



October 5, 1998 ^{5 7 9 4} '98 OCT -5 P4:56

By Hand Delivery

Dockets Management Branch (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

RE: Docket No. 98D-0265; Section 111 Pediatric Studies of Drugs

The Generic Pharmaceutical Industry Association ("GPIA") and the National Pharmaceutical Alliance ("NPA") hereby submit the enclosed documents to Docket No. 98D-0265 as comments regarding the Food and Drug Administration ("FDA") guidance titled Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act. See 63 Fed. Reg. 36707 (July 7, 1998). The documents are a Citizen Petition and a Petition for Stay of Action requesting the Commissioner of FDA to take certain actions relating to the implementation of section 505A.

If you have any questions, please contact Kathleen D. Jaeger of McKenna & Cuneo, L.L.P. at (202) 496-7591.

Respectfully,

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Enclosures (2)

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CITIZEN PETITION

The Generic Pharmaceutical Industry Association (“GPIA”) and the National Pharmaceutical Alliance (“NPA”) submit this petition under section 701(a) of the Federal Food, Drug, and Cosmetic Act¹ (the “Act”), section 4 of the Administrative Procedure Act (the “APA”),² and sections 10.25-10.30 of Title 21, Code of Federal Regulations. This petition requests the Commissioner of the Food and Drug Administration (“FDA”) to terminate and suspend all actions taken pursuant to section 505A of the Act, and to undertake notice and comment rulemaking to develop regulations for the implementation of the Pediatric Studies of Drugs provision of the Food and Drug Administration Modernization Act (“FDAMA”).³

GPIA and NPA are trade associations comprised of manufacturers and distributors of affordable pharmaceuticals, as well as the providers of technical services and goods to these firms. These trade associations are committed to providing high quality, affordable, safe and effective medicines to all patients. GPIA and NPA members and their customers have a significant interest in the proper exercise of the authority granted to FDA by Congress under section 505A of the Act; specifically, whether FDA’s implementation of section 505A yields meaningful pediatric information and labeling statements, and whether FDA’s implementation is legally permissible.

¹ 21 U.S.C. § 371(a) (1994).

² 5 U.S.C. §§ 553 (1994).

³ Pub. L. No. 105-115, § 111, 1997 U.S.C.C.A.N. (111 Stat.) 2296, 2305 (1997).

Action Requested

FDA has recently issued the List of Drugs For Which Additional Pediatric Information May Produce Health Benefits In the Pediatric Population⁴ (the "List") and the guidance document titled Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act⁵ (the "Guidance"). Pursuant to the List and Guidance, FDA also has issued Written Requests for pediatric studies and has granted exclusivity extensions. GPIA and NPA submit that FDA's implementation of section 505A through these actions is arbitrary and capricious and conflicts with the purpose and plain meaning of the statute. GPIA and NPA also submit that implementation of section 505A should be undertaken through notice and comment rulemaking. GPIA and NPA accordingly request that the Commissioner take the following actions:

1. Immediately rescind and declare invalid the List, the Guidance, existing Written Requests, and pediatric exclusivity grants, because the agency's implementation of section 505A is legally inconsistent and impermissible.
2. Suspend all future action taken pursuant to section 505A until appropriate regulations are promulgated in accordance with the APA. Notice and comment rulemaking is required in this instance because FDA's implementation policy constitutes substantive rulemaking, as that term has been defined by the federal courts, and has a substantial adverse effect on the generic industry and consumers alike.

Background

The legislative effort that produced section 505A began in 1992 with the introduction by Senator Nancy Kassebaum (R-Kansas) of the Better Pharmaceuticals for Children Act. S. 3337, 102d Cong., 2d Sess. (1992) (the "BPCA"). The BPCA was intended to increase the availability of information on the safety and effectiveness of pharmaceutical products used by children by providing

⁴ See 63 Fed. Reg. 27733 (May 20, 1998). The statute required FDA to develop and publish the List within 180 days of the enactment of FDAMA. FDCA § 505A(b), 21 U.S.C. § 355A(b). For drugs already on the market, FDA may not issue a written request for the submission of pediatric studies under section 505A until the drug is first placed on the List. FDCA § 505A(c), 21 U.S.C. § 355A(c).

⁵ See 63 Fed. Reg. 36707 (July 7, 1998).

market incentives to manufacturers. 138 Cong. Rec. S16998-99 (Oct. 5, 1992) (statement of Sen. Kassebaum).

At about the same time that Senator Kassebaum introduced the BPCA, FDA began administrative action aimed at improving pediatric use labeling. In 1994, the agency finalized pediatric labeling regulations that, among other things, required manufacturers to determine whether additional pediatric use labeling could be provided based on existing data and information and if so, to submit a supplemental application proposing such changes. 59 Fed. Reg. 6420 (Dec. 13, 1994) (promulgating 21 C.F.R. § 201.57(f)(9)). In other words, while the regulation did not require the performance of pediatric research, it did require product labeling to be updated based on existing information.

Because the 1994 regulation lacked a mandate to perform pediatric research, Congress continued to consider the enactment of the BPCA.⁶ FDA subsequently proposed a regulation that would mandate pediatric studies for all new drugs. 62 Fed. Reg. 43900 (Aug. 15, 1997). This proposal also would grant FDA the authority, under certain conditions, to require manufacturers of currently marketed drugs to perform pediatric studies. Specifically, the proposal would allow the agency to require studies on approved drugs "in compelling circumstances" where the product is "widely used in pediatric patients, or indicated for a very serious or life threatening illness." *Id.* at 43913. Finalization of the proposed regulation is listed as a significant priority in a recent FDA regulatory plan. 62 Fed. Reg. 57003, 57048-49 (Oct. 29, 1997).

Following the issuance of the proposed rule in 1997, there was some debate in Congress regarding the continued need for passage of the BPCA. This debate did not concern FDA's authority to mandate pediatric studies, as Congress apparently believed that current statutory provisions confer such authority on the agency. Rather, the debate revolved around whether offering exclusivity to encourage pediatric studies was necessary in light of the proposed rule.⁷ It appears, however, that Congress concluded the incentives contained in the BPCA would be an appropriate means for encouraging pediatric labeling in most situations, leaving mandated studies under FDA's proposed rule as a means reserved for unusual

⁶ See S. 2010, 103d Cong., 2d Sess. (1994); H.R. 4427, 103d Cong., 2d Sess. (1994); S. 2178, 104th Cong., 2d Sess. (1996); H.R. 4277, 104th Cong., 2d Sess. (1996); S. 713, 105th Cong., 1st Sess. (1997); H.R. 1727, 105th Cong., 1st Sess. (1997).

⁷ See, e.g., Antibiotic, Pediatric Labeling Market Exclusivity Provisions Included in House FDA Reform Draft Bill, F-D-C Reports "The Pink Sheet," Sept. 15, 1997, at 6 (reporting comments made by Sen. Orrin Hatch (R-Utah)).

circumstances. The new law is therefore intended to supplement the proposed rule, not to preempt it. Ultimately, the BPCA was approved as part of FDAMA, which was signed into law by the President on November 21, 1997.

FDA has issued two final documents regarding the implementation of section 505A. The first is the List of approved drug products for which FDA has allegedly determined that additional information regarding use in the pediatric population may produce health benefits for that population. The second document is the Guidance which provides FDA's interpretation and implementation of section 505A. GPIA and NPA have significant concerns regarding both the substance of these documents and the procedure by which they were developed and implemented.

Statement of Grounds

I. FDA'S POLICY, AS IMPLEMENTED IN THE LIST AND THE GUIDANCE, IS UNSUPPORTED BY THE STATUTORY LANGUAGE, ARBITRARY AND CAPRICIOUS, AND INCONSISTENT WITH CONGRESSIONAL INTENT

Through the List and the Guidance, the agency has implemented a policy with respect to section 505A that is (1) unsupported by the clear language of the Act and (2) arbitrary and capricious, and inconsistent the unambiguous Congressional intent underlying the statute. As such, FDA's implementation of section 505A is unlawful. The List and the Guidance should therefore be withdrawn or modified through notice and comment rulemaking so as to comply with the applicable requirements of the Act and the APA. Furthermore, all actions taken to implement section 505A should be terminated and/or suspended pending the establishment of an implementation policy, pursuant to the notice and comment rulemaking requirements of the APA. Finally, existing Written Requests and exclusivity grants, which derived from the List and the Guidance, should be withdrawn.

A. The List and Guidance Should be Rescinded Because They Fail to Comport with the Plain Language of the Statute

1. The agency's List is procedurally flawed

Section 505A(b) mandates that the agency "after consultation with experts in pediatric research, develop, prioritize, and publish an initial list of approved drugs for which additional pediatric information may produce health benefits in the pediatric population" (the "List"). 21 U.S.C. § 355a (b) (emphasis added). On May 20, 1998, FDA published a document informing the

public that, rather than compiling a separate list of drugs in accordance with section 505A(b), the agency considers all drugs that are approved for indications occurring in children to be on the List. See 63 Fed. Reg at 27733; see also Guidance at n.6. The agency's approach ignores the plain language of the statute by failing to adequately consult with pediatric research experts on this issue. The phrase "consultation with experts in pediatric research" clearly implies more than informally seeking comments from a few trade associations and governmental agencies. To comply with the statutory requirement, FDA must conduct a formal process (e.g., a task force or advisory committee with public participation) that ensures meaningful input by pediatric researchers (i.e., university hospitals, individual research specialists, academia, etc.).

Moreover, nothing in the administrative record indicates that the agency performed the statutorily required two-part informational assessment as to each Listed drug. Specifically, the agency failed to determine (1) whether additional information is needed, and (2) if so, whether such information may provide the requisite health benefits. Rather, the agency merely dispensed with this mandate by including all drugs that have approved indications that occur in children. The fact that Congress provided FDA with 180 days to compile the List lends strong support to the notion that Congress intended FDA to do more than list the drugs approved for an indication occurring in children.

Although the agency attempts to minimize the importance of the List, see List at 1, it cannot be denied that inclusion on the List is at least an assertion that a drug may be eligible for pediatric exclusivity. See 21 U.S.C. § 355a (c). The mere fact that the List is not the final step in determining whether exclusivity will be granted does not justify disregarding the clear language of the statute. Because FDA's current version of the List was compiled without adequate informational assessments and adherence to the statutorily mandated meaningful participation by the pediatric research community, the agency's action in developing and publishing the "List" is inconsistent with the plain language of the statute and therefore unlawful. See Chevron U.S.A., Inc. v. National Resources Defense Council, Inc., 467 U.S. 837, 842 (1984); see also Univ. of the District of Columbia Faculty Association/NEA v. Board of Trustees of the Univ. of the District of Columbia, 994 F. Supp. 1 (D.D.C. 1998).

2. Exclusivity cannot lawfully be extended to drugs approved under section 505(b)(2)

Section 505A(a) and (c) state that only new drug applications submitted or approved under section 505(b)(1) are eligible for exclusivity. Notwithstanding this clear statutory language, FDA's policy allows sponsors and holders of applications

submitted or approved under section 505(b)(2) to be eligible for exclusivity. Guidance at 2, n.4. FDA's position is without merit.

Nothing in the statute or the legislative history supports the agency's contention. Congress made a clear distinction between the types of 505(b) applications when it explicitly provided that only 505(b)(1), not 505(b)(2), applications are eligible for pediatric exclusivity. Had Congress intended to extend exclusivity to all 505(b) applications, it would have so provided. For example, within section 505A itself, subsection 505A(e) allows FDA to delay the approval of "application[s] under section 505(b)(2)" until it makes a determination under subsection (d). Likewise, the phrase "applications submitted under section 505(b)" is used throughout section 505 to identify applications submitted under subsection (b)(1) or (b)(2).⁸ Thus, when drafting section 505A, Congress decided not to use the inclusive "505(b)" language, opting instead for the more limited and exclusive "505(b)(1)" language. FDA cannot ignore Congress' choice of specific words and read the terms "505(b)" and "505(b)(1)" to have identical meanings (i.e., including 505(b)(1) and (b)(2) applications). Congress intended exactly what is stated by the plain language of the statute – that only full 505(b)(1) NDAs be granted exclusivity.

3. FDA's position on granting exclusivity to other drug products containing the same active moiety as the studied drug product is contrary to the plain language of the statute _____

Contrary to the plain language of the statute, FDA will attach pediatric exclusivity to "any exclusivity or patent protection that is, or will be, listed in the *Orange Book* for any drug product containing the same active moiety as the drug studied." Guidance at 12. In other words, FDA seeks to alter the definition of the term "drug" by expanding the definition to include identical, related, and similar drug products containing the same active moiety⁹ as the "drug" studied. Simply put, FDA's position is that the word "drug" in section 505A means "active moiety." This contention conflicts with the plain language of the statute.

⁸ See 21 U.S.C. §§ 355 (a), (c)(1), (c)(2), (c)(3), (d)(1), (d)(6), (e)(5), (j)(2)(B)(i)(II), (j)(5)(D) (general references to subsection 505(b) intended to include both 505(b)(1) and 505(b)(2)).

⁹ FDA defines an "active moiety" as "the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivatives (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance." 21 C.F.R. § 314.108(a).

Nothing in the statute or legislative history supports FDA's interpretation. Rather, FDA and the courts have consistently interpreted the term "drug" in section 505 to mean "drug product." See United States v. Generix Drug Corp., 460 U.S. 453 (1983); see also Pfizer, Inc. v. Food and Drug Administration, 753 F. Supp. 171 (D. Md. 1989). Furthermore, this position is entirely consistent with FDA's regulations on 505(b) drug applications, and comports with the Congress' vision of section 505A as a natural extension of the section 505 exclusivity provisions. See 138 Cong. Rec. S16999 (Oct. 5, 1992).

Moreover, Congress designed section 505A to be application specific, not active moiety specific. For example, section 505A uses the terms "drug," "the application," "the holder of an application," and a "supplemental application." 21 U.S.C. § 355a(a) and (c). Likewise, subsections 505(c)(3)(D)(iii) and 505(j)(5)(D)(iii) provide exclusivity to the drug product studied, not all of the firm's related products containing the same active moiety. Similarly, section 505(j)(8)(A) defines bioavailability in terms of absorption of the active ingredient (or therapeutic ingredient) from the "drug." Congress could have easily substituted the phrase "active moiety" for the term "drug;" yet, it did not. See Cabazon Band of Mission Indians v. Nat'l Indian Gaming Comm'n, 827 F. Supp. 26, 32 (D.D.C. 1993) cert. denied, 512 U.S. 1221 (1994) ("the court must give effect to Congress' explicit language and to each word and provision of the statute [citations omitted]"). Thus, the grant of exclusivity is product specific, and is limited to the drug product subject to the application referenced in the Written Request.

B. FDA's Policy is Arbitrary and Capricious and Inconsistent with the Congressional Intent

At least three other provisions of FDA's policy, as implemented under the Guidance, are so unreasonable, or contrary to the express Congressional intent, as to be fatally flawed. FDA's actions must be "reasoned" in the sense that it must consider the relevant facts and their impact upon the underlying policy of the implementing statute. When an agency's actions are not properly reasoned the federal courts have held that such actions are "arbitrary or capricious" under the APA, and therefore unlawful. 5 U.S.C. § 706 (2) (A); See Citizens to Preserve Overton Park, Inc. v. Volpe, 401 U.S. 402 (1971). Mere "reasoned" actions, however, are not enough to ensure compliance with the APA. An agency's actions "must also be true to the congressional mandate from which [they] derive [] authority." Farmers Union Central Exchange, Inc. v. F.E.R.C., 734 F.2d 1486, 1500 (D.C. Cir. 1984). The following are examples of provisions in the Guidance that are inconsistent with the Congressional intent and, therefore, are "arbitrary or capricious."

1. FDA fails to require that studies supporting exclusivity be designed to yield data which would support a meaningful labeling change

FDA has failed to recognize that Congress intended section 505A to increase the number of drug products labeled for pediatric use. For example, Senator Dodd, a cosponsor of the original legislation, stated that the provision was intended to induce manufacturers to “test their products for use by children” and “to make the extra effort needed to label their products for use by children.” 143 Cong. Rec. S4277 (May 9, 1997); 142 Cong. Rec. S11992 (Sept. 30, 1997) (emphasis added). Despite this clear mandate, the agency’s policy fails to establish a standard with respect to study significance. See Guidance at 10-12.

To comply with the clear intent of the statute, FDA must require that a study be designed to yield meaningful and informative labeling statements to be eligible for exclusivity. The statute also requires that the information be “additional” (i.e., derived from new studies) and capable of improving the existing body of knowledge concerning pediatric indications (i.e., of such a nature as to result in a significant label change). See 21 U.S.C. §§ 355a (b), (k)(1). Furthermore, studies that support exclusivity under another section of the Act (e.g., “new use” exclusivity under sections 505(c)(3)(D)(iv) and (j)(5)(D)(iv)) are not “additional” pediatric studies and therefore should not also be the basis for pediatric exclusivity. The statute does not contemplate grants of two exclusivity periods for the same study. The language of section 505A establishes a minimum standard for studies that will qualify for exclusivity, and prevents the statute from becoming an incentive to conduct unnecessary and unethical studies on pediatric patients when the only perceived benefit is extra profits for the manufacturer.

Furthermore, because a grant of market exclusivity comes at a significant cost to the public, exclusivity should not be granted unless there is a corresponding reasonable probability of public benefit (i.e., study yields information to support a material labeling change).¹⁰ Drug manufacturers who receive exclusivity stand to reap millions of dollars in extra profits as a result. Despite the monetary cost to both the private and public sectors, grants of exclusivity result in reduced availability of lifesaving and life enhancing affordable pharmaceuticals, especially to those in the lower socioeconomic classes. In exchange, the public is supposed to have improved information about pediatric uses. See 21 U.S.C. 355a(k)(1). This premise collapses if doctors and parents never receive meaningful and informative

¹⁰ See S. Rep. 105-43 at 52 (Report of the Senate Committee on Labor and Human Resources) (exclusivity is to be granted when a manufacturer “conducts pediatric studies to support pediatric labeling”) (emphasis added).

labeling information and/or directions for use.¹¹ This would be particularly true if the agency fails to exercise its discretion to limit the use of pharmacokinetic studies to support exclusivity. Because these studies do not require the extensive investment that warrants exclusivity, the agency should accept these studies only in exceptional cases where compelling circumstances justify a grant of exclusivity.

Thus, the clear statutory language, combined with the underlying legislative intent, compel the agency to adopt a rigorous standard requiring studies be designed to yield, with a high probability, meaningful labeling information as contemplated by Congress.¹²

2. FDA's prioritization scheme is arbitrary
and inconsistent with the statutory mandate

Section 505A(b) instructs FDA to "prioritize" the List of pediatric drug products potentially eligible for exclusivity. Yet, instead of putting at the forefront the unmet medical needs of children suffering from life-threatening, serious and/or chronic conditions, economic considerations are driving FDA's system. Specifically, FDA is granting priority to products based on diminishing marketing protections regardless of whether these agents fill a meaningful therapeutic void.¹³ While we acknowledge that FDA is entitled to establish an orderly system to issue Written Requests and review study reports, FDA's system preserves certain monopolistic firm profits, to the extreme detriment of pediatric patients. Because FDA's Congressional mandate is to protect the public health, the agency must revamp its priority system. The system should be based foremost on the derived therapeutic benefit to the pediatric population and independent of economic interests.

¹¹ See 138 Cong. Rec. S16999 (Oct. 5, 1992) (comments of Senator Kassebaum) (the legislation is intended to give physicians and parents "more confidence in using appropriately labeled drugs" for pediatric uses).

¹² See 143 Cong. Rec. S4277 (statement by Senator Dodd that "it is about time that we have labels that parents and physicians can rely on when they give children medicine").

¹³ According to the Guidance, FDA will give priority to proposals for Written Requests that concern drug products whose current patent term or market exclusivity will expire on or before March 31, 1999. Guidance at 7-8.

3. FDA arbitrarily grants exclusivity regardless of the timing and sponsor of the study

FDA not only intends to grant exclusivity for studies conducted prior to the issuance of FDA's Written Request, but also, in some cases, for studies conducted before the enactment of section 505A. See Guidance at 4. The legislative history is contrary to FDA's position on this point. Congress intended section 505A to be an incentive for manufacturers to conduct studies when it is not otherwise in their pecuniary interest to do so and when the information does not already exist. See, e.g., 138 Cong. Rec. S16999. Section 505A(a) explicitly calls for "additional" pediatric studies, not existing data. Moreover, to allow manufacturers to benefit from prior studies when the firms are already legally bound to include such studies in their labeling is unjust and contrary to FDA regulations. Specifically, FDA regulations state that "if a manufacturer knows, or has knowledge of facts that would give him notice, that a drug introduced into interstate commerce by him is to be used for other conditions, purposes, or uses other than the ones for which he offers it, he is required to provide adequate labeling for such a drug which accords with such other uses." 21 C.F.R. § 201.128. FDA's position therefore runs counter to existing requirements and public policy. There is no legal basis, nor reasonable policy justification for FDA to grant exclusivity for studies performed either before the enactment of section 505A or the issuance of an FDA Written Request.

Likewise, studies conducted or sponsored by someone other than the submitter, should not form the basis of exclusivity. The common thread running through the Hatch-Waxman Act¹⁴ exclusivity provisions is that exclusivity is intended to be a reward to innovators for incurring research and development costs. Pediatric exclusivity, which is modeled after the Hatch-Waxman Act provisions, likewise should reward only those manufacturers who have incurred the requisite research costs. See 138 Cong. Rec. S16999 (Oct. 5, 1992). Specifically, section 505A clearly contemplates that "the applicant" conduct the requisite study, not benefit from piggy backing off the efforts of others. See 21 U.S.C. §§ 355a(a), (d). Therefore, neither literature reviews nor studies conducted or sponsored by others are costs related to innovative activity and, therefore, should not support an exclusivity reward.

¹⁴ The Drug Price Competition Act and Patent Term Restoration Act of 1984, Pub. L. 98-417, 98 Stat. 1585 (1984).

**II. FDA'S IMPLEMENTATION OF SECTION 505A
REQUIRES NOTICE AND COMMENT RULEMAKING**

A. Implementation of section 505A represents substantive agency action requiring notice and comment rulemaking

GPIA and NPA also assert that the implementation of section 505A should be undertaken through notice and comment rulemaking. Because the establishment of clear FDA policies and procedures governing the implementation of section 505A is critical to the underlying pediatric exclusivity objectives, the APA mandates that notice and comment rulemaking be undertaken before the agency implements such policies and procedures. See National Motor Freight Traffic Ass'n v. United States, 268 F. Supp. 90, 96 (D.D.C. 1967), aff'd, 393 U.S. 18 (1968). In fact, by stating that it plans to proceed with notice and comment rulemaking at a later date, FDA acknowledges that implementation of its policy requires such rulemaking. Guidance at 1; 63 Fed. Reg. at 36707. Nevertheless, the agency has proceeded to engage in implementing agency policy in clear violation of the APA. Given the fact that these policies have a substantial effect on the generic drug industry and consumers alike, FDA cannot lawfully dispose of notice and comment rulemaking under the theory that it needs to implement FDAMA. See 36 Fed. Reg. at 36707. The APA makes no allowances for Congressionally imposed deadlines nor does it grant special rulemaking powers to agencies subject to such Congressional mandates.

Not only is the agency's adoption of policies important to implementation, but those policies undoubtedly will have an immediate and significant impact upon private interests, a factor that the courts have relied upon in finding an agency action to comprise a substantive rule, requiring notice and comment. See, e.g., Batterton v. Marshall, 648 F.2d 694, 701-02, 708 (D.C. Cir. 1980); see also Continental Broadcasting System, Inc. v. United States, 316 U.S. 407, 420-22 (1942). The policies contained in the List and the Guidance clearly will impact dramatically the ability of generic manufacturers to offer their products to consumers, of consumers to obtain affordable pharmaceuticals, and of physicians, parents and pediatric patients to derive benefits from improved product labeling. The availability of such exclusivity creates the possibility that the marketing plans of potential generic competitors will be delayed, to the detriment of consumers and the generic industry.

Moreover, the very nature of section 505A intensifies the impact upon interested parties and renders it, in some cases, irreversible. For example, by placing a drug on the List and subsequently issuing a Written Request for studies, FDA will create a statutory entitlement to pediatric exclusivity that, in some cases, cannot be modified or rescinded by subsequent notice and comment rulemaking.

Once a manufacturer has commenced studies in accordance with an FDA approved protocol, the firm will receive a grant of exclusivity provided that the study reports are submitted to FDA within the specified timeframe. The Supreme Court's opinion in Continental Broadcasting demonstrates that, due to such substantial effects, it is imperative that all interested parties, particularly generic manufacturers and consumers, have the opportunity to comment on the agency's regulatory scheme before it is implemented. The agency, therefore, must suspend the issuance of additional Written Requests until notice and comment rulemaking is completed.

Along with its substantial effect on private interests, the implementation of section 505A will require FDA to engage in the type of "quasi-legislative" functions for which notice and comment rulemaking was intended to apply. In other words, many of the policies and procedures FDA must adopt to implement section 505A cannot be viewed as mere interpretation of the statutory language adopted by Congress. For example, with regard to the term "written request," neither the statute nor the legislative history provide clarification as to the appropriate breadth or scope of such a request, even though that scope is central to the operation of the statute.¹⁵ Yet, from the simple statutory term "written request," and without any reference to other portions of the statute or the legislative history, FDA has written two pages defining what will and will not be considered a Written Request under section 505A. Guidance at 4-5. Clearly, these numerous pronouncements cannot be viewed as merely an interpretation, based upon statutory language and legislative history, of what Congress meant by "written request." Rather, they represent FDA's own judgement as to how best to implement section 505A, a judgement that the APA contemplates will be made with the input of the public as provided by notice and comment. See United Technologies Corp. v. EPA, 821 F.2d 714, 719-720 (D.C. Cir. 1987); see also Syncor International Corp. v. Shalala, 127 F.3d 90, 94-95 (D.C. Cir. 1997) (an agency is acting by its own authority unless its interpretation "is drawn linguistically from the actual language of the statute.") (quoting Paralyzed Veterans of America v. D.C. Arena L.P., 117 F.3d 579, 587 (D.C. Cir. 1997)).

This is not to say that GPIA and NPA believe the agency should simply withdraw the Guidance and proceed with the implementation of section 505A on a case-by-case basis. To the contrary, as noted above, we believe that a careful, prospective consideration and determination of certain aspects of the implementation is critical to ensuring that the statute operates in the manner intended by Congress. In other words, without public participation in designing the

¹⁵ A manufacturer may only gain exclusivity if the studies are submitted in accordance with the Written Request. 21 U.S.C. § 355a(d)(2)-(3).

implementation of section 505A, there is a significant chance that certain manufacturers will gain additional market exclusivity, the cost of which will be borne by consumers, without yielding any additional, beneficial pediatric information as contemplated by the statute. Furthermore, the lack of binding regulations developed through notice and comment rulemaking will have a substantial adverse effect on the interests of multiple parties including generic manufacturers, and patients who would benefit from improved pediatric use labeling. Considering the importance of the private interests at stake, the need for consistent administration and certainty on issues of market access, and the potential cost to the public of the agency's 505A implementation, GPIA and NPA assert that further action taken pursuant to section 505A must be suspended until appropriate regulations are promulgated.

B. FDA's failure to undertake notice and comment rulemaking has deprived GPIA and NPA of a meaningful opportunity to comment on FDA's implementation of section 505A

Had GPIA and NPA been afforded the opportunity to comment on FDA's implementation of section 505A during a notice and comment rulemaking, industry would have raised concerns and offered comments regarding this important matter. Examples of where industry has been deprived of a meaningful opportunity to comment are set forth below.

1. The inclusion of an approved drug product on the List mandated by section 505A(b) should be based upon a compelling demonstration that additional information regarding the pediatric use of that drug is needed

Throughout this petition, and particularly in Part I.A.1., GPIA and NPA have demonstrated that Congress itself established the standard to determine which approved drug products would be eligible to receive additional exclusivity in return for pediatric studies. Congress stated that approved drug products are to be placed on the List of eligible products only if "additional pediatric information may produce health benefits." Unfortunately, FDA abdicated its duty to responsibly administer section 505A for the public benefit when it crafted the List. The agency gave no consideration to whether each approved drug product is actually used, or even potentially may be used, for the treatment of children, or to whether adequate information on such use is already available to physicians and parents. FDA looked only to whether an indication for the use of some form of the drug occurs in children. This broad standard has resulted in the listing of drug products for which there is no clear need for additional information, and certainly no need for the public to "buy" such information from the drug manufacturer.

To meet its mandate under section 505A, FDA should require that no approved drug product be included on the new List unless it is clearly demonstrated that: (1) information currently available is inadequate to ensure its safe and effective use in children; (2) there is a significant potential that the approved drug product is being or will be used in the pediatric population; and (3) a determination by FDA, in consultation with pediatric researchers, is made that additional information may provide a meaningful benefit to pediatric patients. The inclusion determination should be made subject to public notice and comment. FDA also should require that any approved drug product added to the List in the future meet the same requirements. Finally, because the need for information on pediatric use may change over time, FDA should establish a process for interested parties to petition the agency for the removal of drug products from the List. Grounds for removal should include a demonstration that additional information is no longer needed or that there is no longer a significant potential for use of the drug product in the treatment of children.

2. Prioritization of the List should be based on the need for additional information, not the interest of the manufacturer in obtaining exclusivity

The statute directs FDA to prioritize the List. The agency, in consultation with pediatric researchers, should prioritize the List using public health objectives, not market factors. At a minimum, FDA should designate drug products as priority products only if: (1) there is evidence that the drug product is being used in the pediatric population and is posing unacceptable risks to pediatric patients due to a lack of essential information¹⁶; or (2) the drug product is not currently used in the pediatric population, but there is a significant potential that such use could provide substantial health benefits, e.g., because currently available treatments are inadequate. FDA should specifically provide "high" priority to drug products that address the unmet needs of serious, life-threatening, and/or chronic conditions where there are no alternative treatments.

¹⁶ Essential pediatric information can be found, among other places, in United States Pharmacopeial Convention, Inc., USP DI (18th ed. 1998); Stephanie J. Phelps and Emily B. Hak, Guidelines for Administration of Intravenous Medications to Pediatric Patients (Amer. Soc. of Health-System Pharmacists, 5th ed. 1996); Thomas E. Young and O. Barry Mangum, Neofax® 1997—A Manual of Drugs Used in Neonatal Care (Amer. Soc. of Health-System Pharmacists, 10th ed. 1997); and Carol K. Takemoto et. al, Pediatric Dosage Handbook (Amer. Pharmaceutical Ass'n, 4th ed. 1997-98).

FDA's current implementation uses two factors to determine the timeframe in which FDA will review a proposal for the issuance of a Written Request. The first is whether the drug product is included in the priority section of the List, which we agree is an appropriate factor, as discussed above. The second is the time left until expiration of the drug product's current patent term or market exclusivity. This factor places the interests of manufacturers ahead of those of the public. FDA's limited resources should be focused on drug products for which there is a material medical need for pediatric information, not how much exclusivity remains. It also may encourage manufacturers to "game" the system, waiting to submit a proposed request until the last possible moment, secure in the knowledge that their application will be given priority. For these reasons, FDA's determination of the order in which drug products will be considered for Written Requests should be made based on the potential public health benefits.

3. Only drug products for which an NDA has been submitted or approved under section 505(b)(1), not 505(b)(2), should be eligible for inclusion on the List and the issuance of a Written Request

As demonstrated above in Part I.A.2., the statutory language clearly and unambiguously limits the drug products eligible for pediatric exclusivity to those covered by full NDAs submitted under section 505(b)(1).

4. FDA's Written Request for studies should be carefully drafted to ensure that studies submitted will provide meaningful health benefits

As noted in the discussion under Part II, once a Written Request is issued, it creates a statutory entitlement to exclusivity in manufacturers who submit studies meeting that request. Thus, the issuance of a poorly designed request could result in the extension of exclusivity without the submission of data providing an additional meaningful health benefit. The requirements established in a Written Request, therefore, are the key criteria that will determine whether the congressional objective underlying section 505A -- the improvement of public health -- will be derived from the submission of studies, or whether the statute will simply produce increased costs for consumers by unproductively delaying the introduction of generic products. Because this result is critical, the following substantive and procedural requirements governing the issuance of Written Requests are necessary for this purpose.

First, FDA must determine that there is a reasonable scientific justification for the need of the "proposed" additional pediatric information. In other words, the study must be designed to yield (with a high probability) new, significant,

meaningful information and should lead to material labeling changes. Otherwise, the study may expose children to unnecessary clinical research.

Second, the Guidance appears to contemplate the issuance of separate Written Requests for different pediatric subgroups, distinguished by age of the patient. Guidance at 6-7. Under section 505A(h), a manufacturer who has received one grant of exclusivity for a drug product pursuant to section 505A may receive one additional extension for a second pediatric study. 21 U.S.C. § 355a(h); Guidance at 12. GPIA and NPA oppose the issuance of Written Requests for studies that are limited to specific pediatric subgroups in the absence of a clear scientific need or rationale. GPIA and NPA assert that studies should encompass all appropriate subgroups for a given indication and produce one, not two, exclusivity periods for that indication.

Third, because of the enormous impact of these issues on affected parties, interested persons should be provided the opportunity to comment on all proposed Written Requests.

5. Exclusivity should be granted only for studies that are conducted by the NDA sponsor after receipt of a Written Request

As previously stated in Part I.B.2., FDA's policy allows exclusivity to be granted for studies conducted prior to the issuance of FDA's Written Request (and even prior to the enactment of Section 505A), as well as for studies that were not conducted by the NDA sponsor. Guidance at 4. Congress clearly intended, however, that exclusivity operate as an incentive for manufacturers to perform studies that might not otherwise be in their interest. Exclusivity extensions either provided to manufacturers who assumed neither the expense nor the risks associated with the study, or for studies that were already undertaken or completed without incentives, provide a windfall to manufacturers that was never intended by Congress. FDA should revise its implementation, therefore, to require that studies submitted under section 505A must be initiated after, and in response to, the issuance of a Written Request. FDA should further require that such studies be conducted under the control, or at least at the expense, of the manufacturer seeking exclusivity.

6. Only the exclusivity of the drug product studied should be extended, not all products with the same active moiety

FDA intends to grant pediatric exclusivity to any drug which contains the same active moiety as the drug studied. Guidance at 12. As demonstrated in

Part I.A.3 above, this position is contrary to the plain language of the statute and would adversely impact the objective of section 505A as a whole. FDA's policy permits a manufacturer to receive extra exclusivity for numerous related or similar drug products even if they contain different drug substances. FDA should restrict a grant of exclusivity under 505A to only the drug product that is the subject of the identified application and specifically named in the Written Request.

Likewise, FDA should not grant more than one exclusivity period for the same study. For example, manufacturers should not be granted both a six month pediatric exclusivity and a three year new use exclusivity for the same study.

7. FDA should adopt requirements for timeliness and publication of submissions and other section 505A actions to protect the legitimate interests of consumers and potential competitors

FDA should establish requirements for the timeliness of proposals for Written Requests, final study reports, or other submissions by drug manufacturers related to pediatric exclusivity. See Guidance at 6, 8-11. These provisions are essential to prevent firms from exploiting the procedural nuances. The legislative history of section 505A clearly states that Congress did not intend for studies "to be artificially timed for market advantage." H.R. Rep. No. 105-399, at 92 (1997).

In addition, FDA's policy fails to provide for adequate public notice regarding any of these submissions, nor does it provide for an opportunity to comment on their consistency with the Congressional objectives embodied in section 505A. Improper grants of exclusivity will affect product affordability and patient access to treatment. Furthermore, the adverse impact of unanticipated or unnecessary extensions of exclusivity reaches beyond the issues of patient access. A serious impact also is felt by generic manufacturers. Under the system established by the Hatch-Waxman Act, generic manufacturers begin preparations for market entry years before the patent term or exclusivity period of the innovator drug has expired. Unanticipated exclusivity extensions can disrupt the well-laid market entry plans of the generic manufacturer, creating substantial costs, which the manufacturer may not be in a position to absorb. To these ends, GPIA and NPA assert that FDA must create adequate safeguards to prevent "gaming" of the system by NDA holders and applicants.

Moreover, FDA should establish dates by which submissions must be received by the agency, measured according to the date on which the current exclusivity or patent term is set to expire. Specifically, except in extraordinary circumstances, FDA should require that studies be filed with FDA by a date that is

no later than 90 days prior to the expiration of the first patent term or exclusivity period that may be eligible for extension.

FDA also should make Written Requests publicly available through FDA dockets, Freedom of Information and/or the agency's internet site. At a minimum, FDA should disclose to the public, as it does in the orphan drug context, that a Written Request has been issued for a specific drug product. Likewise, the submission of pediatric study reports should be disclosed in a similar, and timely manner.

8. FDA should clarify that holds placed on pending ANDAs under section 505A will only stay the effective date of the applications, and structure Written Requests to minimize the use of holds

Section 505A(e) provides that when a sponsor submits studies, the FDA shall delay the acceptance or approval of any ANDA for the drug until after the agency has determined whether the studies qualify for exclusivity, but no longer than 90 days. 21 U.S.C. § 355a(e). This provision could be subject to abuse. Manufacturers could submit studies that are insufficient to support exclusivity just prior to the expiration of their exclusivity in order to obtain a *de facto* 90 day exclusivity extension. To prevent such abuse, GPIA and NPA request that FDA adopt the following two policies. First, as requested above, FDA can avoid unnecessarily placing holds on ANDAs by requiring that study reports be submitted at least 90 days prior to the expiration of the exclusivity period. Second, if a hold on a pending ANDA pursuant to section 505A(e) is imposed, FDA should specify that the hold only delays the ANDA approval date, not its review. There is no reasonable policy justification for suspending the review of generic applications during the hold. Doing so would adversely affect the public and unfairly benefit the original application holder. The review of ANDAs should proceed during the hold. If they meet other requirements, the applications should be approved as soon as FDA either denies the request for exclusivity or the additional six month period expires.

Environmental Impact

The actions requested herein are subject to categorical exclusion under 21 C.F.R. § 25.24 (1997).

Economic Impact

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

Certification

The undersigned certify that, to the best knowledge and belief of the undersigned, this petition includes all information and views upon which the petition relies, and that it includes representative data and information known to the petitioners which are unfavorable to the petition.

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October 5, 1998

VIA HAND DELIVERY

Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
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PETITION FOR STAY OF ACTION

The Generic Pharmaceutical Industry Association ("GPIA") and the National Pharmaceutical Alliance ("NPA"), in the interest and on behalf of their members, hereby submit this Petition for Stay of Action ("petition") pursuant to section 701 of the Federal Food, Drug, and Cosmetic Act ("the Act"), 21 U.S.C. § 371, and its implementing regulations, 21 C.F.R. §§ 10.25, 10.30 and 10.35 (1998). This petition is submitted in conjunction with, and incorporates by reference all relevant portions of, the corresponding Citizen Petition, dated October 5, 1998 ("the Citizen Petition"), which requests the Commissioner of Food and Drugs ("the Commissioner") to take the following actions:

1. Immediately rescind and declare invalid the List of Drugs For Which Additional Pediatric Information May Produce Health Benefits In the Pediatric Population, the agency's guidance document titled Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act, existing Written Requests and pediatric exclusivity grants, because the agency's implementation of section 505A is legally inconsistent and impermissible.
2. Suspend all future action taken pursuant to section 505A until appropriate regulations are promulgated in accordance with the APA. Notice and comment rulemaking is required in this instance because the Food and Drug Administration's ("FDA's") implementation policy constitutes substantive rulemaking, as that term has been defined by the federal courts, and has a substantial adverse effect on the generic industry and consumers alike.

The members of GPIA and NPA, consisting of manufacturers and distributors of affordable pharmaceuticals, are being significantly, adversely, and irreparably

harmed by FDA's implementation of section 505A. We respectfully request, therefore, that the Commissioner stay further implementation of section 505A pending resolution of the Citizen Petition and the promulgation of final regulations.

A. Decisions Involved

This petition concerns FDA's interpretation and implementation of, and decision making under, section 505A of the Act, 21 U.S.C. § 355a. Section 505A grants to the agency the authority to request that drug manufacturers conduct clinical investigations of the use of their drug products in pediatric populations. Manufacturers who submit to FDA data from studies meeting the terms of the agency's Written Request are entitled to six months of additional market exclusivity for the drug product studied. To implement section 505A, FDA has:

1. issued a List of Drugs For Which Additional Pediatric Information May Produce Health Benefits In the Pediatric Population ("the List"), see 63 Fed. Reg. 27733 (May 20, 1998) (Docket No. 98N-0056), as required by section 505A(b);
2. issued a "guidance" document entitled Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act ("the Guidance"), see 63 Fed. Reg. 36707 (July 7, 1998) (Docket No. 98D-0265), establishing policies and procedures for the implementation of section 505A;
3. issued Written Requests for pediatric studies to manufacturers of several approved drug products;¹ and
4. granted exclusivity under section 505A to at least 13 products, including finished drug products containing ibuprofen manufactured by McNeil Consumer Products Company and Whitehall-Robins Healthcare.²

¹ As of the date of this petition, the agency has issued Written Requests for pediatric studies to six drug manufacturers covering 15 approved drug products. See FDA, Approved Drug Products to which FDA has issued a Written Request for Pediatric Studies under Section 505A of the Federal Food, Drug, and Cosmetic Act, <<http://www.fda.gov/cder/pediatric/wrlist.htm>> (viewed Oct. 5, 1998) (attached). Because FDA has provided no notification procedure for Written Requests covering unapproved drug products, it is unknown if any such requests have been issued.

B. Action Requested

As set forth more fully in the Citizen Petition, to implement section 505A, FDA first developed the List of approved drugs for which it allegedly believes that additional pediatric studies may produce a health benefit. See Section 505A(b), 21 U.S.C. § 355a(b). As described in the Citizen Petition, FDA failed to comply with its clear statutory mandate in compiling the List. Following the issuance of the List, FDA drafted and issued, in final form and without prior notice or the opportunity for public comment, the Guidance providing the agency's interpretation and implementation of section 505A. As with the issuance of the List, many of the provisions of the Guidance clearly conflict with the language and intent of section 505A. Finally, since the issuance of the Guidance, FDA has begun issuing Written Requests for pediatric studies of various drugs,³ and granting exclusivity for submitted studies.⁴

GPIA and NPA maintain that the FDA's implementation is unlawful because it is arbitrary and capricious, inconsistent with the language of the statute and congressional intent, and was undertaken without notice and comment rulemaking as required by the APA. GPIA and NPA now request that the Commissioner stay the issuance of Written Requests for pediatric studies, the acceptance or review of studies for which there has already been a request, the issuance of pediatric exclusivity extensions, or any other action taken pursuant to section 505A until the conclusion of all administrative and judicial proceedings relating to the Citizen Petition, including any rulemaking proceedings which result. GPIA and NPA further request the Commissioner to rescind and declare invalid the List, the Guidance, and all previously issued Written Requests and exclusivity grants.

(Footnote cont'd from previous page.)

² FDA Docket No. 95S-0117, Patent Term Extension and New Patents (Sept. 16, 1998) (attached).

³ See supra note 1.

⁴ See supra note 2.

C. Statement of Grounds

The standard for granting an administrative stay of action is set forth in an FDA regulation, 21 C.F.R. § 10.35(e) (1998). In ruling on a petition for stay of action, the Commissioner must grant a stay if the following factors exist: (1) the petitioner will otherwise suffer irreparable injury; (2) the petitioner's case is not frivolous and is being pursued in good faith; (3) the petitioner has demonstrated sound public policy grounds to support the stay; and (4) the delay resulting from the stay is not outweighed by public health or other interests. In this case, the Commissioner should grant the petitioner's request for a stay of action because this petition, in conjunction with the Citizen Petition submitted by GPIA and NPA concurrently herewith, fully satisfies the regulatory criteria set forth above.

1. Without a Stay of Action, Petitioners Will Suffer Irreparable Injury

As demonstrated in the Citizen Petition, FDA's implementation of section 505A will result in extensions of exclusivity that are not warranted—and, in fact, unlawful—under the statute. In fact, this result has occurred already. For example, from the listing of Written Requests posted on FDA's website (attached hereto), it appears that a Written Request was issued to McNeil Consumer Products for pediatric studies of the use of two OTC ibuprofen products for fever reduction and temporary relief of certain minor aches and pains in children between the ages of 1 month to 2 years.⁵ The entry in FDA's Docket No. 95S-0117, dated Sept. 16, 1998, however, indicates that FDA subsequently granted extensions for at least eight of McNeil's Motrin® ibuprofen products. Included are extensions for three products—prescription Motrin suspension and prescription Motrin chewable tablets (50 and 100 mg)—that are already labeled for use to reduce fever and relieve mild to

⁵ The NDA numbers on the list of Written Requests correspond to two OTC products—Children's Motrin oral suspension and Children's Motrin oral drops. According to the Pediatric Priority List of approved products for which pediatric studies may be requested, Docket No. 98N-0056 (May, 20, 1998), the indications to be studied for these products under section 505A are limited to fever reduction in children 1 month to 2 years of age.

moderate pain in the great majority of the population studied.⁶ GPIA and NPA have presented clear evidence in the Citizen Petition that Congress intended exclusivity extensions to cover only the finished drug product for which the Written Request for study was issued. Granting extensions of exclusivity to drug products for which additional pediatric information was neither requested nor needed conflicts with the language and intent of section 505A.

Without a stay of action, such unlawful extensions of exclusivity under the implementation policy are causing, and will continue to cause, substantial and irreparable harm to the members of GPIA and NPA. The associations' member generic manufacturers make substantial investments prior to the expiration of the patent and/or exclusivity protection of brand drugs so that they may enter the market immediately following such expiration. Any delay in entering the market—including a delay resulting from an extension granted under section 505A—will result in substantial financial loss to the generic manufacturer. For example, sales for the anti-allergy drug Claritin® (loratadine) totaled approximately \$870 million in 1997. Based upon such sales, and assuming that a generic loratadine would secure 30 percent of the market during its first 6 months of sales and sell at 40 to 70 percent of the cost of Claritin—figures that reflect the typical generic drug experience—a 6-month extension of market exclusivity would cost the generic manufacturer between \$52 million and \$90 million in lost revenues. That is \$290,000 to \$500,000 for every day the generic drug is delayed. Furthermore, although multiple generic manufacturers may eventually market loratadine, experience shows that the first firm to enter the marketplace will likely receive a market share advantage lasting for several years. If one generic manufacturer is poised to enter the loratadine market ahead of its competitors, the delay caused by pediatric exclusivity may decrease or erase that advantage, resulting in additional lost profits.

Under FDA's current policy, pediatric exclusivity extensions often will be granted only a short time before the original date on which exclusivity will expire. Thus, generic manufacturers have little, if any, opportunity to seek reversal of the extension before they suffer economic loss. Moreover, as described in the Citizen

⁶ The labeling of the two products provides directions for use to reduce fever and relieve pain in patients 6 months of age and older. Physicians' Desk Reference 1543-45 (52d ed. 1998).

Petition, the issuance of a Written Request itself creates a statutory entitlement to exclusivity for the submission of studies meeting that request. Because requests issued under FDA's current policy may not be able to be modified or rescinded by subsequent notice and comment rulemaking, generic manufacturers whose interests are adversely affected will have no adequate remedy at law to recover damages against the government or the brand drug manufacturer. See Megapulse, Inc. v. Lewis, 672 F.2d 959, 970 (D.C. Cir. 1982); New York State Trawlers Ass'n v. Jorling, 764 F. Supp. 24, 25-26 (E.D.N.Y.), aff'd mem., 940 F.2d 649 (2d Cir. 1991). As representatives of the generic manufacturing industry, GPIA and NPA maintain, therefore, that their member generic manufacturers will suffer irreparable harm unless the Commissioner stays the implementation of section 505A and grants the other relief requested.

2. This Petition Is Filed In Good Faith,
And Warrants Consideration By The Agency

This petition is not frivolous and is being pursued in good faith. As previously noted, this petition accompanies, and incorporates by reference all relevant portions of, a Citizen Petition in which GPIA and NPA have made compelling arguments that FDA's implementation of section 505A is arbitrary and capricious and inconsistent with both the language and intent of the statute. Furthermore, GPIA and NPA put forth compelling justification in the Citizen Petition, and continue to assert, that the implementation of section 505A requires notice and comment rulemaking before implementation.

3. The Public Interest Will Be Served By Granting A Stay Of Action

A stay of action is in the public interest because FDA has failed to assure under its current policy that the public will receive the benefits contemplated by Congress—namely, the incorporation of additional pediatric use information in product labels. In the Citizen Petition, GPIA and NPA have provided specific, compelling examples of this failure. The public interest clearly will be served only if the granting of additional market exclusivity under section 505A is limited to those situations in which the public receives a substantial health benefit.

Unwarranted extensions of exclusivity also will harm the public interest by greatly increasing the cost of drug products for consumers who need them. For example, we have already demonstrated that an extension of the exclusivity for Claritin could cost generic manufacturers up to \$500,000 each day that the introduction of a competitive product is delayed. During the term of the extension,

consumers will be unable to purchase an affordable generic product. Therefore, each day of market delay means that consumers could be forced to pay \$217,000 to \$435,000 in additional cost for loratadine. For some drugs, that difference in cost between the brand and the generic product could determine whether a patient receives the drug therapy, and the resulting health benefits, or not.

Finally, public policy dictates that FDA's actions follow the law, as drafted, and comply with applicable APA requirements. In other words, to properly limit exclusivity grants to those situations in which the public interest will benefit, the agency must solicit the input of members of the public who will be affected by such a determination, weigh carefully the critical issues involved, and adopt final regulations that are consistent with the language and intent of the statute. New Jersey v. Dept. of HHS, 670 F.2d 1262, 1281 (3d Cir. 1981) (rulemaking requirements are designed to "ensure that unelected administrators, who are not directly accountable to the populace, are forced to justify their quasi-legislative rulemaking before an informed and skeptical public.") Until that process is complete, only the stay of action requested by this petition can protect the public from the adverse effects of unwarranted and unlawful exclusivity extensions.

4. The Delay Resulting From The Stay
Of Action Is Not Outweighed By the Public Interest

Section 505A is a complex statute. It represents a careful balancing by Congress of competing interests. For example, Congress recognized that physicians, parents and patients are greatly interested in using drugs that have been adequately studied and are appropriately labeled for pediatric use. Nevertheless, drug manufacturers often have little incentive to conduct such studies for various economic, ethical and other reasons. Furthermore, while additional market exclusivity can provide incentives for manufacturers to conduct such studies, market exclusivity also delays the availability of affordable, competitive drug products. It also increases the cost of health care for both individual patients and society in general.

Congress burdened FDA with maintaining this careful balance during its implementation of section 505A. Congress did not, on the other hand, identify urgent or extenuating circumstances necessitating a rapid and ill-considered implementation. To the contrary, it has been over six years since the Better Pharmaceuticals for Children Act, which eventually became section 505A, was first introduced in Congress. S. 3337, 102d Cong., 2d Sess. (1992). Furthermore, the agency's own effort to require pediatric investigations of drugs, which was

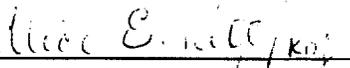
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specifically referenced in the legislative history, was proposed more than one year ago, but still has not been finalized. See 62 Fed. Reg. 43900 (Aug 15, 1997). These facts demonstrate the lack of urgency. Therefore, the public interest supporting a stay of action—during which the agency can consult with all interested parties and undertake a careful, well-reasoned consideration of the issues involved--clearly outweighs the interests of a few individual drug manufacturers in quick implementation of the statute. Furthermore, rescinding the actions FDA previously has taken to implement section 505A obviously is consistent with the public interest, to remedy agency action that is contrary to law.

D. Conclusion

For the foregoing reasons, petitioners' petition for stay of action should be granted.

Respectfully,



Alice E. Till, Ph.D

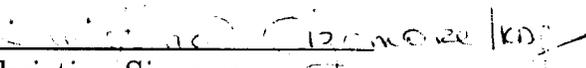
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U.S. Food and Drug Administration
Center for Drug Evaluation and Research

Approved Drug Products to which FDA has issued a Written Request for Pediatric Studies under Section 505A of the Federal Food, Drug, and Cosmetic Act

NOTE: This list simply identifies approved drug products to which FDA has issued a Written Request for pediatric studies. If a product appears on this list, it does not imply that studies have been conducted or submitted to the Agency, nor does it mean that the studies described in the Written Request will be conducted. A sponsor is NOT required to perform pediatric studies in response to a Written Request. Conducting pediatric studies in response to a Written Request is voluntary.

NDA Number	Drug Product	Sponsor
20-603 20-516	Ibuprofen Suspension	McNeil Consumer Products Company
20-589 20-812	Ibuprofen Suspension	Whitehall-Robins Healthcare
18-654	Midazolam Hydrochloride Injection	Hoffmann-La Roche, Inc.
20-636 20-933	Nevirapine Tablets Nevirapine Oral Suspension	Boehringer Ingelheim Pharmaceuticals
18-703 19-090 19-593 19-675 20-095 20-251 20-520	Ranitidine Hydrochloride Tablets Ranitidine Hydrochloride Injection Ranitidine Hydrochloride Injection Ranitidine Hydrochloride Syrup Ranitidine Hydrochloride Capsules Ranitidine Hydrochloride Granules Ranitidine Hydrochloride Tablets	Glaxo Wellcome, Inc.
21-024	Rifapentine Tablets	Hoechst-Marion Roussel, Inc.

September 23, 1998

<http://www.fda.gov/cder/pediatric/wrlist.htm>

PATENT TERM EXTENSION AND NEW PATENTS - SEPTEMBER 16, 1998
 DOCKET NUMBER *95S-0117
 *PED and PED represent Pediatric Exclusivity

APPL/PROD NUMBER	INGREDIENT NAME; TRADE NAME	PATENT NUMBER	PATENT/PED EXCL EXPIRES	USE CODE	EXCLUS CODE	EXCLUS EXPIRES
020738 004	EPROSARTAN MESYLATE; TEVETEN	5185351	FEB 09, 2010	U-3		
020738 005	EPROSARTAN MESYLATE; TEVETEN	5185351	FEB 09, 2010	U-3		
020718 001	EPTIFIBATIDE; INTEGRILIN				NCE	MAY 18, 2003
020718 002	EPTIFIBATIDE; INTEGRILIN				NCE	MAY 18, 2003
020375 003	ESTRADIOL; CLIMARA	5223261	JUN 29, 2010			
083209 001	ESTROGENS, ESTERIFIED; ESTRATAB				I-214	MAR 10, 2001
086715 001	ESTROGENS, ESTERIFIED; ESTRATAB				I-214	MAR 10, 2001
020363 001	FAMCICLOVIR; FAMVIR				NCE	JUN 29, 1999
020752 001	FAMOTIDINE; PEPICID RPD	4283408	OCT 15, 2000			
		4305502	DEC 15, 1998			
		4371516	JAN 31, 2000	U-241		
020752 002	FAMOTIDINE; PEPICID RPD	4283408	OCT 15, 2000			
		4305502	DEC 15, 1998			
		4371516	JAN 31, 2000	U-241		
020786 001	PEXOFENADINE HYDROCHLORIDE; ALLEGRA-D	4254129	APR 10, 1999		NCE	JUL 25, 2001
		5375693	AUG 03, 2012			
		5578610	NOV 26, 2013			
		5547957	OCT 15, 2013	U-236		
020788 001	FINASTERIDE; PROPECIA					
020180 001	FINASTERIDE; PROSCAR				I-221	MAR 20, 2001
018830 001	FLECAINIDE ACETATE; TAMBOCOR	4642384	FEB 10, 2004			
018830 002	FLECAINIDE ACETATE; TAMBOCOR	4642384	FEB 10, 2004			
018830 003	FLECAINIDE ACETATE; TAMBOCOR	4642384	FEB 10, 2004			
018830 004	FLECAINIDE ACETATE; TAMBOCOR	4642384	FEB 10, 2004			
018554 001	FLUTAMIDE; EULEXIN	4472382	SEP 18, 2001	U-24		
		5712251	SEP 18, 2001	U-216		
020121 001	FLUTICASONE PROPIONATE; FLONASE				I-224	OCT 31, 2000
020378 001	FOLLITROPIN ALFA/BETA; GONAL-F	4589402	JUL 26, 2004	U-242		
		5767251	JUN 16, 2015			
020378 002	FOLLITROPIN ALFA/BETA; GONAL-F	4589402	JUL 26, 2004	U-242		
		5767251	JUN 16, 2015			
020450 001	FOSPHENYTOIN SODIUM; CEREBYX	4260769	APR 07, 2003			
020695 001	GREPAPFLOXACIN HYDROCHLORIDE; RAXAR	5563138	OCT 08, 2013			
020818 001	HYDROCHLOROTHIAZIDE; DIOVAN HCT	5399578	MAR 21, 2012	U-3	NCE	DEC 23, 2001
					NC	MAR 06, 2001
020818 002	HYDROCHLOROTHIAZIDE; DIOVAN HCT	5399578	MAR 21, 2012	U-3	NCE	DEC 23, 2001
					NC	MAR 06, 2001
020716 001	HYDROCODONE BITARTRATE; VICOPROFEN	4587252	DEC 18, 2004	U-55		
016295 002	HYDROXYUREA; DROXIA				ODE	FEB 25, 2005
016295 003	HYDROXYUREA; DROXIA				ODE	FEB 25, 2005
016295 004	HYDROXYUREA; DROXIA				ODE	FEB 25, 2005
>ADD>	019771 001	IBUPROFEN; ADVIL COLD AND SINUS	4552899	NOV 12, 2002		
>ADD>			4552899*PED	MAY 12, 2003		
>ADD>	019833 002	IBUPROFEN; CHILDREN'S ADVIL	4788220	NOV 29, 2005		
>ADD>			4788220*PED	MAY 29, 2006		
>ADD>	020589 001	IBUPROFEN; CHILDREN'S ADVIL	4788220	JUL 08, 2007	NP	JUN 16, 1998
>ADD>			4788220*PED	JAN 08, 2008	PED	DEC 16, 1998
>ADD>	020516 001	IBUPROFEN; CHILDREN'S MOTRIN	5374659	DEC 20, 2011	NP	JUN 16, 1998
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>ADD>	020601 001	IBUPROFEN; CHILDREN'S MOTRIN	5215755	JUN 01, 2010	NP	NOV 15, 1999
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PATENT TERM EXTENSION AND NEW PATENTS - SEPTEMBER 16, 1998
DOCKET NUMBER *95S-0117
*PED and PED represent Pediatric Exclusivity

APPL/PROD NUMBER	INGREDIENT NAME; TRADE NAME	PATENT NUMBER	PATENT/PED EXCL USE EXPIRES	EXCLUS CODE	EXCLUS EXPIRES
>ADD> 020603 001	IBUPROFEN; CHILDREN'S MOTRIN	5374659	DEC 20, 2011	NP	JUN 16, 1998
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>ADD> 020135 001	IBUPROFEN; MOTRIN	5215755	JUN 01, 2010		
>ADD>		5320855	JUN 14, 2011		
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020903 001	INTERFERON ALFA-2B; REBETRON	4530901	JUL 23, 2002	NP	JUN 03, 2001
		4211771	JUL 08, 1999	U-234	
		5767097	JAN 23, 2016	U-235	
020923 001	IOVERSOL; OPTIRAY 240	4396598	DEC 30, 2002		
020923 002	IOVERSOL; OPTIRAY 320	4396598	DEC 30, 2002		
020923 003	IOVERSOL; OPTIRAY 350	4396598	DEC 30, 2002		
020393 001	IPRATROPIUM BROMIDE; ATROVENT			I-223	APR 01, 2001
020657 001	ITRACONAZOLE; SPORANOX	4267179	JUN 23, 2000		
019927 001	KETOCONAZOLE; NIZORAL	4942162	FEB 11, 2003		
020406 001	LANSOPRAZOLE; PREVACID			I-227	MAR 12, 2001
				D-42	JUL 20, 2001
				I-227	MAR 12, 2001
				D-42	JUL 20, 2001
020406 002	LANSOPRAZOLE; PREVACID			ODE	MAR 06, 2005
				NCE	MAR 06, 2003
020807 001	LEPIRUDIN; REFLUDAN	5180668	JAN 19, 2010		
019732 001	LEUPROLIDE ACETATE; LUPRON DEPOT	5716640	SEP 02, 2013		
020011 001	LEUPROLIDE ACETATE; LUPRON DEPOT	5716640	SEP 02, 2013		
020517 001	LEUPROLIDE ACETATE; LUPRON DEPOT	5716640	SEP 02, 2013		
020263 002	LEUPROLIDE ACETATE; LUPRON DEPOT-PED	5716640	SEP 02, 2013		
020263 003	LEUPROLIDE ACETATE; LUPRON DEPOT-PED	5716640	SEP 02, 2013		
020263 004	LEUPROLIDE ACETATE; LUPRON DEPOT-PED	5716640	SEP 02, 2013		
020263 005	LEUPROLIDE ACETATE; LUPRON DEPOT-PED	5716640	SEP 02, 2013		
020263 006	LEUPROLIDE ACETATE; LUPRON DEPOT-PED	5716640	SEP 02, 2013		
020708 001	LEUPROLIDE ACETATE; LUPRON DEPOT-3	5716640	SEP 02, 2013		
020517 002	LEUPROLIDE ACETATE; LUPRON DEPOT-4	5716640	SEP 02, 2013		
019941 001	LIDOCAINE; EMLA			I-215	FEB 04, 2001
020962 001	LIDOCAINE; EMLA			NP	FEB 04, 2001
020606 001	LOPERAMIDE HYDROCHLORIDE; IMODIUM ADVANCED	5716641	MAY 21, 2012	U-226	
020803 001	LOTEPREDNOL ETABONATE; ALREX	4996335	FEB 26, 2008		
		5540930	OCT 25, 2013	NCE	MAR 09, 2003