DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

JUL 2 2004

Bert W. Rein
William A. McGrath
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1776 K Street, N.W.
Washington, D.C. 20006

Re: Docket No. 2004P-0227/CP1

Dear Messrs. Rein and McGrath:

This letter responds to your citizen petition dated May 11, 2004 (Petition), submitted on behalf of Pfizer Inc (Pfizer). In the Petition, you ask that the Food and Drug Administration (FDA or the Agency): (1) acknowledge that the market exclusivity ("180-day exclusivity") awarded under section 505(j)(5)(B)(iv) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 355(j)(5)(B)(iv)) cannot be waived; (2) deny any request for the Agency to issue a final approval for abbreviated new drug applications (ANDAs) 75-435 and 75-827 submitted by Teva Pharmaceutical Industries, Ltd. (Teva), or for any other ANDAs for gabapentin capsules or tablets, until the expiration of the 180-day exclusivity period applicable to the ANDA held by Purepac Pharmaceutical Co. (Purepac) for gabapentin capsules; and (3) deny any other requests for transfer or waiver of the statutory bar "set forth in section 505(j)(5)(B)(iv)". Petition at 2. This letter also considers the comments, dated June 4, 2004, submitted on behalf of Teva and Purepac (Comments).[1]

As discussed below, the Agency's legal interpretation and practice have long permitted both waiver and relinquishment of 180-day exclusivity. This practice: (1) is based on a permissible statutory construction as acknowledged by the courts, (2) is consistent with the Agency's long-standing allowance of waiver and relinquishment of other forms of market exclusivity,

[1] The Petition does not request, and this response does not provide, an Agency interpretation of section 505(j)(5)(B)(iv) as amended by the Access to Affordable Pharmaceuticals provisions at Title XI of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA), Pub. L. No. 108-173, 117 Stat. 2066 (December 8, 2003). *See* Petition at n.1. As the Petition indicates, the MMA made a number of changes to the statutory scheme in section 505(j) governing 180-day exclusivity, including providing for forfeiture of the exclusivity. *See* 21 U.S.C. 355(j) (2004). However, the relevant Title XI provisions concerning 180-day exclusivity apply only to drug products for which the first ANDA containing a paragraph IV certification to a listed patent (*see* section I.A *infra* explaining the certification process) was submitted after December 8, 2003. *See* MMA, section 1102(b)(1), 117 Stat. 2066, 2460 (2003). Accordingly, the non-amended version of section 505(j)(5)(B)(iv) governs 180-day exclusivity for gabapentin and is referred to throughout this response, unless otherwise indicated. The Agency has not yet assessed whether the changes made by the MMA should result in a different approach to waiver or relinquishment for those applications subject to the new exclusivity provisions. The Agency requested public comment regarding the need for regulatory action to address the amendments Title XI makes to section 505. *See* 69 FR 9982, March 3, 2004 (comments were due by May 3, 2004).

(3) promotes marketplace competition among pharmaceuticals in furtherance of the objectives of the 1984 Drug Price Competition and Patent Term Restoration Act (Hatch-Waxman amendments), and (4) is consistent with FDA's role in regulating the public health as opposed to competitive business arrangements. In short, in the absence of a specific statutory directive to do so, we see no reason to prevent these private arrangements, which are not barred by the Act.

Petitioner argues, to the contrary, that (1) the plain meaning of the statutory language precludes waiver, (2) the courts demand such a reading, (3) waiver of other exclusivities is distinguishable, and (4) permitting waiver of 180-day exclusivity would create an incentive to file ANDAs to obtain a marketable waiver "asset." For the reasons presented below, we do not find these arguments persuasive.

FDA is a public health agency. We generally do not interfere with business arrangements of private parties unless there is a particular defined public health impact or the arrangement otherwise directly contravenes the Act. In the absence of a specific statutory mandate to deny parties the ability to contract with one another, FDA generally sees no reason to, and does not, restrict these business dealings.

Accordingly, the Agency denies the petitioned requests.

I. Waiver and Relinquishment of 180-Day Exclusivity Are Permissible Under the Act

A. 180-Day Exclusivity

An NDA holder must identify for inclusion with the listing for its approved drug in *Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book), patents claiming this "listed" drug or a method of using it. *See* section 505(b)(1) of the Act (21 U.S.C. 355(b)(1)). An ANDA applicant must include with its application a certification regarding each of these patents for the listed drug product upon which the ANDA relies. Specifically, an ANDA applicant must make one of the following four certifications (named for the statutory paragraph establishing each):

- Patent information has not been filed with the agency ("paragraph I");
- The patent has expired ("paragraph II");
- The date the patent will expire ("paragraph III"); or
- The patent is invalid, not infringed by the ANDA applicant's product, or unenforceable ("paragraph IV").[2]

An applicant need not certify to patents claiming uses for which the applicant is not seeking approval. *See* section 505(j)(2)(A)(viii) of the Act (21 U.S.C. 355(j)(2)(A)(viii)).

[2] 21 U.S.C. 355(j)(2)(A)(vii); 54 FR 28,872, 28,885-88, July 10, 1989. Section 505(b)(2)(A) establishes equivalent certification requirements for applications submitted under section 505(b)(2) (21 U.S.C. 355(b)(2)), but the 180-day exclusivity provisions do not apply to these applications. *See* 21 U.S.C. 355(b)(2)(A), 355(j)(5)(B)(iv).

As described in Agency regulations and guidances, section 505(j)(5)(B)(iv) of the Act provides that an ANDA applicant is eligible for 180-day exclusivity if (1) the applicant includes in its application a paragraph IV certification challenging the validity or applicability to its product of a listed patent, and (2) the applicant is first to submit a paragraph IV certification to that patent. As interpreted by the Agency and the courts, exclusivity with respect to a patent is triggered by the earlier of (1) a court decision of non-infringement or invalidity of the patent, or (2) commercial marketing of the drug by an ANDA applicant eligible to receive 180-day exclusivity. 21 U.S.C. 355(j)(5)(B)(iv); 21 C.F.R. 314.107(c); *Granutec Inc. v. Shalala*, 139 F.3d 889, 1998 WL 153410 (4th Cir. 1998) (unpublished table opinion) (holding that 180-day exclusivity is not triggered solely by a ruling in favor of an applicant eligible for the exclusivity). Because exclusivity can be triggered by a court decision or by the commercial marketing of another applicant who shares exclusivity, it may begin to run before an eligible ANDA applicant can market its own product.[3]

Section 505(j)(5)(B)(iv) of the Act states:

> If the application contains a certification described in subclause (IV) of paragraph (2)(A)(vii) and is for a drug for which a previous application has been submitted under this subsection [containing] such a certification, the application *shall be made effective not earlier than one hundred and eighty days after—*
>
> (I) the date the Secretary receives notice from the applicant under the previous application of the first commercial marketing of the drug under the previous application, or
>
> (II) the date of a decision of a court . . . holding the patent which is the subject of the certification to be invalid or not infringed,
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> whichever is earlier.[4] (emphasis added)

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[3] 21 U.S.C. 355(j)(5)(B)(iv); 21 C.F.R. 314.107(c). Multiple ANDA applicants can be eligible for 180-day exclusivity if they each submit a paragraph IV certification on the first day that any applicant submits a paragraph IV certification to the patent. In other words, multiple ANDA applicants can potentially share 180-day exclusivity as to the same patent. *See* FDA guidance for industry on *180-Day Exclusivity When Multiple ANDAs Are Submitted on the Same Day* (July 2003) (all FDA guidances are available on the Internet at http://www.fda.gov/cder/guidance/index.htm). Similarly, shared exclusivity can arise because different ANDA applicants are first to submit paragraph IV certifications to different patents for the same drug. *See* Letter from Gary Buehler, Director, Office of Generic Drugs, to Diane Servello, Andrx Pharmaceuticals, Inc. (Nov. 16, 2002) (available on the FDA Web site at http://www.fda.gov/cder/ogd/shared_exclusivity.htm); *Apotex Inc. v. FDA*, No. 04-0605 (D.D.C. June 3, 2004), *appeal pending* No. 04-5211 (D.C. Cir.). Waiver and relinquishment are permitted in these situations as well.

[4] Courts reviewing the statute have commented that the word "continuing" reflects a typographical error and should be "containing." *See, e.g., Purepac Pharm. Co. v. Friedman*, 162 F.3d 1201, 1203 n.3 (D.C. Cir. 1998); *Mova Pharm. Corp. v. Shalala*, 140 F.3d 1060, 1064 n.3 (D.C. Cir. 1998).

B. Ambiguity of Statutory Language

The apparently mandatory statutory language "*shall* be made effective not earlier than . . ." (emphasis added) in section 505(j)(5)(B)(iv) presents as a threshold question whether the Agency has discretion to interpret the provision to permit waiver or relinquishment of the 180-day exclusivity conferred. If a statute is ambiguous or silent, the implementing agency may base its interpretation on a permissible construction. *See Mova*, 140 F.3d at 1067 (citing *Chevron U.S.A. Inc. v. Natural Resources Defense Council, Inc.*, 467 U.S. 837, 843 (1984)).

The section can reasonably be considered ambiguous on the issue of waiver and relinquishment. Although the provision compels the Agency to delay approval of subsequent applications, it has the effect of conferring a specific benefit (marketing exclusivity) upon specific private entities (eligible ANDA applicants). As a result, it is not clear whether the statute requires the Agency to impose this 180-day delay without exception, or only unless an alternate approach (*e.g.*, waiver or relinquishment) would better serve the beneficiary of the exclusivity. By binding the Agency to impose this delay, the statute ensures that the Agency will provide the specific beneficiary with the specific benefit. Although the provision could reasonably be interpreted to preclude the Agency from curtailing or withholding the benefit even if the beneficiary were to prefer such a course of action, the plain meaning does not compel that conclusion. Rather, the provision could also be interpreted to establish a default compelling the Agency to confer the benefit, *unless* a beneficiary prefers to limit or relinquish it.

The section also can reasonably be viewed as silent on the question of waiver and relinquishment. Plainly, it does not expressly address the permissibility of either. Furthermore, waiver (or relinquishment) in this context presents a somewhat special case for statutory construction. Where, as here, statutory language compelling government action has the effect of benefiting specific private entities (in this case, granting 180 days of marketing exclusivity to eligible ANDA applicants), judicial precedent, as discussed below, supports inferring from silence a legislative intent to allow an alternative course of action more favorable to the beneficiary of the government act (such as permitting eligible ANDA applicants to waive or relinquish the exclusivity).

C. Agency Permitted Waiver and Relinquishment of 180-Day Exclusivity and Judicial Acknowledgement

Since first considering the question in 1997 with regard to a request by Genpharm to waive its exclusivity for ranitidine hydrochloride (a treatment for acid reflux disease) in favor of Granutec (*see Boehringer Ingelheim Corp. v. Shalala*, 993 F. Supp. 1, 2 (D.D.C. 1997), FDA has consistently interpreted section 505(j)(5)(B)(iv) of the Act to permit both waiver and relinquishment of 180-day exclusivity benefits. In a proposed rule published in August 1999, the Agency described its practice and proposed regulations to codify it. (The Agency subsequently withdrew the proposal on unrelated grounds; *see* 67 FR 66,593, 66,594, November 1, 2002 (explaining Agency decision to withdraw the proposed rule in light of subsequent court decisions at odds with portions of the proposal unrelated to waiver or relinquishment of exclusivity)). As explained in that notice, an ANDA applicant who has obtained 180-day exclusivity may relinquish its exclusivity entirely or selectively waive the exclusivity in favor of a single ANDA,

or multiple ANDAs, containing a paragraph IV certification. Before the exclusivity period has been triggered, an applicant may only relinquish its exclusivity; after the exclusivity has been triggered, it may be selectively waived.[5]

The Agency has permitted many ANDA applicants to waive or relinquish 180-day exclusivity. These waivers have led to approvals of ANDAs for ranitidine, ibuprofen, terazosin, verapamil, omeprazole, bupropion, calcitriol, and metformin.

As to Purepac, it has obtained 180-day exclusivity by having been the first applicant to challenge one of the listed patents for gabapentin. *See Purepac Pharm. Company v. Thompson*, 354 F.3d 877, 881-83 (D.C. Cir. 2004). Teva has ANDAs that are tentatively approved for gabapentin tablets and capsules that include a paragraph IV certification to the same patent challenged by Purepac. *Id.* at 882-83. Accordingly, once Purepac's exclusivity has begun to run with a court decision or commercial marketing, long-standing Agency policy and practice would permit Purepac to selectively waive its 180-day exclusivity to permit approval and marketing of gabapentin by Teva (or any other otherwise eligible applicant with a gabapentin ANDA).

No court that has addressed the issue has questioned the practice of permitting waiver and relinquishment of 180-day exclusivity. Indeed, the district court for the District of Columbia upheld the practice in *Boehringer*, 993 F. Supp. at 2. The court addressed a motion filed by

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[5] *See* 64 FR 42,873, 42,881, August 6, 1999. The Agency has limited the availability of selective waiver in this manner based on two factors: (1) the extent to which the right to block approval of subsequent ANDAs has actually "vested" in an ANDA applicant and (2) Agency concern that permitting selective waiver before exclusivity is triggered could lead to the "commercialization" of the first applicant "seat." Such an approach might encourage applicants to submit only marginally adequate ANDAs solely to obtain the economic benefit of waiving the exclusivity as to an applicant with a more viable ANDA.

Regarding "vesting," there are many reasons why an ANDA applicant might lose its eligibility before the exclusivity period has been triggered. For instance, the applicant could withdraw its ANDA containing the paragraph IV certification, the patent could expire necessitating a change to a paragraph II certification to that effect, or the applicant could lose or settle its patent litigation resulting in the change to a paragraph III certification (which signals that the applicant is not seeking approval until after the patent expires). *See* 21 U.S.C. 355(b)(2)(A), (j)(2)(A)(vii); 21 C.F.R. 314.94(a)(12)(viii). Each of these situations has arisen, and in each case the first applicant has lost its claim to exclusivity. *See, e.g., Mylan Pharms. Inc. v. Henney*, 94 F. Supp. 2d 36, 56-58 (D.D.C. 2002) (amendment from a paragraph IV to a paragraph III certification terminated eligibility for 180-day exclusivity under Agency regulations), *vacated as moot*, 276 F.3d 627 (D.C. Cir. 2002); *Dr. Reddy's Labs., Inc. v. Thompson*, 302 F. Supp. 2d 340, 350-58 (D.N.J. 2003) (180-day exclusivity lost upon patent expiration compelling the applicant to amend a paragraph IV to a paragraph II certification for the patent).

As to potential "gaming," if the first applicant could selectively waive its exclusivity at any time, the Agency could reasonably expect the development of a "market" for 180-day exclusivity, with a resulting increase in ANDAs submitted solely to claim exclusivity. Although these ANDAs might never qualify for approval, FDA would nonetheless have to review them as substantially complete, thus potentially wasting limited Agency resources.

Although FDA has stated that it does not consider exclusivity to be a property right that transfers separately and apart from an application (59 FR 50,338, 50,359, October 3, 1994), the Agency could foresee being drawn into complex private disputes regarding the economic and competitive impacts of a selective waiver "right" that is never "perfected" because the first applicant loses eligibility for that exclusivity. In short, FDA believes that by permitting selective waiver only once the exclusivity is triggered, it can prevent "gaming" of exclusivity, avoid unnecessary exclusivity disputes, and still maintain exclusivity as an adequate incentive and reward.

Boehringer to obtain a temporary restraining order to undo the Genpharm waiver permitting approval of Granutec's ranitidine hydrochloride (noted above). In its decision, the court acknowledged that the provision "does contain mandatory language" but concluded that that language did not speak to the permissibility of waiver. The court found that "[t]he statute is simply silent on the point, and certainly does not clearly express a statutory policy precluding waivers."[6] Two other courts have expressly recognized the legitimacy of the practice.[7] A fourth court has implicitly acknowledged its permissibility.[8]

As noted above, waiver of a mandate for a government agency to grant a benefit to a private entity presents a somewhat distinct question of statutory construction. Here, FDA does not simply interpret statutory language intended to achieve a regulatory intent. We interpret language intended to benefit specific private entities. *See Mova*, 140 F.3d at 1074-75. Accordingly, it is reasonable and appropriate for the Agency to take into consideration the interests and preferences of these entities, particularly to allow them to decide whether and to what extent to use the proffered benefit.

In interpreting equivalent, facially mandatory language in other contexts, courts have supported waiver in the absence of some affirmative indication of Congressional intent to preclude it, where the statutory mandate implicates a private benefit and waiver would not be inconsistent with legislative intent or the public interest.[9] Further, case law supports construction favorable to

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[6] 993 F. Supp. at 2. As discussed below, we disagree with petitioner's interpretation of the decision of the Court of Appeals for the District of Columbia Circuit in *Mova Pharmaceutical Corp. v. Shalala* as rejecting the rationale of the *Boehringer* decision. The court's holding did not preclude the Agency from interpreting the statute to address gaps or ambiguous language (*see* 140 F.3d at 1067).

[7] *See Dr. Reddy's*, 302 F. Supp. 2d at 350 (relying on Dr. Reddy's "entitlement under the law" to sell to another ANDA holder Dr. Reddy's exclusivity derived from a paragraph IV certification with respect to one patent, to conclude that a judicial finding that Dr. Reddy's product infringed a different patent did not moot judicial review of the Agency's 180-day exclusivity regulations); *Granutec*, 1998 WL 153410 at *9, 10 (concluding that loss of opportunity to market "does not strip exclusivity of all value . . . the ability to waive exclusivity in favor of another generic manufacturer can be quite lucrative," and holding that a subsequent ANDA applicant had not violated the period of exclusivity at issue because the exclusivity holder had "waived its exclusivity" with regard to that applicant).

[8] *See Valley Drug Co. v. Geneva Pharms., Inc.*, 344 F.3d 1294, 1310 n.23 (11th Cir. 2003) (noting that "it seems reasonable to assume" that a portion of the payments made by a brand drug company to a generic drug company under an agreement that, in part, required the generic not to waive its 180-day exclusivity, were made in return for that commitment not to waive exclusivity).

[9] *See, e.g., New York v. Hill*, 528 U.S. 110, 116-17 (2000) (holding defense counsel's agreement to a trial date outside the time period required by Article III of the Interstate Agreement on Detainers constituted a waiver of the requirement, the court found that a right conferred on a private party which also affects the public interest can be waived if its waiver does not "contravene the statutory policy"); *United States v. Mezzanatto*, 513 U.S. 196, 200-01 (1995) (holding waiver of exclusionary provisions of a plea agreement permissible unless entered into unknowingly or involuntarily, the court based its analysis on the presumption, to which "we instead have adhered " (citing criminal and civil rights cases), that waiver is available absent some affirmative indication of Congressional intent to preclude it).

those for whom a statutory benefit is chiefly intended.[10] In addition, courts have considered evidence of legislative intent, the nature and objective of the act as a whole, the relative benefit and harm to the public interest of alternate interpretations, and a comparison of the results to which each construction would lead.[11]

D. Plain Meaning Counter-Argument Fails

Pfizer asserts the Agency does not have discretion to permit waiver because the "plain meaning" of section 505(j)(5)(B)(iv) of the Act is clear. We disagree. Pfizer attempts to rely upon the *Mova* decision, among others, to support a plain meaning argument against the Agency's interpretation of the section, and to challenge the continued validity of the *Boehringer* decision that supports this Agency policy. The Petition quotes language from *Mova* and other courts to the effect that the specific statutory language at issue must be applied as written without regard for the statutory scheme as a whole or the legislative objectives. *See* Petition at 5, 8. We do not dispute whether a "plain meaning" approach is appropriate. However, we do not believe the approach need be applied in as crabbed a fashion as the petitioner suggests.[12] Rather, courts

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[10] *See, e.g., Brock v. Pierce County*, 476 U.S. 253, 261-62 (1986) (holding that the Secretary of Labor did not lose the authority to recover misused funds under the Comprehensive Employment and Training Act by failing to make a final determination within 120 days even though the statute stated that he "shall" make the determination within that time period, relying, in part, on the fact that a contrary conclusion would "prejudice individual complainants seeking to enforce their rights under CETA"); *Ralpho v. Bell*, 569 F.2d 607, 626-28 (D.C. Cir. 1977) (finding to be directory (as opposed to mandatory) a provision of the Micronesian Claim Act stating that the Micronesian Claims Commission "shall wind up its affairs . . . not later than three years after . . . the time for filing claims . . . ," the court looked to the "fundamental motivations for the congressional action," the congressional "design" as evidenced by the "mischief to be remedied" and contemporaneous statements, and a construction "that bestows the benefits of the Act on those for whom it was chiefly intended").

[11] *See, e.g., Brock*, 476 U.S. at 262-63 (basing its holding (*see supra* n.10) upon considerations of (1) injury to an underlying public interest in protection of the public fisc, (2) lack of evidence of Congressional intent to harm that interest, and (3) legislative history reflecting a desire to enhance agency efforts to address misuse of funds); *Conoco, Inc. v. Skinner*, 970 F.2d 1206, 1225-26 (3d Cir. 1992) (finding permissible a Maritime Administration interpretation of the phrase "shall be deemed a citizen" with respect to the operation of corporations as common carriers under the Shipping Act, the court relied upon the interpretive standard that whether "shall" should be construed as directory or mandatory is dependent on an examination of Congressional intent, including consideration of related statutory language); *United States v. St. Regis Paper Co.*, 355 F.2d 688, 691 (2d Cir. 1966) (holding to be jurisdictional (mandatory) the statutory requirement that the Federal Trade Commission "shall certify the facts" to the Attorney General if the Commission has reason to believe anyone is subject to a Commission cease and desist order, relying on the principle of statutory construction that whether "shall" should be construed as directory or jurisdictional is dependent on an examination of Congressional intent, including consideration of related statutory language, and also upon comparison of the results to which each statutory construction would lead); *Holbrook v. United States*, 284 F.2d 747, 752 (9th Cir. 1960) (holding the written consent of the Commissioner of the Internal Revenue Service not indispensable to the validity of a tax collection waiver, the court relied upon the principle of statutory construction that consideration should be given to the comparative results of the constructions in the absence of direct evidence of legislative intent).

[12] We note as well that petitioner's attempt to rely on this narrow application of "plain meaning" seems at odds with petitioner's support for, and policy arguments in favor of, current Agency practice that allows waiver of other marketing exclusivities, a practice based on Agency interpretation of parallel statutory language in other provisions of the Act. *See* section II.B *infra*.

seeking the plain meaning of a statutory provision consider statutory context, structure, and purpose, among other things.[13]

In *Mova*, the court did not base its holding on a facial reading of the language at issue in isolation, nor did it conclude that the Agency could not interpret statutory language in light of the larger statutory framework or the Act's objectives. 140 F.3d at 1067-68. Rather, the court concluded that the Agency could not interpret a statutory provision so as to nullify or be inconsistent with statutory language. In short, the court held that the specific interpretation adopted by the Agency could not "be reconciled" with the language of the statute.

The *Mova* court considered an Agency regulation implementing section 505(j)(5)(B)(iv) of the Act. The regulation required that the ANDA applicant eligible for 180-day exclusivity must win in court (have the patent found invalid or not infringed) to maintain its eligibility for the exclusivity (a "successful defense" standard). *See* 21 C.F.R. 314.107(c)(1) (1998). The court concluded that the Agency could have adopted a more narrowly tailored interpretation to effectuate its goal (of not allowing a first applicant to benefit from the exclusivity if the applicant either was not sued for patent infringement or was found infringing) and that the Agency's interpretation was inconsistent with the language of section 505(j)(5)(B)(iv). *Mova*, 140 F.3d at 1074. First, the court concluded that, by permitting approval of subsequent ANDAs before either trigger for 180-day exclusivity had been satisfied, the Agency's successful defense standard inappropriately stripped a first applicant of the exclusivity benefit "simply because the first applicant's [patent infringement] litigation has not yet come to a successful conclusion." *Id.* at 1069. Second, the court concluded that the Agency's interpretation nullified the commercial marketing trigger provided in the statute. The court reasoned that because an eligible ANDA applicant could not satisfy the successful defense standard unless it had won a patent infringement suit, the standard precluded triggering of the exclusivity, even if the applicant began marketing its product, until the applicant had won in court. *Id.* at 1069-70.

Such challenges cannot successfully be made to the Agency's interpretation of section 505(j)(5)(B)(iv) as permitting waiver and relinquishment of 180-day exclusivity. The interpretation does not nullify or conflict with other statutory language. In fact, as discussed below, the Agency has consistently interpreted equivalent statutory language in other marketing exclusivity provisions to permit waiver and relinquishment. As to the *Mova* court's particular concern with approval of subsequent applicants before any exclusivity trigger had been satisfied, as noted above, the reason the court gave for its concern was unfairness to the eligible applicant that had not yet been able to satisfy the Agency's successful defense standard and, thereby, trigger the exclusivity. In contrast, the Agency's allowing eligible applicants to relinquish or waive the exclusivity enables them to exercise the exclusivity as they deem most beneficial. Further, permitting complete relinquishment prior to the triggering of the exclusivity (the Agency does permit selective waiver before exclusivity is triggered as discussed above) cannot be considered irreconcilable with the language of section 505(j)(5)(B)(iv), providing for a 180-

[13] Statutory construction is a "holistic endeavor" in which the court examines not the "isolated context" of one subsection of a statute but "the remainder of the statutory scheme." *United Savings Ass'n v. Timbers of Inwood Forest Associates*, 484 U.S. 365, 371 (1988); see also *Robinson v. Shell Oil Co.*, 519 U.S. 337, 341 (1997) ("The plainness or ambiguity of statutory language is determined by reference to the language itself, the specific context in which that language is used, and the broader context of the statute as a whole.").

day delay before approval of subsequent ANDA applicants, when viewed in the context of the larger statutory framework. Since *Mova*, the courts have established that amending the patent certification from paragraph IV to paragraph III, as provided for under Agency regulations, would have this same effect—loss of exclusivity benefits. *See Mylan*, 94 F. Supp. 2d at 56-58.

Further, the Agency's interpretation comports with the objective of section 505(j)(5)(B)(iv) and of the Hatch-Waxman amendments as a whole. As the *Mova* court stated, section 505(j)(5)(B)(iv) is intended to encourage patent challenges to promote marketplace competition. 140 F.3d at 1074-75. Allowing waiver and relinquishment helps maintain the value of the exclusivity for the beneficiary, strengthening the incentive to challenge patents and, thereby, promote competition.

The other decisions upon which Pfizer attempts to rely similarly also do not compel a "plain meaning" reading inconsistent with the Agency's interpretation of section 505(j)(5)(B)(iv) as permitting waiver and relinquishment of 180-day exclusivity.[14]

II. Waiver and Relinquishment of 180-Day Exclusivity Is Consistent with Permitting Waiver of Other Forms of Marketing Exclusivity

A. Equivalent Language of Other Market Exclusivity Provisions

The statutory language stating that subsequent ANDAs "shall not be made effective earlier than . . ." parallels in construction and effect three other statutory marketing exclusivity provisions. These provisions provide that: (1) "no [subsequent] application may be submitted" for review of a drug product containing a new chemical entity for five years after the initial approval of a product containing that new chemical entity (new chemical entity exclusivity);[15] (2) the Agency "may not make the approval effective" for a product that depends upon new clinical data for three years after the approval of the initial product for which those data were submitted (new clinical investigation exclusivity);[16] and (3) the Agency cannot accept or approve, as appropriate, a product for an additional six months after these other exclusivities (or patent protection) would

[14] The court in *Teva Pharmaceuticals, USA, Inc. v. FDA* (182 F.3d 1003 (D.C. Cir. 1999)), in fact, relied, in part on the ambiguity of the statutory language at issue, "court decision," in finding arbitrary and capricious the Agency's interpretation of the language as excluding a dismissal of a declaratory judgment action). 182 F.3d at 1009. In *Granutec*, the court, like the D.C. Circuit in *Mova*, found invalid the Agency's "successful defense" interpretation, concluding that adding the requirement neither interpreted the statute nor filled a gap. 1998 WL 153410 at *7. However, the court also expressly acknowledged the availability of waiver. *Id.* at *9, 10; *see* note 7 *supra*. In *Torpharm, Inc. v. Shalala*, 1997 WL 33472411 at *1 (D.D.C. Sept. 5, 1997) (unpublished opinion), a district court found the Agency's interpretation of "the court" (to mean a court from which no appeal "can be or has been taken") unsupportable in light of other uses of the same term in the statute. In contrast, the Agency's interpretation here comports with its long-standing interpretation of equivalent statutory language to permit waiver of other forms of market exclusivity established in the Act. *See* section II.B *infra*.

[15] 21 U.S.C. 355(c)(3)(D)(ii) ("no application . . . may be submitted . . . before the expiration of five years .."), (j)(5)(D)(ii) ("no application may be submitted . . . before the expiration of five years . . . "); 21 C.F.R. 314.108(b)(2).

[16] 21 U.S.C. 355(c)(3)(D)(iii), (iv), (j)(5)(D)(iii) (all stating in pertinent part, "the Secretary may not make the approval . . . effective before the expiration of three years . . ."); 21 C.F.R. 314.108(b)(4),(5).

ordinarily end with respect to the product when the product's sponsor has submitted pediatric studies (pediatric exclusivity).[17]

B. Equivalent Agency Practice

The Agency has a long-standing and consistent practice of permitting waiver and relinquishment of these three forms of marketing exclusivity as well, as a means to best effectuate the underlying legislative objectives.[18] Congress intended 180-day exclusivity to encourage patent challenges to promote competition for pharmaceuticals, in accordance with one fundamental objective of the Hatch-Waxman amendments. *See Mova*, 140 F.3d at 1074-75. New chemical entity and new clinical investigation exclusivity were intended to promote the other fundamental objective of the amendments, and a fundamental objective of the Food and Drug Administration Modernization Act of 1997 with respect to pediatric exclusivity, to encourage pharmaceutical innovation.[19]

The first waiver requests submitted to the Agency after passage of the Hatch-Waxman amendments came from innovator companies wishing to waive new clinical investigation and new chemical entity exclusivity to permit approval of specific ANDAs. For example, in 1988, the Agency allowed Stuart Pharmaceuticals to waive new clinical investigation exclusivity to permit approval of an ANDA for atenolol submitted by ICI Pharmaceuticals Group. The Agency also permitted Ciba-Geigy Corp. to waive new chemical entity exclusivity in 1993 to permit review and approval of an ANDA for diclofenac sodium submitted by Geneva Pharmaceuticals,

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[17] 21 U.S.C. 355a(a), (c) (extending unexpired patent or other market exclusivities by six months). These three bars to review and approval do not apply to subsequent full NDAs (which are applications that include all the data necessary to support approval without reference to any data or information the sponsor does not own or to which it does not have a right of reference). *See id.*; 21 U.S.C. 355(c)(D), (j)(5)(D).

[18] The Agency notes that section 527 of the Act, which establishes an exclusivity period for the marketing of drugs for rare diseases and conditions ("orphan drug" exclusivity), expressly provides for the holder of the exclusivity to consent to approval of other applications during the exclusivity period. *See* 21 U.S.C. 360cc(b)(2); 21 C.F.R. 316.31(a)(3). Orphan drug exclusivity, however, was addressed through separate legislation to deal with a separate legislative concern from those addressed by the Hatch-Waxman amendments. In contrast, the provisions addressing 180-day, new chemical entity, new clinical investigation, and pediatric exclusivity all arise from or relate to the Hatch-Waxman amendments and, where silent or ambiguous, are appropriately interpreted collectively and consistently in light of the overall structure and purpose of those amendments. *See Apotex, Inc. v. Thompson*, 347 F.3d 1335, 1352 (Fed. Cir. 2003) ("Deference is due to an administrative agency's regulations particularly when the subject matter of the regulatory authority is a 'highly detailed' regulatory program to which the agency has brought its 'specialized expertise,' . . . a characterization that aptly describes the FDA's role in the context of the regulatory scheme created pursuant to the Hatch-Waxman Act"); *Granutec*, 1998 WL 153410 at *9 (deferring to the Agency's interpretation of the "complicated legislative [Hatch-Waxman] framework that reflects a considered balance of competing statutory goals").

[19] Pub. L. No. 105-115. *See* Drug Price Competition and Patent Term Restoration Act, House Report No. 98-857, Part I 15 (stating that Title II of the act created new incentives for increased pharmaceutical research and development expenditures); Statement of Senator Orrin Hatch, 130 Cong. Rec. S 10503-04 (daily ed. Aug. 10, 1984) (explaining that new chemical entity and new clinical investigation exclusivity would compensate for the time and money expended for product testing and review); Food and Drug Administration Modernization and Accountability Act of 1997: Report from the Committee on Labor and Human Resources of the U.S. Senate (Oct. 6, 1997) 3 (explaining that the legislation would create incentives to test the safety and efficacy of drugs for children).

Inc. The preamble to the 1994 implementing regulations for the Hatch-Waxman amendments described this practice and expressly recognized the permissibility of waiver of new chemical entity and new clinical investigation exclusivity (*see* 59 FR at 50,539). Subsequently, in 2002, the Agency permitted Bristol-Myers Squibb Company to waive both pediatric exclusivity and new clinical investigation exclusivity, to allow immediate approval of ANDAs for metformin and buspirone bearing pediatric labeling.

C. Exclusivity Provisions Not Distinguishable

You assert that waiver and relinquishment should be permitted for new chemical and new clinical investigation exclusivity under section 505(j)(5)(D) of the Act but not for 180-day exclusivity under section 505(j)(5)(B)(iv) because 180-day exclusivity is not tied to any property right, while these other forms of exclusivity relate to underlying, marketable proprietary data (Petition at 9). There is no basis in the statutory language for drawing such a distinction. Just as section 505(j)(5)(B)(iv) states that the application "shall be made effective not earlier than . . ." , section 505(j)(5)(D) provides that "no application may be submitted . . . before the expiration of five years" (regarding new chemical entity exclusivity) (21 U.S.C. 355(j)(5)(D)(ii)) and "the Secretary may not make the approval . . . effective before the expiration of three years" (regarding new clinical investigation exclusivity) (21 U.S.C. 355(j)(5)(D)(iii), (iv)).[20] As discussed above, all of these provisions may permissibly be interpreted to provide for waiver and relinquishment.

Further, FDA does not consider this distinction relevant as a policy matter. The Agency allows waiver of all three of these forms of exclusivity, and of pediatric exclusivity, to ensure that the beneficiary of the exclusivity (whether an innovator that has invested in research and development for a new chemical entity, new clinical indication, or pediatric use, or an ANDA applicant that has challenged a listed patent) is able to realize as fully as possible the benefit Congress intended to confer as an incentive for the activity. Waiver and relinquishment do not depend upon the existence of a property right in the exclusivity or on a relationship between the exclusivity and some other property interest. *See* 59 FR at 50,359.

Petitioner also argues that allowing waiver of 180-day exclusivity would encourage the submission of ANDA applications to realize a "lucrative 'waiver' asset." Petition at 10. As discussed at note 5 *supra*, the Agency agrees that a potential for abuse exists. Partly for this reason, the Agency has adopted a policy permitting relinquishment, but not selective waiver, before the triggering of eligibility. However, in the absence of evidence to the contrary, we do not believe that the speculative potential for abuse outweighs the demonstrable, pro-competitive benefits of allowing waiver and relinquishment.[21] *See* section III *infra*.

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[20] *See also* 21 U.S.C. 355(c)(3)(D)(iii), (iv).

[21] *See* 59 FR at 50,359. As Teva and Purepac note, in any event, ANDA applicants, like NDA holders, have commercially marketable assets to sell or license relating to their drug products. *See* Comments at 15.

We also note, with regard to 180-day exclusivity, that precluding waiver could be expected primarily to benefit the innovator, rather than other ANDA applicants or the public through increased competition and lower prices. Yet, the provision was intended to benefit ANDA applicants, not innovators, to promote competition consistent with a

III. Relinquishment and Waiver of 180-Day Exclusivity Promote the Purpose of the Exclusivity—to Encourage Patent Challenges and Increase Marketplace Competition

As noted above, the Hatch-Waxman amendments reflect two fundamental legislative goals: continued pharmaceutical innovation and enhanced competition in the pharmaceutical marketplace. In granting 180-day exclusivity, Congress intended to reward patent challenges based on non-infringement or invalidity to promote the latter of these basic legislative objectives-- enhanced marketplace competition. *See Pharmachemie B.V. v. Barr Labs., Inc.*, 276 F.3d 627, 629 (D.C. Cir. 2002); *Mova*, 140 F.3d at 1074-75. If waiver and relinquishment were not permissible, the value of 180-day exclusivity would be significantly reduced and, in some cases, could be eliminated.[22] This would diminish the effectiveness of this incentive to challenge patents. Further, market access for subsequent ANDA holders could be substantially delayed, potentially for years. Consequently, marketplace competition could be anticipated to develop more slowly, a result that would be inconsistent with this legislative objective.

As noted above, the Agency has permitted waiver and relinquishment of 180-day exclusivity on multiple occasions, facilitating approvals of subsequent ANDAs that might otherwise have been significantly delayed. Petitioner offers no evidence to suggest that permitting waiver and relinquishment undermines the objectives of the Hatch-Waxman regime. Permitting waiver and relinquishment allows the private entities concerned to arrange, to their mutual best advantage and to the benefit of the public health, for more rapid introduction of competition to the pharmaceutical marketplace. The Agency sees no reason to interfere with these pro-competitive business arrangements.

IV. Conclusion

FDA has concluded that waiver and relinquishment of 180-day exclusivity are permitted under section 505(j)(5)(B)(iv) of the Act; this practice is consistent with the Agency's permitting

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fundamental objective of the Hatch-Waxman amendments. *See Mova*, 140 F.3d at 1074-75. As a policy matter, therefore, this outcome would be inconsistent with the purpose of the provision and this basic legislative objective.

[22] For example, an ANDA applicant might be eligible for exclusivity based on certifications with respect to more than one patent. If the applicant were to lose the patent infringement suit for one patent, it would no longer be eligible for exclusivity with respect to that patent, and would not be able to market its product during the term of that patent (without infringing the patent). *See* 21 C.F.R. 314.94(a)(12)(viii)(A). However, the applicant would still have eligibility with respect to the other patent(s). Depending on whether or not there is a court decision finding the other patent(s) invalid or not infringed, and thus beginning the exclusivity period, the eligible ANDA applicant (which cannot market its own product) might relinquish or selectively waive exclusivity, permitting FDA to approve one or more ANDAs for the drug product.

Another example would be an eligible applicant ("Applicant A") that is still in patent litigation when the exclusivity period is triggered either by a court decision finding that another ANDA applicant's product is not infringing or, in the case of multiple eligible applicants as described in note 3 *supra*, by another eligible applicant's commercial marketing. In both of these situations, the exclusivity period might expire before Applicant A could market its product.

waiver and relinquishment of new chemical entity, new clinical investigation, and pediatric exclusivity; and waiver and relinquishment of 180-day exclusivity advance a fundamental objective of the Hatch-Waxman amendments by promoting competition in the pharmaceutical marketplace. The Agency sees no reason to alter its existing policy. We see no compelling public health consideration and no specific statutory mandate to interfere with these private business arrangements. For all these reasons, the Agency denies your requests.

Sincerely yours,

William K. Hubbard
Associate Commissioner
for Policy and Planning