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Division of Dockets Management
U.S. Food and Drug Administration
5630 Fishers Lane, Room 1061 (HFA-305)
Rockville, Maryland 20857

CITIZEN PETITION
EXPEDITED DECISION REQUESTED

ACTIONS REQUESTED

On behalf of Teva Pharmaceuticals USA, Inc. ("Teva"), the undersigned submits this Petition pursuant to section 505 of the Federal Food, Drug, and Cosmetic Act ("FDCA"), 21 U.S.C. § 355, 21 C.F.R. § 10.30, and the Administrative Procedure Act, 5 U.S.C. § 701, *et seq.* Teva hereby urgently requests the Commissioner of Food and Drugs ("FDA" or the "Agency") to take immediate action to enforce FDA's existing regulations and established policy in order to prevent Pfizer Inc. from marketing a generic version of its Accupril® (quinapril) drug products until after the expiration of Teva's 180-day exclusivity period for generic quinapril products. Specifically, Teva requests that FDA:

(1) Enforce its existing regulations and policies to require Pfizer to submit a pre-approval supplemental NDA ("Pre-approval sNDA") before it markets or distributes any version of its Accupril® product which has been changed, by way of any manufacturing, labeling, packaging, or product code changes, such that the product purports to be, resembles, or could be confused with, a generic (unbranded) version of Accupril, if a product with such changes is proposed to be distributed prior to the expiration of Teva's 180-day exclusivity period for generic quinapril drug products;

(2) Delay the approval of such sNDA until after the expiration of Teva's 180-day generic exclusivity period for generic quinapril drug products.

2004P-0261

CP1

Teva has reason to believe that Pfizer, through its subsidiary, Greenstone Ltd., will imminently begin selling Accupril® as a "brand generic" drug[1] as soon as Teva begins to sell its generic quinapril products and then throughout Teva's 180-day exclusivity period.[2] Such action by Pfizer would deprive Teva of its lawful exclusivity rights and undermine the Congressional intent of the 180-day exclusivity period provisions. FDA is authorized, and indeed compelled, by current law, FDA regulations, and FDA policy, to take the action requested herein. Failure by FDA to take the action requested herein would be arbitrary, capricious, and otherwise contrary to law, and thereby would violate the Administrative Procedure Act, 5 U.S.C. § 706.

Teva already has final approval of its quinapril ANDA and may be in a position to launch its product soon, at which time its 180-day exclusivity period would commence. Accordingly, **Teva respectfully requests that FDA expedite its consideration of this petition, and issue a final decision forthwith. If FDA fails to respond to this Petition by taking immediate effective action to prevent the launch of Pfizer's generic quinapril product prior to the expiration of Teva's 180-day exclusivity period, Teva will be irreparably harmed and will be prepared to take all appropriate steps to compel such agency action and protect its lawful exclusivity interests.**[3]

STATEMENT OF GROUNDS

I. EXECUTIVE SUMMARY

Generic drug companies such as Teva operate under the highly structured, incentive-oriented provisions of the FDCA, as amended by the Drug Price Competition and Patent Term Restoration Act of 1984, P.L. 98-417 (commonly known as the "Hatch-Waxman Amendments" or simply "Hatch-Waxman"). The core purpose of the generic drug approval provisions of Hatch-Waxman is to expedite and maximize the introduction of cost-saving generic drugs, while protecting all *legitimate* patent rights of drug product innovators, but without providing unintended windfalls to crafty companies. The key mechanism for achieving this goal is a 180-day generic exclusivity period. Before the expiration of that exclusivity period, only qualified ANDA applicants are entitled to provide generic versions of a brand drug product.[4]

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[1] The term "brand generics" as used herein is synonymous with so-called "authorized generics," a term that is used by others in the pharmaceutical industry.

[2] Teva has learned from its customers that Pfizer is already in the process of offering incentives to purchase its quinapril brand generic upon its launch prior to the expiration of Teva's exclusivity period.

[3] A copy of this petition is also being submitted as a comment in support of Mylan Pharmaceutical's Citizen Petition, Docket No. 2004P-0075/CP1.

[4] As FDA has long acknowledged, the 180-day exclusivity period, like comparable brand drug exclusivities, is subject to waiver by the eligible ANDA applicant, which can choose to allow generic market entry by other applicants during the 180-day period. *See* 64 Fed. Reg. 42873, 42881 (Aug. 6, 1999); *Boehringer Ingelheim, Corp. v. Shalala*, 993 F. Supp. 1 (D.D.C. 1997). Pfizer has filed a Citizen Petition, Docket No. 2004P-0227 (May 11, 2004), challenging FDA's longstanding 180-day exclusivity period waiver policy, but that Petition is wholly without merit, as described in Teva's comments to that Petition filed June 4, 2004, and otherwise has no bearing on the issues presented herein.

Recently however, certain brand and generic drug companies have adopted a strategy that is designed to, and in fact does, eviscerate the 180-day exclusivity period incentive. That strategy involves the brand company offering, either on its own or in concert with a generic company, a generic version of its own brand drug (i.e., a "brand generic") before the expiration of the rightful 180-day exclusivity period of the first Paragraph IV ANDA filer for that drug. Such brand generic products are actually the brand product, but are produced, distributed, and marketed as if they were ANDA-approved generic products. The effect of this strategy is to deprive the first Paragraph IV filer of its statutory right to exclusivity in the marketing of generic versions of the drug for 180 days. The brand companies thereby inflict irreparable harm both on the first Paragraph IV filer and on the public interest, as the introduction of brand generics prior to the expiration of the 180-day exclusivity period threatens the very viability of the Paragraph IV generic drug approval system under Hatch-Waxman.

FDA has already established a policy by which it treats brand generics as the legal and functional equivalent of ANDA generics for purposes of applying and enforcing the 180-day exclusivity period provisions of Hatch-Waxman. When that policy was challenged in court, FDA vigorously, and successfully, defended its interpretation. The Agency has never rescinded or modified its interpretation that brand generics must be treated as ANDA generics for purposes of applying the statutory 180-day exclusivity period provisions. A federal court and Congress itself have expressly endorsed that policy.

To preserve the incentive structure and purposes of Hatch-Waxman, and to comply with the mandates of the Administrative Procedure Act, FDA is compelled to take action to prevent the sale of brand generics prior to the expiration of another company's 180-day exclusivity period. More specifically, FDA should enforce its existing statutory and regulatory authority to require a pre-approval sNDA for any labeling or product changes to an approved new drug that will permit the sale of a brand generic before the expiration of an applicable exclusivity period because such changes are not "minor" in nature. Failure by FDA to take effective action to preserve the 180-day exclusivity period against intrusion by brand generics would be arbitrary and capricious in violation of the APA.

FDA must act now by granting the relief requested in this Petition. Failure to do so will leave Teva with no choice but to seek judicial review.

II. BACKGROUND

Brand (or "innovator") and generic drugs are marketed, distributed, and sold in distinctly different ways, and the Hatch-Waxman amendments were designed in recognition of, and to specifically address, these differences. Innovator drugs are sold under brand names, are typically promoted heavily, advertised to prescribers and consumers, and sold for high monopoly prices. Once an innovator company loses its various legal and regulatory means of precluding FDA approval of generic versions of a brand drug, generic versions are commercially introduced, thereby drastically lowering the drug price to patients. Generic drugs are typically sold without brand names, are generally not advertised or promoted to prescribers or consumers, and are priced much lower than the previous monopoly brand prices. Generic companies generate sales

of their products primarily due to the fact that under state laws and the rules of public and private health insurance providers, pharmacists are generally permitted, and often required, to dispense a "generic" version of a prescribed brand drug.

"Brand generic" drug products are modified versions of the brand drug, produced by the NDA holder, but sold, directly or indirectly, with labeling and product configurations that mimic ANDA generic versions of brand products. Brand generics are marketed and distributed through channels of trade as though they are in fact ANDA generic products. This approach blurs the line between innovator and generic products, causing generic drug company customers (wholesalers, chain drug stores, etc.) to purchase, and pharmacists to dispense, the brand product as if it were an ANDA-approved generic product. In the highly regulated realm of prescription pharmaceuticals, when this phenomenon occurs before expiration of a 180-day exclusivity period, it is contrary to law, contrary to past FDA practice and policy, contrary to existing FDA regulations, undermines Congressional intent, and threatens to seriously reduce the force of generic competition and the lower consumer prices that result.

Congress recognized the foregoing differences between brand and generic drugs,[5] and Hatch-Waxman is widely recognized as reflecting and embodying a careful and delicate balance between the interests of brand and generic companies. *See, e.g., Abbott Labs. v. Young*, 920 F.2d 984, 985 (D.C. Cir. 1990); *Allergan, Inc. v. Alcon Labs., Inc.*, 324 F.3d 1322, 1325-26 (Fed. Cir. 2003); S. Rep. No. 105-36(1) at 125 (1997). Thus, Hatch-Waxman provided special patent term protection rights for innovator drug companies, and also created incentives, in the form of additional marketing protections, for innovative research and development of new drugs. *See, e.g.*, 35 U.S.C. § 156 (patent term extensions for innovative drug products to compensate for delays in FDA approval); 21 U.S.C. § 355(j)(5)(D) (establishing 5-year and 3-year regulatory exclusivities for innovative drug products); 21 U.S.C. §§ 355(b)(1), 355(j)(2)(A)(vii) (patent listing rights for innovator drug sponsors and patent certification obligations for generic drug applicants). Generic drugs are not eligible for these statutory incentives.

Hatch-Waxman also created a streamlined approval process for generic versions of brand drugs. The 180-day exclusivity period in particular was devised as an incentive to encourage generic companies to challenge the validity or applicability of patents purporting to cover brand drugs. 21 U.S.C. § 355(j) (ANDA process for generic drugs); and 21 U.S.C. § 355(j)(5)(B)(iv) (180-day exclusivity period for generic drugs). Brand drugs are not eligible for the 180-day generic exclusivity period.

[5] Title I of Hatch-Waxman was intended "to make available more low cost generic drugs by establishing a generic drug approval procedure for pioneer drugs first approved after 1962." H.R. Rep. No. 857, pt. 1, at 14 (1984), reprinted in 1984 U.S.C.C.A.N. 2647. Title II of Hatch-Waxman was intended to provide a new incentive for increased expenditures for research and development of pioneer drug products by "restoration of some of the time lost on patent life while the product is awaiting pre-market approval." H.R. Rep. No. 857, pt. 1, at 15 (1984), reprinted in 1984 U.S.C.C.A.N. 2647, 2648.

III. FDA MUST INTERPRET THE STATUTE TO PREVENT BRAND GENERIC PRODUCTS FROM BEING MARKETED PRIOR TO EXPIRATION OF ANOTHER COMPANY'S 180-DAY EXCLUSIVITY PERIOD

The statutory 180-day exclusivity period provisions have been the subject of numerous administrative and judicial challenges, which have led to an agreed set of core principles that must govern the FDA's interpretation and implementation of those provisions. Specifically, FDA must apply and enforce the statute:

- "in a manner consistent with 'the statute's interest in affording market access and incentives for both generic and non-generic makers,' and to maintain 'an incentive for the parties to fulfill the purposes of Hatch-Waxman.'"
- to "avoid an interpretation that excessively favors the first generic and the innovator parties' 'anticompetitive hold' over the drug," and
- to "avoid interpreting Hatch-Waxman so the decision on whether a generic applicant is entitled to exclusivity rests entirely in the patent holder's hands."

Exhibit A, Nifedipine Petition Response (Feb. 6, 2001) at 5 (quoting *Mylan Pharms., Inc. v. Henney*, 94 F. Supp. 2d 36, 53-54 (D.D.C. 2000)). Allowing brand generics to be marketed prior to expiration of another company's 180-day exclusivity period violates each of these principles.

First, the 180-day exclusivity period is a critical incentive to generic drug companies to fulfill Hatch-Waxman's purpose and intent to expedite and maximize generic drug competition prior to expiration of questionable brand drug patents. This incentive is vital because the statutory patent challenge system poses many costly and time-consuming barriers to generic entry. Specifically, the filing of a generic patent challenge (by way of a Paragraph IV ANDA) allows the patent holder to sue the applicant and obtain a 30-month stay of approval of the generic product while the case is litigated. 21 U.S.C. § 355(j)(5)(B)(iii). The 180-day exclusivity period was designed to encourage patent challenges because Congress recognized that the risks and costs (both direct and opportunity costs) of attempting to overcome a brand drug patent are extremely high. As one court explained:

> As an incentive to the first generic maker to expose himself to the risk of costly patent litigation, the Hatch-Waxman regime provides that the first to file a Paragraph IV certified ANDA ("the first filer") is eligible for a 180-day period of marketing protection, commonly known as the 180-day exclusivity period ("the Exclusivity Incentive"). By its terms, the Exclusivity Incentive affords the first filer protection from competition from subsequent generic makers for 180 days beginning from the earlier of a commercial marketing or court decision.

Mylan v. Henney, 94 F. Supp. 2d at 40 (emphasis added) (internal citations omitted).[6]

If brand generics are permitted to be marketed before the expiration of another company's 180-day exclusivity period, the obvious and devastating effect will be to undermine the Congressional intent by severely devaluing (if not eliminating) the incentive to file patent challenges. Thus, any statutory interpretation by FDA that allows the marketing of brand generics prior to expiration of the 180-day exclusivity period violates the first interpretive principle by failing to apply the law "in a manner consistent with the statute's interest in affording market access and incentives for both generic and non-generic makers, and to maintain an incentive for the parties to fulfill the purposes of Hatch-Waxman."

Second, any interpretation that allows brand generic marketing prior to expiration of the exclusivity period improperly puts brand companies on both sides of the Hatch-Waxman "balance" and thus "excessively favors" their "anticompetitive hold" over the drug. This is because brand companies start out with a monopoly hold for a brand drug, and under the statute, generic companies that challenge that monopoly hold are supposed to be rewarded with a 180-day exclusivity period. The exclusivity reward has value not only because it allows temporarily greater generic profits as recoupment for the generic patent challenger's risks and investments, but also because it allows the eligible generic company to establish a first-movers position in the generic supply chain *vis-à-vis* later generic entrants. Brand generic marketing prior to expiration of the exclusivity period effectively transfers much of the profit value from the generic challenger, but it also allows the brand generic marketer to seize a significant share of the generic supply chain from the deserving generic challenger. Thus, allowing brand generic infringement of the 180-day exclusivity period violates the second core principle that the statute should not be implemented in a way that excessively favors brand companies' hold over the market.

Third, allowing brand generics to market prior to expiration of the 180-day exclusivity period improperly gives brand companies control over whether the first generic patent challenger can actually receive exclusivity. There can be no dispute that the 180-day exclusivity period is intended to give a first Paragraph IV filer the right to prevent the entry of generic products prior to the expiration of the 180-day period – indeed that is the definitional essence of "exclusivity." As FDA itself has explained:

> The 180-day exclusivity acts as an incentive for the first ANDA applicant to challenge a listed patent.... Only an application containing a paragraph IV certification may be eligible for exclusivity.

See Exhibit A, Nifedipine Petition Response at 3-4 (emphasis added); *see also Mylan v. Henney*, 94 F. Supp. 2d at 40. Thus, courts and FDA have rejected implementing the statute in a way that

[6] *See also Mylan Pharms., Inc. v. Shalala*, 81 F. Supp. 2d 30, 33 (D.D.C. 2000) (The 180-day exclusivity period is intended to "encourage generic drug makers to incur the potentially substantial litigation costs associated with challenging pioneer drug makers' patents."); *In re Cardizem CD Antitrust Litig.*, 105 F. Supp. 2d 682, 686 (E.D. Mich. 2000).

allows a brand company (or patent holder) to control whether exclusivity will actually be available to the eligible generic challenger. *See Mylan v. Henney*, 94 F. Supp. 2d at 54 (rejecting an FDA "interpretation [that] places the decision as to whether a generic manufacturer will be entitled to exclusivity entirely in the hands of the patent holder").

That principle requires that a company that was the first to undertake the risks associated with a Paragraph IV patent challenge have the right to sell exclusively a generic version of the drug during the 180-day exclusivity period. The first-filer should not be joined in the sale of the relevant generic product by the brand company that has been exclusively on the market during the patent term. Indeed, to permit brand companies to do so would be to eliminate the first-filer's exclusivity.

In addition, it would be especially egregious for a brand company that erected unmeritorious patent barriers to generic competition to, in the end, benefit from a generic company's challenge of those patents by being permitted to market a brand generic product during the exclusivity period and before subsequently filed Paragraph IV ANDA applicants are allowed to do so. The brand company, inequitably and improperly, would thereby participate in and benefit from the exclusivity period by being insulated from all generic competitors except the first-filed Paragraph IV ANDA holder. The FDCA would then be turned on its head. Congress intended, and the courts have affirmed, that only the first Paragraph IV ANDA filer (and those to which the first filer grants its consent) is to benefit from the limited competition resulting from the 180-day exclusivity period, not the drug company whose patents the first-filer encouraged to challenge. Indeed, if the brand company were to launch a brand generic before the exclusivity period commences, the brand company itself would be the sole seller of a generic product, a status expressly reserved for the first Paragraph IV ANDA filer.

As discussed in this section, it is simply contrary to the Congressional intent to allow brand companies to misappropriate the value of the 180-day exclusivity period -- the very device designed by Congress to encourage generic companies to attack the unwarranted monopolies of brand companies -- by marketing a brand generic prior to expiration of that exclusivity period. It is also contrary to the judicially mandated interpretive principles for FDA to interpret the statute in a way that allows brand generics to be marketed prior to expiration of another company's 180-day exclusivity period. As discussed in the following sections, FDA already has established policies, and statutory and regulatory authorities that, if properly adhered to and enforced by the Agency, would prevent unauthorized marketing of brand generics prior to the expiration of the 180-day exclusivity period.

IV. FDA, THE COURTS, AND CONGRESS ALREADY HAVE DETERMINED THAT MARKETING OF A BRAND GENERIC IS THE SAME AS MARKETING AN ANDA GENERIC DURING THE 180-DAY EXCLUSIVITY PERIOD

Prohibiting the marketing and sale by Pfizer of generic Accupril, or of any other brand generics, before the expiration of an applicable 180-day exclusivity period is compelled by established FDA, judicial, and Congressional policy equating brand generics with ANDA generics during the 180-day exclusivity period.

In 2000, Mylan Pharmaceuticals began marketing a brand generic version of Pfizer's Procardia (nifedipine) 30 mg. extended release tablets, pursuant to an agreement with Pfizer. In that case, Mylan was the first Paragraph IV ANDA filer for a generic version of Procardia®, but had not actually sold the product that was the subject of its ANDA. Mylan took the position that ANDA generics were legally and functionally distinct from brand generics for exclusivity purposes because brand generic products are not the specific subject of approved ANDAs. Thus, Mylan argued, its marketing of a brand generic version of Procardia did not constitute "commercial marketing" of a generic drug for purposes of triggering the start of its 180-day exclusivity period under 21 U.S.C. § 355(j)(5)(B)(iv). *See Mylan v. Thompson*, 207 F. Supp. 2d 476, 482-83 (N.D. W. Va. 2001). Teva was the marketing partner of a subsequent Paragraph IV nifedipine applicant that was blocked from receiving final ANDA approval until Mylan's exclusivity period was triggered and had expired. Teva petitioned FDA to issue a ruling that Mylan's marketing of the brand generic constituted "commercial marketing" of Mylan's own ANDA product, and thus triggered the start of Mylan's 180-day exclusivity period. *See* Exhibit B, Nifedipine Petition (Aug. 9, 2000); Exhibit A, Nifedipine Petition Response.

FDA granted Teva's nifedipine Petition, and in its ruling enunciated the core interpretive principles (previously articulated by the court in *Mylan v. Shalala*, 94 F. Supp. 2d at 53-54), that must guide the Agency's actions in implementing and enforcing the 180-day exclusivity period provisions of Hatch-Waxman:

> [T]he *Mylan* court identified three factors to consider in interpreting the 180-day exclusivity provision of Hatch-Waxman. First, the statute is to be interpreted in a manner consistent with "the statute's interest in affording market access and incentives for both generic and non-generic makers," and to maintain "an incentive for the parties to fulfill the purposes of Hatch-Waxman." Second, FDA should avoid an interpretation that excessively favors the first generic and the innovator parties' "anticompetitive hold" over the drug. The court observed that "Hatch-Waxman intended to provide an incentive for drug companies to explore new drugs, not a market 'windfall' for crafty, albeit industrious, market players." Finally, **FDA should avoid interpreting Hatch-Waxman so the decision on whether a generic applicant is entitled to exclusivity rests entirely in the patent holder's hands**.

Exhibit A, Nifedipine Petition Response at 5 (emphasis added) (internal citations omitted).

Applying these principles to determine the status of Mylan's brand generic nifedipine product, FDA noted that the key result intended by Congress in enacting the 180-day exclusivity provision was that "ANDA applicants who speed the availability of generic drugs by challenging patents are given the opportunity to reap the economic benefit of ***limited competition*** for a period of 180 days." *See id.* at 8 (emphasis added). FDA thus concluded that to effectuate the Congressional intent, it was necessary and appropriate to classify brand generics as legally and functionally equivalent to ANDA generics in the 180-day exclusivity context: "**Whether Mylan markets the product approved in its ANDA or the product approved in Pfizer's NDA is of**

little import to the statutory scheme; Mylan has begun commercial marketing of **generic** nifedipine. Permitting Mylan to market nifedipine without triggering the beginning of exclusivity would be inconsistent with the intent of the statutory scheme." *Id.* at 7-8 (emphasis added).

FDA's decision prompted a judicial challenge by Mylan. Mylan's lawsuit raised the very issue FDA must address here: whether the technical distinction that its brand generic product was approved under Pfizer's NDA and not under Mylan's Paragraph IV ANDA precluded FDA from treating the brand generic product as an ANDA generic product for purposes of the 180-day exclusivity period provisions. *Mylan v. Thompson,* 207 F. Supp. 2d at 483. The district court rejected Mylan's proposed distinction between brand generics and ANDA generics, and denied its motion for a preliminary injunction on the basis that FDA reasonably interpreted the statute to equate a brand generic with an ANDA generic for purposes of the 180-day exclusivity period provisions. *Id.* at 488.

Mylan appealed the denial of a preliminary injunction. In the briefing of the appeal, FDA further elucidated its policy decision to equate brand generics with ANDA generics for 180-day exclusivity period purposes. FDA explained that "until FDA approved Biovail's ANDA in February 2001, Mylan was the sole marketer of a '**generic**' 30 mg. nifedipine product (Pfizer's) for over ten months, far longer than the 180-day exclusivity period provided by the statute." Exhibit C, Brief of Federal Defendants-Appellees [FDA], *Mylan v. Thompson*, No. 01-1554 (4th Cir. 2001) ("FDA Nifedipine Appeal Brief") at 2-3 (emphasis added). FDA further explained that under this interpretation it made ***"no difference"*** whether Mylan marketed the generic product approved in its ANDA or the brand generic product produced by Pfizer because "Mylan has begun commercial marketing of a nifedipine product and has already obtained 180 days to reap the economic benefit of being Pfizer's sole competition." *Id.* at 34-35. FDA further argued that adopting Mylan's narrow interpretation of the exclusivity statute would harm consumers "by denying access to multiple safe and effective generic [] products that are ready for final approval and would give Mylan and Pfizer a windfall." *Id.* at 35.

FDA appropriately rejected a narrow formalistic approach to classifying Mylan's brand generic product, noting that it is "appropriate to examine the **practical effect**" of the exclusivity provisions. *Id.* at 38. As FDA informed the Court of Appeals, the 180-day exclusivity period "was intended to allow a generic manufacturer 180 days of marketing a drug ***without competition from other generic drugs***." *Id.* (emphasis added) (citing *Mylan v. Henney*, 94 F. Supp. 2d at 40). FDA further noted that Mylan had enjoyed 180 days without competition from other generics when it had been marketing Pfizer's product as a generic, and argued that the district court had thus correctly held that the 180-day exclusivity period was triggered when Mylan began marketing Pfizer's brand generic. *Id.* at 38. Finally, based on the fact that Mylan's brand generic was for all practical and statutory purposes a "generic" drug, FDA noted that the start of "[t]he 180-day exclusivity period... occurred here when Mylan began marketing Pfizer's

product. Therefore, the district court correctly held that the 180-day exclusivity period was triggered when Mylan began marketing Pfizer's product." *Id.*[7]

Congress itself has recently codified the FDA's previous interpretation that brand generics must be equated with ANDA generics for purposes of carrying out the intent of the 180-day exclusivity period provisions. Specifically, in the Medicare Prescription Drug Improvement and Modernization Act of 2003, P.L. 108-173, § 1102(a)(1), Congress provided that the marketing of a brand generic product by the first Paragraph IV ANDA applicant triggers the start of its 180-day exclusivity period to the same extent that marketing of its own ANDA generic product would. This ratification of the Mylan nifedipine case further compels Agency action to treat a brand generic version of Accupril as an ANDA generic, and prevent marketing of such a brand generic prior to the expiration of Teva's 180-day exclusivity period.

The result in the Mylan nifedipine case and the recent Congressional amendment are consistent with FDA's own initial interpretation of how licensing agreements between brand and generic companies would impact the 180-day exclusivity period provisions. Specifically, in promulgating its original regulations implementing Hatch-Waxman, FDA emphatically rejected the possibility that a generic company could circumvent another company's 180-day exclusivity period by way of a license with the brand patent holder. In its original proposed regulations, FDA proposed to allow a generic company that had a patent license, and the consent of the patent owner, to receive immediate approval of its generic drug. *See* 54 Fed. Reg. 28872, 28923 (July 10, 1989).[8]

However, when it issued its final regulations, FDA noted that because "**patent licensees are subject to 180-day exclusivity that has been granted to another applicant**" the proposed license certification would have no practical effect, and therefore deleted that proposal. 59 Fed. Reg. 50338, 50346 (Oct. 3, 1994) (emphasis added). Furthermore, in response to a request that FDA adopt a regulation "to state that the 180-day exclusivity period does not apply to delay the effective date of approval of licensees to the NDA holder," FDA emphatically refused, stating that "**FDA does not believe that an ANDA applicant who has made a paragraph IV certification and obtained a license should be able to circumvent a 180-day exclusivity period**." *Id.* at 50353 (emphasis added). The same interpretive reasoning must be applied today

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[7] Mylan's appeal of the district court's decision was dismissed voluntarily on October 12, 2001, before the circuit court had ruled in the matter.

[8] That proposed regulation, 21 C.F.R. § 314.94(a)(12)(v), would have provided:

> (v) *Licensing agreements.* If the abbreviated new drug application is for a drug or method of using a drug claimed by a patent and the applicant has a licensing agreement with the patent owner [it should file a Paragraph IV Certification] as to that patent and a statement that it has been granted a patent license. If the patent owner consents to an immediate effective date upon approval of the abbreviated application, the abbreviated application shall contain a written statement from the patent owner that it has a licensing agreement with the applicant and that it consents to an immediate effective date.

Related proposed regulations would have allowed immediate approval of such licensed generic products without regard to the 30-month approval stay. 54 Fed. Reg. at 28923 (proposed 21 C.F.R. § 314.107(b)(1)(iv)(B)).

in the context of brand generic products, which are typically sold under license (or equivalent authorization) from the brand company, and which also should not be allowed to "circumvent" the 180-day exclusivity period of the first Paragraph IV ANDA applicant.

Finally, Pfizer itself has taken the position before the courts that denying a first applicant the full value of its 180-day period of exclusive generic marketing would be contrary to the statutory intent, and Pfizer has specifically supported Teva's right to enjoy a 180-day generic exclusivity period with respect to generic quinapril products. In a recent case in the U.S. District Court for the District of Columbia, Pfizer opposed the effort of another generic company (Mutual Pharmaceutical) to obtain a declaratory judgment of patent non-infringement that would have deprived Teva of its 180-day exclusivity period. As Pfizer argued, "[t]he first generic applicant...is entitled to have the only generic version of the drug at issue on the market [during]." Thus, Pfizer further argued, "Mutual's interest in spoiling Teva's statutory benefit ... undermines the Congressional intent set forth in the Hatch-Waxman Act." *See* Exhibit D, *Mutual Pharmaceutical Company Inc. v. Pfizer Inc.*, No. 1:03CV01116 (RMU) (D.D.C), Memorandum of Points and Authorities in Support of Defendant Pfizer Inc.'s Motion to Dismiss For Lack of Subject Matter Jurisdiction (July 8, 2003) at 5, 3 (emphasis added). Pfizer's memorandum in the *Mutual* case is consistent with FDA's established policy of treating brand generics as legally and functionally equivalent to ANDA generics for purposes of defining the scope of the 180-day exclusivity period. *See id.* at 14-15 (noting that the exclusivity is a Congressionally mandated "benefit" intended to allow first Paragraph IV filers to prevent other generic approval and marketing prior to the expiration of the initial 180-day period of generic competition).

In light of FDA's policy equating ANDA generics and brand generics in the context of the 180-day exclusivity period, and the subsequent judicial and Congressional endorsement of that policy, FDA is compelled to take action to prevent the sale of any brand generic version of quinapril before the expiration of Teva's 180-day exclusivity period.

V. FDA ALREADY HAS REGULATORY AND STATUTORY AUTHORITY TO PREVENT MARKETING OF BRAND GENERICS BEFORE THE EXPIRATION OF ANOTHER COMPANY'S EXCLUSIVITY PERIOD

FDA has existing regulatory provisions that require FDA to prevent marketing of brand generics prior to expiration of another company's 180-day exclusivity period. Specifically, FDA must require that changes to a brand drug that are designed to create and sell a brand generic product prior to the expiration of an applicable 180-day exclusivity period must be the subject of a pre-approval sNDA, and the approval of such sNDAs, absent consent by the first-filer, must be delayed until after expiration of the applicable 180-day exclusivity period. And, as discussed, *infra*, failure by FDA to enforce these requirements would be arbitrary and capricious, in violation of the Administrative Procedure Act.

A. FDA's Current Regulations Require Pre-Approval sNDAs for Changes That Create a Brand Generic Because Such Changes Are Not "Minor"

One tactic that brand companies use to create a brand generic that mimics an ANDA generic product is to change the appearance of the tablet or capsule by omitting any brand-specific codes or trademarks and/or replacing such codes and trademarks with the code or trademark of the company which will pass the drug off as its own. For example, Procter & Gamble recently permitted the launch of a brand generic version of its Macrobid® (nitrofurantoin) drug product, but modified the capsule by replacing the trademark "Macrobid" with "Watson," the name of the generic company that distributes the brand generic version. *Compare* Exhibit E, Watson Product Labeling *with* Exhibit F, Proctor & Gamble Macrobid® Product Information. Similarly, Pfizer may be expected to create a brand generic version of its Accupril® tablets product by omitting or changing the current brand codes "PD 527" (5 mg tablets), "PD 530" (10 mg), "PD 532" (20 mg), and "PD 535" (40 mg), because "PD" stands for "Parke Davis," the Pfizer subsidiary that first marketed Accupril®. These types of dosage form changes, when introduced prior to the expiration of the relevant 180-day exclusivity period, require pre-approval of a supplemental NDA under FDA's existing regulations.

Specifically, 21 C.F.R. § 314.70 provides that certain changes to approved drug products may be made only pursuant to a pre-approval sNDA. Such changes include changes to an existing code imprint on a non-modified release solid oral dosage form product if such change is *not* "a minor change." *See* 21 C.F.R. § 314.70(d)(9). This regulation, by its terms, permits a "***minor change*** in an existing code imprint" to be made without pre-approval. Where, however, a brand product is changed prior to the expiration of the applicable 180-day exclusivity period to replace the brand company or product name or code, with a generic company's code or name that disguises the fact that the product is in fact the brand product (i.e., it creates the illusion of an ANDA generic product), as Pfizer is threatening here, such change simply cannot be considered "minor." This is because, as discussed above, when such changes are designed to create a brand generic product that would improperly be marketed prior to the expiration of another company's 180-day exclusivity period, the consequences are to significantly harm the protected exclusivity rights of the first Paragraph IV ANDA filer and to undermine the Congressional intent underlying the Hatch-Waxman amendments. Thus, such changes are not "minor" and must be the subject of a pre-approval sNDA.

Another key tactic used by brand companies to create brand generic products is to modify the brand labeling to create the false appearance that the brand generic product is separate and distinct from the actual brand product. This is accomplished by omitting labeling references to the brand company and the brand name of the product, and substituting the name of the third party that will market the brand generic product as its own. Thus, Pfizer may be expected to change its approved Accupril® labeling by replacing the 84 references to the brand name "Accupril®" with the generic name "quinapril hydrochloride" and changing the references to Parke Davis being the manufacturer and distributor to instead state that the brand generic version is "manufactured for" another company (presumably Pfizer's captive generic company Greenstone Ltd.). Corresponding changes would presumably be made on the container label as distributed to wholesalers, pharmacies, and patients. Such labeling changes would create the appearance that the brand generic is in fact the generic product of a different company, thus

facilitating the market deception that brand generic strategies rely upon to usurp the value of the first Paragraph IV ANDA applicant's 180-day exclusivity period.

Prior to the expiration of any applicable 180-day exclusivity period, labeling changes such as those described above may only be made pursuant to a pre-approval sNDA. FDA's existing regulations require an sNDA approval prior to making "any change in labeling, except one described in paragraphs (c)(2) or (d)" of section 314.70 . 21 C.F.R. § 314.70(b)(3). The types of brand generic labeling changes described above are *not* "described in paragraphs (c)(2) or (d)" of section 314.70, and therefore must be the subject of a pre-approval sNDA. Specifically, paragraph (d) describes, in relevant part, "editorial or similar ***minor changes*** in labeling." 21 C.F.R. § 314.70(d)(3) (emphasis added). To the extent labeling changes are made prior to the expiration of another company's 180-day exclusivity period and those changes have the effect of creating a brand generic product, such changes simply cannot be considered "minor" or "editorial" because they have the effect of eviscerating the value and intent of the 180-day exclusivity period provisions.[9]

Teva recognizes that FDA has recently issued a non-binding Guidance, *Changes to an Approved NDA or ANDA* (April 2004), which addresses "major," "moderate," and "minor" changes for purposes of 21 C.F.R. § 314.70, and describes "minor change" to include "a change that has minimal potential to have an adverse effect on the identity, strength, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product," and permits NDA sponsors to "describe minor changes in its next annual report" as opposed to in a pre-approval sNDA. *Id.* at 3. However, the Change Guidance does not address the phenomenon of brand generic products, particularly when those products are marketed prior to the expiration of an applicable 180-day exclusivity period. If such changes had been properly considered, they could not have been deemed "minor" since they have the effect of nullifying the Congressionally-intended operation of the 180-day exclusivity period provisions. Thus, the Guidance does not override FDA's obligation to enforce its regulations as written, by deeming brand generic product and labeling modifications to be non-minor changes, and to require a pre-approved sNDA when the changes are designed to introduce a generic drug prior to expiration of an applicable 180-day exclusivity period.

Procedurally, the brand generic sNDA requirement could be easily achieved by FDA notifying Pfizer that generic quinapril products are subject to Teva's 180-day exclusivity period and that no Accupril product that incorporates the product or labeling changes described above may be marketed prior to the expiration of the exclusivity period without prior approval of an sNDA, and that such approval will not be granted (without Teva's consent) until expiration of Teva's exclusivity period. Going forward, FDA could implement a system whereby it would send notice to the sponsor of the Reference Listed Drug ("RLD") immediately upon FDA acceptance of the first Paragraph IV ANDA for a generic version of the drug. Such notice would state: (1) that a Paragraph IV ANDA has been received by FDA; (2) that no brand generic version of the RLD may be marketed prior to the expiration of the 180-day period without an

[9] Paragraph (c)(2) is inapplicable as it describes labeling changes concerning warnings, precautions, and other safety information, and changes to delete false or misleading efficacy claims.

approved sNDA; and (3) that approval of such sNDAs will not be granted until expiration or forfeiture of the 180-day exclusivity period, unless the holder of the 180-day exclusivity period rights consents to the marketing of the brand generic product prior to the end of the exclusivity period.

B. Independent Of Section 314.70, The FDCA And The Administrative Procedure Act Compel FDA Action To Prevent Sale Of Brand Generics Prior To The Expiration Of Another Company's 180-Day Exclusivity Period

Wholly independent of FDA's obligation to enforce section 314.70 to require pre-approval sNDAs for brand generic changes to approved brand products and labeling prior to the expiration of an applicable exclusivity period, the FDCA empowers FDA to take action to protect against brand generic violations of the 180-day exclusivity period provisions, and the Administrative Procedure Act ("APA") compels such action.

Specifically, even if FDA were to improperly deem product code and labeling changes that create a brand generic before the expiration of the 180-day exclusivity period to be non-major changes, it would still be arbitrary and capricious for FDA to refuse to require a pre-approval sNDA for such changes. This is because the FDCA, 21 U.S.C. § 356a(d) authorizes FDA to regulate and require pre-approval sNDAs for changes to approved drug products that "are not major manufacturing changes." That provision states, in relevant part,

> (1) In General. – For purposes of subsection (a)(2)(B), the Secretary may regulate drugs made with manufacturing changes *that are not major manufacturing changes* as follows:
>
> * * *
>
> (B) The Secretary may in accordance with paragraph (3) require that, prior to the distribution of such drugs, holders submit to the Secretary supplemental applications for such changes.
>
> * * *
>
> (3) Changes Requiring Supplemental Application. –
>
> (A) Submission of Supplemental Application. – The supplemental application required under paragraph (1)(B) for a manufacturing change shall contain such information as the Secretary determines to be appropriate,...
>
> (B) Authority for Distribution.– In the case of a manufacturing change to which paragraph (1)(B) applies:

> (i) The holder involved may commence distribution of the drug involved 30 days after the Secretary receives the supplemental application under such paragraph, unless the Secretary notifies the holder within such 30 day period that prior approval of the application is required before distribution may be commenced.

Thus, there is specific and clear statutory authority for FDA to require supplemental NDA submissions ("sNDAs") for changes to labeling or tablet or capsule embossing, debossing, or printing, even if FDA considers such changes to be non-major. Moreover, FDA may require such sNDAs to contain "such information as the Secretary determines to be appropriate." 21 U.S.C. § 356a(d)(3)(A). Importantly, there are no specific limitations on the information which FDA may require to be submitted, nor on the bases for which FDA may delay approval of such sNDAs. Thus FDA may require such sNDAs to include information on whether the first-filing exclusivity holder has consented to the approval of the sNDA before the expiration of the exclusivity period and, absent such consent, may withhold approval of the sNDA until such exclusivity period has expired. Such a requirement derives from FDA's fundamental authority to regulate prescription drugs in a manner necessary to further the purposes of the FDCA, and the APA's mandate that agencies adhere to established policy unless any departure is reasonably and fully explained.

In addition, and more generally, section 701 of the FDCA and the Administrative Procedure Act compel FDA to require a pre-approval sNDA before a brand generic violates an applicable exclusivity period. Under section 701 of the FDCA, 21 U.S.C. § 371(a), Congress has delegated broad authority to FDA to "promulgate regulations for the efficient enforcement" of the FDCA. Similar authority, to promulgate regulations "necessary for the administration" of the Act, has been specifically granted under the Hatch-Waxman amendments in section 505 of the FDCA, *see* 21 U.S.C. § 355 note, Pub. L. No. 98-417, § 105, 98 Stat. 1585, 1597 (1984). *See also Dr. Reddy's Labs., Inc. v. Thompson*, 302 F. Supp. 2d. 340, 349 (D.N.J. 2003). FDA has previously used this authority to establish its policy that brand generics must be treated as ANDA generics for purposes of the 180-day exclusivity period provisions of the FDCA. *See, supra,* § IV. Failure by FDA to apply this policy as requested herein would be unlawful.

The APA requires that an agency action, or failure to act, that is "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law" must be set aside. 5 U.S.C. § 706(2)(A); *Citizens to Preserve Overton Park Inc. v. Volpe*, 401 U.S. 402, 416 (1971); *see also, Federal Election Commission v. Akins*, 524 U.S. 11, 25 (1998); *GTE Serv. Corp. v. FCC*, 205 F.3d 416-420-421, 427 (D.C. Cir. 2000). Moreover agency action that represents an unexplained departure from the agency's own precedent is inherently arbitrary and capricious. *Motor Vehicle Mfrs. Assoc. v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 42 (1983); *See also Mylan v. Henney*, 94 F. Supp. 2d at 36 ("**Internally inconsistent reasoning by a government agency** is not entitled to any deference by the courts and **is inherently arbitrary and capricious**.") (emphasis added) (internal citations omitted); *Nat'l Black Media Coalition v. FCC*, 775 F.2d 342, 355-56, n.17 (D.C. Cir. 1985) (agency may not "repudiate precedent simply to conform with a shifting political mood."). Failure by FDA to respond to this Petition would also constitute an arbitrary and capricious departure from the Agency's established policy. *See Teva*

Pharmaceuticals v. FDA, 2000 U.S. App. LEXIS 38667 (D.C. Cir. 2000) (affirming mandatory injunction against FDA due to FDA's failure to act, or to reasonably explain its failure to act, when such failure was inconsistent with a prior FDA decision).

Because FDA has previously ruled that a brand generic is the functional and legal equivalent of ANDA generic products for purposes of the 180-day exclusivity period provisions, FDA simply has no option other than to regulate a brand generic version of Accupril® in such a way as to preserve Teva's 180-day exclusivity period rights. As discussed above, FDA's existing regulations require FDA to do so via a pre-approval sNDA requirement, with approval of the sNDA delayed until after expiration of Teva's exclusivity, but Teva would not object if FDA were to establish an alternative, equally effective means of preserving its exclusivity against the premature marketing of a brand generic quinapril product.

Importantly, in this case, exercise of FDA's authority under section 701 does not require formal rulemaking, and there is no need for FDA to delay implementation of an sNDA pre-approval requirement for brand generic quinapril products until formal Guidance or regulatory clarifications are adopted. Given the imminent threat to Teva that Pfizer will launch a brand generic quinapril product as soon as Teva launches its own ANDA generic product, good cause exists under the APA, 5 U.S.C. § 553(b)(3)(B), for FDA to take immediate action and announce that action by way of a direct response to this Petition.

Indeed, that is precisely what FDA did when it established its brand generic policy in the Mylan nifedipine situation. In defending Mylan's appeal of the district court's denial of injunctive relief, FDA correctly noted that its authority to "make rules carrying the force and effect of law" under section 701 does not require notice and comment rulemaking, but can be exercised legitimately through the Citizen Petition process. *See* FDA Nifedipine Appeal Brief at 20-21 ("[W]ith respect to the Hatch-Waxman Amendments, Congress delegated to the agency the authority to 'make rules carrying the force of law.'") (citing *United States v. Mead Corp.*, 121 S.Ct. 2164, 2171 (2001)). Thus, as asserted by FDA, a decision granting this Petition will be "entitled to *Chevron* deference under the *Mead* analysis because [FDA] was delegated authority to act with the force of law with respect to [interpreting 180-day exclusivity period provisions of] the Hatch-Waxman amendments." *Id.*

Immediate direct action to prevent brand generic quinapril products from eroding Teva's exclusivity rights is also consistent with FDA's Guidance For Industry: *180-Day Generic Drug Exclusivity Under the Hatch-Waxman Amendments to the Federal Food, Drug, and Cosmetic Act* (June 1998). In that Guidance FDA announced that it "will regulate directly from the statute, and will make decisions on 180-day generic drug exclusivity on a case-by-case basis." *Id.* at 4. FDA's asserted authority to make decisions regarding 180-day exclusivity period issues on a "case-by-case basis" without formal rulemaking was upheld by the courts. *Purepac v. Friedman*, 162 F.3d 1201, 1204 (D.C. Cir. 1998).

VI. CONCLUSION

In the absence of immediate agency action as requested herein, brand or so-called "authorized generics" will continue to intrude upon and violate other companies' exclusivity periods and contravene the purposes of Hatch-Waxman and FDA's established policy as articulated in the *Mylan* nifedipine proceedings. FDA therefore must enforce its existing regulations to require pre-approval sNDAs for labeling and product changes that would create a generic version of Pfizer's Accupril® before the expiration of Teva's exclusivity period. FDA should delay approval of such a supplement, absent Teva's consent to approval, until the expiration of Teva's 180-day exclusivity period for generic quinapril products.

FDA should take similar action with respect to any and all other existing or pending brand generic products that may be launched prior to the expiration of an applicable 180-day exclusivity period. Such action is necessary to effectuate FDA's current policy governing exclusivity periods and conform with the factors outlined by FDA to be considered in interpreting the 180-day exclusivity provision of Hatch-Waxman. Specifically, delayed approval of brand generic sNDAs until the expiration of the exclusivity period would: **(1)** be "consistent with '[Hatch-Waxman's] interest in affording market access and incentives for both generic and non-generic makers,' and to maintain 'an incentive for the parties to fulfill the purposes of Hatch-Waxman;' **(2)** preserve the intent of the statute "to provide an incentive for drug companies to explore new drugs, not a market 'windfall' for crafty, albeit industrious, market players;" and **(3)** "avoid interpreting Hatch-Waxman so the decision on whether a generic applicant is entitled to exclusivity rests entirely in the patent holder's hands." *See* Nifedipine Petition Response at 5 (citing *Mylan v. Henney*, 94 F. Supp. 2d. at 53-54). In contrast, failure to act would result in subversion of Hatch-Waxman.

This Petition presents FDA with a clear choice of actions: (1) do nothing, and allow brand generics to blatantly and dramatically eviscerate the crucial and indisputable Congressional intent behind the 180-day exclusivity period provisions, as well as FDA's brand generic policy enunciated in *Mylan v. Thompson*; or (2) exercise its existing statutory and regulatory authority to temporarily delay the marketing of brand generics until the term of any 180-day exclusivity period for the first-filed Paragraph IV ANDA applicant has expired. Given FDA's clear authority to act immediately to preserve the intent of Hatch-Waxman's 180-day exclusivity period incentive, and the Agency's existing policy that brand generics must be treated as the legal and functional equivalent of ANDA-approved generic products, the Agency is compelled to take action to prevent the sale of brand generic quinapril products during the term of Teva's 180-day exclusivity period. Failure to do so would be arbitrary and capricious in violation of the APA. As noted above, Teva requests an expedited response to this Petition, so that any necessary judicial review can be sought in time to preserve Teva's specific exclusivity rights with respect to generic quinapril drug products.

ENVIRONMENTAL IMPACT

The actions requested by this Petition are subject to categorical exclusion pursuant to 21 C.F.R. § 25.30.

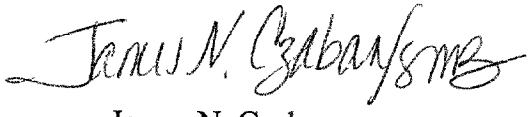
ECONOMIC IMPACT

An Economic Impact Statement will be provided at the request of the Commissioner.

CERTIFICATION

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the Petition.

Sincerely,



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