] Though it left FDA's interpretation in place, the court's decision left uncertain FDA's ability to defend its interpretation going forward. The proposed legislation would address those questions by adopting FDA's interpretation.

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[125] *Actavis Elizabeth LLC*, 625 F.3d at 765-66.

[126] *Id.*

[127] *Id.*

[128] The three bills are S. 1636, S. 1895, and H.R. 4955. S. 1636, and H.R. 4955 are stand-alone bills that would only amend the term "active ingredient (including any ester or salt of the active ingredient)." S. 1895 is a larger bill intended to address multiple facets of healthcare costs, with the active moiety component being found in Section 208. Though the exact provisions vary slightly, each of the bills would replace "active ingredient (including any ester or salt of the active ingredient)" with active moiety as defined by FDA regulations in the provisions identified. Accordingly, the three bills together are referred to as the "proposed legislation."

[129] *See generally* S. 1636, 116th Cong. (2019); S. 1895, 116th Cong. § 208 (2019); H.R. 4955, 116th Cong. (2019).

[130] *See generally* S. 1636; S. 1895; H.R. 4955. Specifically, the bills would amend 21 U.S.C. § 355(c)(3)(E)(ii) & (iii); 21 U.S.C. § 355(j)(5)(F)(ii) & (iii); 21 U.S.C. § 355(l)(2)(A)(i); 21 U.S.C. § 355(s); 21 U.S.C. § 355(u)(1); 21 U.S.C. § 360b(c)(2)(F)(i), (ii), and (v); 21 U.S.C. § 360n(a)(4)(C); 21 U.S.C. § 360ff(a)(4)(A)(ii); and 21 U.S.C. § 360bbb-4a(a)(4)(D). Note that it is unclear whether FDA currently uses its definition of active moiety in 21 C.F.R. § 314.3 when administering all of these provisions.

[131] S. 1636; S. 1895; H.R. 4955.

[132] 106 F. Supp. 3d 196, 219 (D.D.C. 2015). *See also* supra note 108.

The proposed legislation would also resolve the questions that have been raised as to whether FDA's decision to include other noncovalent derivative forms of the molecule in its definition of active moiety, but not other covalent derivatives, accords with congressional intent and a justifiable distinction. The proposed legislation would both adopt FDA's current approach, by incorporating FDA's current definition, and allow FDA to modify its approach going forward as its understanding changed, by including any successor regulations.[133] In effect, the proposed legislation would commit the decision as to which molecules should be deemed effectively the same and therefore not innovative enough to merit NCE exclusivity to FDA's judgment.

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[133] S. 1636; S. 1895; H.R. 4955.