December 2, 1999

Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
Room 1–23
12420 Parklawn Drive
Rockville, MD 20857

CITIZEN PETITION

The undersigned, on behalf of the American Association of Physicians and Surgeons, the Competitive Enterprise Institute, and Consumer Alert, submits this petition under sections 201(n) and (p), 301(a) and (d), 502(a), (f), and (j), 505(a), (d)(7), (i), and (k), and 701(a) of the Federal Food, Drug, and Cosmetic Act and section 351 of the Public Health Service Act to request the Commissioner of Food and Drugs to revoke FDA's regulations concerning pediatric testing of drugs, as published at 63 Fed. Reg. 66,632 (1998), and to refrain from taking any form of administrative action pursuant to those rules.

A. Action requested

The Commissioner should immediately revoke the following provisions of Title 21 of the Code of Federal Regulations:

> **PART 201 – LABELING**
> Sec. 201.23 Required pediatric studies.
> (a) A manufacturer of a marketed drug product, including a biological drug product, that is used in a substantial number of pediatric patients, or that provides a meaningful therapeutic benefit over existing treatments for pediatric patients, as defined in Secs. 314.55(c)(5) and 601.27(c)(5) of this chapter, but whose label does not provide adequate information to support its safe and effective use in pediatric populations for the approved indications may be required to submit an application containing data adequate to assess whether the drug product is safe and effective in pediatric populations. The application may be required to contain adequate evidence to support dosage and administration in some or all pediatric subpopulations, including neonates, infants, children, and adolescents, depending upon the known or appropriate use of the drug product in such subpopulations. The applicant may also be required to develop a pediatric formulation for a drug product that represents a meaningful therapeutic benefit over existing therapies for pediatric populations for whom a pediatric formulation is necessary, unless the manufacturer demonstrates that reasonable attempts to produce a pediatric formulation have failed.
> (b) The Food and Drug Administration (FDA) may by order, in the form of a letter, after notifying the manufacturer of its intent to require an assessment of pediatric safety and effectiveness of a pediatric formulation, and after offering an opportunity for a written response and a meeting, which may include an advisory committee meeting, require a manufacturer to submit an application containing the

information or request for approval of a pediatric formulation described in paragraph (a) of this section within a time specified in the order, if FDA finds that:

(1) The drug product is used in a substantial number of pediatric patients for the labeled indications and the absence of adequate labeling could pose significant risks to pediatric patients; or

(2) There is reason to believe that the drug product would represent a meaningful therapeutic benefit over existing treatments for pediatric patients for one or more of the claimed indications, and the absence of adequate labeling could pose significant risks to pediatric patients.

(c)(1) An applicant may request a full waiver of the requirements of paragraph (a) of this section if the applicant certifies that:

(i) Necessary studies are impossible or highly impractical because, e.g., the number of such patients is so small or geographically dispersed, or

(ii) There is evidence strongly suggesting that the product would be ineffective or unsafe in all pediatric age groups.

(2) An applicant may request a partial waiver of the requirements of paragraph (a) of this section with respect to a specified pediatric age group, if the applicant certifies that:

(i) The product:

(A) Does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in that age group, and

(B) Is not likely to be used in a substantial number of patients in that age group, and

(C) The absence of adequate labeling could not pose significant risks to pediatric patients; or

(ii) Necessary studies are impossible or highly impractical because, e.g., the number of patients in that age group is so small or geographically dispersed, or

(iii) There is evidence strongly suggesting that the product would be ineffective or unsafe in that age group, or

(iv) The applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for that age group have failed.

(3) FDA shall grant a full or partial waiver, as appropriate, if the agency finds that there is a reasonable basis on which to conclude that one or more of the grounds for waiver specified in paragraphs (c)(2) or (c)(3) of this section have been met. If a waiver is granted on the ground that it is not possible to develop a pediatric formulation, the waiver will cover only those pediatric age groups requiring that formulation. If a waiver is granted because there is evidence that the product would be ineffective or unsafe in pediatric populations, this information will be included in the product's labeling.

(d) If a manufacturer fails to submit a supplemental application containing the information or request for approval of a pediatric formulation described in paragraph (a) of this section within the time specified by FDA, the drug product may be considered misbranded or an unapproved new drug or unlicensed biologic.

PART 312 – INVESTIGATIONAL NEW DRUG APPLICATION

Sec. 312.23 IND content and format.

(a) * * *

(10) * * *

(iii) Pediatric studies. Plans for assessing pediatric safety and effectiveness.

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Sec. 312.47 Meetings.

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(b) * * *

(1) End-of-Phase 2 meetings – (i) Purpose. The purpose of an end-of-phase 2 meeting is to determine the safety of proceeding to Phase 3, to evaluate the Phase 3 plan and protocols and the adequacy of current studies and plans to assess pediatric safety and effectiveness, and to identify any additional information necessary to support a marketing application for the uses under investigation.

* * * * *

(iv) Advance information. At least 1 month in advance of an end-of-Phase 2 meeting, the sponsor should submit background information on the sponsor's plan for Phase 3, including summaries of the Phase 1 and 2 investigations, the specific protocols for Phase 3 clinical studies, plans for any additional nonclinical studies, plans for pediatric studies, including a time line for protocol finalization, enrollment, completion, and data analysis, or information to support any planned request for waiver or deferral of pediatric studies, and, if available, tentative labeling for the drug. * * *

(v) Conduct of meeting. * * * The adequacy of the technical information to support Phase 3 studies and/or a marketing application may also be discussed. FDA will also provide its best judgment, at that time, of the pediatric studies that will be required for the drug product and whether their submission will be deferred until after approval. * * *

(2) "Pre-NDA" and "pre-BLA" meetings. * * * The primary purpose of this kind of exchange is to uncover any major unresolved problems, to identify those studies that the sponsor is relying on as adequate and well-controlled to establish the drug's effectiveness, to identify the status of ongoing or needed studies adequate to assess pediatric safety and effectiveness, to acquaint FDA reviewers with the general information to be submitted in the marketing application (including technical information), to discuss appropriate methods for statistical analysis of the data, and to discuss the best approach to the presentation and formatting of data in the marketing application. * * *

To permit FDA to provide the sponsor with the most useful advice on preparing a marketing application, the sponsor should submit to FDA's reviewing division at least 1 month in advance of the meeting the following information:

* * * * *

(iii) Information on the status of needed or ongoing pediatric studies.
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Sec. 312.82 Early consultation.
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(a) Pre-investigational new drug (IND) meetings. * * * The meeting may also provide an opportunity for discussing the scope and design of phase 1 testing, plans for studying the drug product in pediatric populations, and the best approach for presentation and formatting of data in the IND.

(b) End-of-phase 1 meetings. * * * The primary purpose of this meeting is to review and reach agreement on the design of phase 2 controlled clinical trials, with the goal that such testing will be adequate to provide sufficient data on the drug's safety and effectiveness to support a decision on its approvability for marketing, and to discuss the need for, as well as the design and timing of, studies of the drug in pediatric patients. For drugs for life-threatening diseases, FDA will provide its best judgment, at that time, whether pediatric studies will be required and whether their submission will be deferred until after approval. * * *

PART 314 – APPLICATIONS FOR FDA APPROVAL TO MARKET A NEW DRUG OR ANANTIBIOTIC DRUG

Sec. 314.50 Content and format of an application.
* * * * *

(d) * * *

(7) Pediatric use section. A section describing the investigation of the drug for use in pediatric populations, including an integrated summary of the information (the clinical pharmacology studies, controlled clinical studies, or uncontrolled clinical studies, or other data or information) that is relevant to the safety and effectiveness and benefits and risks of the drug in pediatric populations for the claimed indications, a reference to the full descriptions of such studies provided under paragraphs (d)(3) and (d)(5) of this section, and information required to be submitted under Sec. 314.55.
* * * * *

Sec. 314.55 Pediatric use information.

(a) Required assessment. Except as provided in paragraphs (b), (c), and (d) of this section, each application for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration shall contain data that are adequate to assess the safety and effectiveness of the drug product for the claimed indications in all relevant pediatric subpopulations, and to support dosing and administration for each pediatric subpopulation for which the drug is safe and effective. Where the course of the disease and the effects of the drug are sufficiently similar in adults and pediatric patients, FDA may conclude that pediatric effectiveness can be extrapolated from adequate and well-controlled

studies in adults usually supplemented with other information obtained in pediatric patients, such as pharmacokinetic studies. Studies may not be needed in each pediatric age group, if data from one age group can be extrapolated to another. Assessments of safety and effectiveness required under this section for a drug product that represents a meaningful therapeutic benefit over existing treatments for pediatric patients must be carried out using appropriate formulations for each age group(s) for which the assessment is required.

(b) Deferred submission. (1) FDA may, on its own initiative or at the request of an applicant, defer submission of some or all assessments of safety and effectiveness described in paragraph (a) of this section until after approval of the drug product for use in adults. Deferral may be granted if, among other reasons, the drug is ready for approval in adults before studies in pediatric patients are complete, or pediatric studies should be delayed until additional safety or effectiveness data have been collected. If an applicant requests deferred submission, the request must provide a certification from the applicant of the grounds for delaying pediatric studies, a description of the planned or ongoing studies, and evidence that the studies are being or will be conducted with due diligence and at the earliest possible time.

(2) If FDA determines that there is an adequate justification for temporarily delaying the submission of assessments of pediatric safety and effectiveness, the drug product may be approved for use in adults subject to the requirement that the applicant submit the required assessments within a specified time.

(c) Waivers – (1) General. FDA may grant a full or partial waiver of the requirements of paragraph (a) of this section on its own initiative or at the request of an applicant. A request for a waiver must provide an adequate justification.

(2) Full waiver. An applicant may request a waiver of the requirements of paragraph (a) of this section if the applicant certifies that:

(i) The drug product does not represent a meaningful therapeutic benefit over existing treatments for pediatric patients and is not likely to be used in a substantial number of pediatric patients;

(ii) Necessary studies are impossible or highly impractical because, e.g., the number of such patients is so small or geographically dispersed; or

(iii) There is evidence strongly suggesting that the drug product would be ineffective or unsafe in all pediatric age groups.

(3) Partial waiver. An applicant may request a waiver of the requirements of paragraph (a) of this section with respect to a specified pediatric age group, if the applicant certifies that:

(i) The drug product does not represent a meaningful therapeutic benefit over existing treatments for pediatric patients in that age group, and is not likely to be used in a substantial number of patients in that age group;

(ii) Necessary studies are impossible or highly impractical because, e.g., the number of patients in that age group is so small or geographically dispersed;

(iii) There is evidence strongly suggesting that the drug product would be ineffective or unsafe in that age group; or

(iv) The applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for that age group have failed.

(4) FDA action on waiver. FDA shall grant a full or partial waiver, as appropriate, if the agency finds that there is a reasonable basis on which to conclude that one or more of the grounds for waiver specified in paragraphs (c)(2) or (c)(3) of this section have been met. If a waiver is granted on the ground that it is not possible to develop a pediatric formulation, the waiver will cover only those pediatric age groups requiring that formulation. If a waiver is granted because there is evidence that the product would be ineffective or unsafe in pediatric populations, this information will be included in the product's labeling.

(5) Definition of "meaningful therapeutic benefit". For purposes of this section and Sec. 201.23 of this chapter, a drug will be considered to offer a meaningful therapeutic benefit over existing therapies if FDA estimates that:

(i) If approved, the drug would represent a significant improvement in the treatment, diagnosis, or prevention of a disease, compared to marketed products adequately labeled for that use in the relevant pediatric population. Examples of how improvement might be demonstrated include, for example, evidence of increased effectiveness in treatment, prevention, or diagnosis of disease, elimination or substantial reduction of a treatment-limiting drug reaction, documented enhancement of compliance, or evidence of safety and effectiveness in a new subpopulation; or

(ii) The drug is in a class of drugs or for an indication for which there is a need for additional therapeutic options.

(d) Exemption for orphan drugs. This section does not apply to any drug for an indication or indications for which orphan designation has been granted under part 316, subpart C, of this chapter.

Sec. 314.81 Other postmarketing reports.
* * * * *

(b) * * *

(2) * * *

(i) Summary. A brief summary of significant new information from the previous year that might affect the safety, effectiveness, or labeling of the drug product. The report is also required to contain a brief description of actions the applicant has taken or intends to take as a result of this new information, for example, submit a labeling supplement, add a warning to the labeling, or initiate a new study. The summary shall briefly state whether labeling supplements for pediatric use have been submitted and whether new studies in the pediatric population to support appropriate labeling for the pediatric population have been initiated. Where possible, an estimate of patient exposure to the drug product, with special reference to the pediatric population (neonates, infants, children, and adolescents) shall be provided, including dosage form. * * * * *

(vi) * * *

(c) Analysis of available safety and efficacy data in the pediatric population and changes proposed in the labeling based on this information. An assessment of data needed to ensure appropriate labeling for the pediatric population shall be included.

(vii) Status reports. A statement on the current status of any postmarketing studies performed by, or on behalf of, the applicant. The statement shall include whether postmarketing clinical studies in pediatric populations were required or agreed to, and if so, the status of these studies, e.g., to be initiated, ongoing (with projected completion date), completed (including date), completed and results submitted to the NDA (including date). To facilitate communications between FDA and the applicant, the report may, at the applicant's discretion, also contain a list of any open regulatory business with FDA concerning the drug product subject to the application. * * * * *

PART 601 – LICENSING

Sec. 601.27 Pediatric studies.

(a) Required assessment. Except as provided in paragraphs (b), (c), and (d) of this section, each application for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration shall contain data that are adequate to assess the safety and effectiveness of the product for the claimed indications in all relevant pediatric subpopulations, and to support dosing and administration for each pediatric subpopulation for which the product is safe and effective. Where the course of the disease and the effects of the product are similar in adults and pediatric patients, FDA may conclude that pediatric effectiveness can be extrapolated from adequate and well-controlled effectiveness studies in adults, usually supplemented with other information in pediatric patients,

such as pharmacokinetic studies. In addition, studies may not be needed in each pediatric age group, if data from one age group can be extrapolated to another. Assessments required under this section for a product that represents a meaningful therapeutic benefit over existing treatments must be carried out using appropriate formulations for the age group(s) for which the assessment is required.

(b) Deferred submission. (1) FDA may, on its own initiative or at the request of an applicant, defer submission of some or all assessments of safety and effectiveness described in paragraph (a) of this section until after licensing of the product for use in adults. Deferral may be granted if, among other reasons, the product is ready for approval in adults before studies in pediatric patients are complete, pediatric studies should be delayed until additional safety or effectiveness data have been collected. If an applicant requests deferred submission, the request must provide an adequate justification for delaying pediatric studies, a description of the planned or ongoing studies, and evidence that the studies are being or will be conducted with due diligence and at the earliest possible time.

(2) If FDA determines that there is an adequate justification for temporarily delaying the submission of assessments of pediatric safety and effectiveness, the product may be licensed for use in adults subject to the requirement that the applicant submit the required assessments within a specified time.

(c) Waivers – (1) General. FDA may grant a full or partial waiver of the requirements of paragraph (a) of this section on its own initiative or at the request of an applicant. A request for a waiver must provide an adequate justification.

(2) Full waiver. An applicant may request a waiver of the requirements of paragraph (a) of this section if the applicant certifies that:

(i) The product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients and is not likely to be used in a substantial number of pediatric patients;

(ii) Necessary studies are impossible or highly impractical because, e.g., the number of such patients is so small or geographically dispersed; or

(iii) There is evidence strongly suggesting that the product would be ineffective or unsafe in all pediatric age groups.

(3) Partial waiver. An applicant may request a waiver of the requirements of paragraph (a) of this section with respect to a specified pediatric age group, if the applicant certifies that:

(i) The product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in that age group, and is not likely to be used in a substantial number of patients in that age group;

(ii) Necessary studies are impossible or highly impractical because, e.g., the number of patients in that age group is so small or geographically dispersed;

(iii) There is evidence strongly suggesting that the product would be ineffective or unsafe in that age group; or

(iv) The applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for that age group have failed.

(4) FDA action on waiver. FDA shall grant a full or partial waiver, as appropriate, if the agency finds that there is a reasonable basis on which to conclude that one or more of the grounds for waiver specified in paragraphs (c)(2) or (c)(3) of this section have been met. If a waiver is granted on the ground that it is not possible to develop a pediatric formulation, the waiver will cover only those pediatric age groups requiring that formulation. If a waiver is granted because there is evidence that the product would be ineffective or unsafe in pediatric populations, this information will be included in the product's labeling.

(5) Definition of "meaningful therapeutic benefit". For purposes of this section, a product will be considered to offer a meaningful therapeutic benefit over existing therapies if FDA estimates that:

(i) If approved, the product would represent a significant improvement in the treatment, diagnosis, or prevention of a disease, compared to marketed products adequately labeled for that use in the relevant pediatric population. Examples of how improvement might be demonstrated include, e.g., evidence of increased effectiveness in treatment, prevention, or diagnosis of disease; elimination or substantial reduction of a treatment-limiting drug reaction; documented enhancement of compliance; or evidence of safety and effectiveness in a new subpopulation; or

(ii) The product is in a class of products or for an indication for which there is a need for additional therapeutic options.

(d) Exemption for orphan drugs. This section does not apply to any product for an indication or indications for which orphan designation has been granted under part 316, subpart C, of this chapter.

Sec. 601.37 Annual reports of postmarketing pediatric studies.

Sponsors of licensed biological products shall submit the following information each year within 60 days of the anniversary date of approval of the license, to the Director, Center for Biologics Evaluation and Research:

(a) Summary. A brief summary stating whether labeling supplements for pediatric use have been submitted and whether new studies in the pediatric population to support appropriate labeling for the pediatric population have been initiated. Where possible, an estimate of patient exposure to the drug product, with special reference to the pediatric population (neonates, infants, children, and adolescents) shall be provided, including dosage form.

(b) Clinical data. Analysis of available safety and efficacy data in the pediatric population and changes proposed in the labeling based on this information. An assessment of data needed to ensure appropriate labeling for the pediatric population shall be included.

(c) Status reports. A statement on the current status of any postmarketing studies in the pediatric population performed by, or on behalf of, the applicant.

> The statement shall include whether postmarketing clinical studies in pediatric populations were required or agreed to, and if so, the status of these studies, e.g., to be initiated, ongoing (with projected completion date), completed (including date), completed and results submitted to the BLA (including date).

B. Statement Of Grounds For Revoking The Pediatric Rule

1. Petitioners

The Association of American Physicians and Surgeons ("AAPS") is a not-for-profit membership organization that represents approximately 4,000 physicians nationwide in all practices and specialties. It was established in 1943 to preserve the practice of private medicine, and has remained dedicated to the Oath of Hippocrates and the sanctity of the patient-physician relationship, which AAPS believes must be protected from all forms of third-party intervention. Indeed, since its founding over fifty years ago, AAPS has been the only national organization consistently supporting free market principles in medical practice. AAPS seeks reconsideration of FDA's Pediatric Rule on the ground that it impedes the ability of physicians to treat their patients by diminishing the choices available to prescribing physicians. AAPS believes that FDA should not direct the research efforts of pharmaceutical companies. Rather, it should expeditiously approve all drugs that are safe and effective for the purposes for which they are intended, and leave to doctors, in consultation with their patients, the decision of whether any "off-label" use is appropriate.[1]

The Competitive Enterprise Institute ("CEI") is a non-profit public policy organization dedicated to the principles of free enterprise and limited government. CEI believes that consumers are best helped by being allowed to make their own choices in a free marketplace, rather than by being forced into decisions because of government regulation. CEI is nationally recognized as a leading voice on a broad range of regulatory issues ranging from environmental laws to antitrust policy to regulatory risk. CEI reaches out to the public and the media to ensure that its ideas are heard, works with policymakers to ensure that they are implemented, and, when necessary, takes its arguments to court to ensure that the law is upheld. CEI objects to FDA's unprecedented assertion of authority to order manufacturers to conduct studies with respect to uses that they do not intend to claim on their labels or otherwise promote. CEI particularly objects to FDA's claim that it can direct a drug company to reformulate a drug if FDA believes

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[1] Use of a product for a purpose or in a manner not suggested by the product's labeling constitutes an "off-label use." "Off-label uses include treating a condition not indicated on the label, or treating the indicated condition but varying the dosing regimen or the patient population" from that indicated on the label. Washington Legal Found. v. Friedman, 13 F. Supp. 2d 51, 55 (D.D.C. 1998), appeal docketed, No. 99-5304 (D.C. Cir. Sept. 9, 1999).

that such a reformulation may have a beneficial pediatric use. Such an approach is not only inefficient, but will dramatically raise the costs and diminish the availability of drugs to consumers.

Consumer Alert is a national, non-profit, non-partisan membership organization for people concerned about the excessive growth of government regulation at the national and state levels. Founded in 1977, Consumer Alert is dedicated to informing the public about the consumer benefits of competitive enterprise and to promoting sound economic, scientific, and risk data in public policy decisions. Consumer Alert's vision of consumerism is that advancing competition is the best regulator of business, and that individual choice is the best expression of consumer interest. Consumer Alert's mission is to enhance understanding and appreciation of the consumer benefits of a market economy so that individuals and policymakers rely more on private, rather than governmental, approaches to consumer concerns. Like CEI, Consumer Alert objects to the Pediatric Rule as an unnecessary and unwarranted governmental intrusion into what should essentially be private manufacturer decisions concerning which drug uses to study and obtain FDA approval to market and which formulations to develop.

On behalf of the doctors, patients, and drug manufacturers who are members of the petitioning organizations, AAPS, CEI, and Consumer Alert ("Petitioners") hereby request that FDA reconsider and withdraw its Pediatric Rule for the following reasons:

- First, the Pediatric Rule conflicts with the pediatric exclusivity provision in the Food and Drug Administration Modernization and Accountability Act of 1997 ("FDAMA"), Pub. L. No. 105-115, 111 Stat. 2296 (1997), that Congress established to encourage voluntary pediatric testing. Since FDA published its Final Rule, actual experience has demonstrated that this mechanism is working well, rendering the Pediatric Rule unnecessary. See App. A., pp. A-1 to A-26.

- Second, the Pediatric Rule conflicts with FDAMA's goal of streamlining the drug approval process by instead increasing the cost of pharmaceuticals, further delaying the introduction of new drugs to market, and hampering new drug innovation. See App. A, pp. A-26 to A-39.

- Third, FDA's decision to characterize pediatric uses as foreseeable and therefore "intended" so that FDA can then compel either pediatric clinical studies or possibly the development of pediatric formulations is a dramatic, unprecedented, and illegal assertion of authority, see App. B, for which FDA has supplied no satisfactory justification, see App. C.
- Finally, as a matter of sound public policy and basic constitutional principles, the Pediatric Rule – which forces manufacturers to conduct expensive clinical research and to reformulate a safe and effective product to sell to persons to whom they do not intend to sell – represents an unnecessary intrusion into manufacturers' basic decisional prerogatives concerning the intended purchasers of its products and a prime example of regulatory overreaching. See App. D.

Although Petitioners did not participate in the rulemaking, the adverse impact of this Rule on their members warrants the action requested in this Petition.[2] Moreover, although FDA may have considered some of the arguments made below in the course of the rulemaking, FDA has failed to justify its unprecedented assertion of authority to (1) deem certain uses "foreseeable" – even for drugs that have not yet actually been sold, and even if the manufacturer disclaims those uses – and (2) treat those allegedly "foreseeable" uses as "intended uses" for which manufacturers must conduct and submit testing information establishing the safety and effectiveness of the drugs.[3] FDA's failure to articulate a theory justifying its assertion of power to direct manufacturers to engage in research to prove the safety and effectiveness even of disclaimed uses, as well as the new evidence confirming the effectiveness of the incentive-based provisions of FDAMA, warrant a thorough reconsideration, and revocation, of the Pediatric Rule.

2. Description of the Pediatric Rule

Without demonstrating the existence of any problem warranting government intervention or providing an adequate legal foundation, FDA has established an extensive layer of regulations forcing manufacturers to seek approval for use on pediatric populations of drugs that are labeled and promoted only for adults. Specifically, with respect to "each application for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration," the Pediatric Rule requires manufacturers to submit "data that are adequate to assess the safety and effectiveness of the drug product for the claimed indications in all relevant pediatric subpopulations, and to support dosing and administration for each pediatric subpopulation for which the drug is safe and effective." 21 C.F.R. § 314.55(a) (1999).[4] The Rule further requires manufacturers to develop and use pediatric formulations appropriate for each age group in which the clinical studies needed to generate the requisite data of safety and effectiveness are conducted. See id.

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[2] Courts have "found injury-in-fact where the defendants' actions impaired the plaintiffs' access to certain goods." Arent v. Shalala, 866 F. Supp. 6, 10 (D.D.C. 1994) (citing Competitive Enter. Inst. v. NHTSA, 901 F.2d 107, 113 (D.C. Cir. 1990)), aff'd in part and remanded in part on other grounds, 70 F.3d 610 (D.C. Cir. 1995). In Arent, the court also found that even "where the plaintiff is not itself the subject of the contested regulatory action," it still may be within the "zone of interests" if it is directly interested as a purchaser of the regulated product. 866 F. Supp. at 12. As physicians whose ability to treat patients will be compromised by the delays and increased costs that the Pediatric Rule will cause, and as representatives of patients whose health will be compromised, Petitioners plainly fall into this "zone of interests."

[3] For an explanation of the term "intended use," see App. B, p. B-1.

[4] All emphasis in this letter and the accompanying appendices is added unless otherwise noted.

The Rule permits deferral of these requirements – at FDA's discretion – to expedite the drug approval process or to address safety concerns with testing the drug on children before its safety and/or effectiveness in adults has been adequately established. See id. § 314.55(b). Similarly, the Rule permits waiver of these requirements if:

(i) The drug product does not represent a meaningful therapeutic benefit over existing treatments for pediatric patients and is not likely to be used in a substantial number of pediatric patients;

(ii) Necessary studies are impossible or highly impractical because, e.g., the number of such patients is so small or geographically dispersed; or

(iii) There is evidence strongly suggesting that the drug product would be ineffective or unsafe in all pediatric age groups.

Id. § 314.55(c).

The Rule does not, however, permit waiver or deferral of these requirements based on a manufacturer's certification that it does not intend to market the drug for pediatric use. See id. § 314.55. Thus, whereas manufacturers once could control the uses for which they conducted clinical studies and sought approval of new drug products, FDA has now forced manufacturers to conduct studies and develop formulations for uses of a new drug that manufacturers may not desire to pursue.[5]

With respect to marketed drugs that have not been approved for pediatric use, the Rule purports to allow FDA to require manufacturers to "submit an application containing data adequate to assess whether the drug product is safe and effective in pediatric populations." Id. § 201.23(a) (1999). This includes, at FDA's discretion, "adequate evidence to support dosage and administration in some or all pediatric subpopulations." Id. The Rule also purports to allow FDA to require manufacturers "to develop a pediatric formulation for a drug product that represents a meaningful therapeutic benefit over existing therapies for pediatric populations for whom a pediatric formulation is necessary, unless the manufacturer demonstrates that reasonable attempts to produce a pediatric formulation have failed." Id.

Although the regulation concerning marketed drugs contains waiver provisions similar to those governing new drugs, a manufacturer cannot obtain a waiver merely because it does not wish to expand the uses of its product to pediatric populations. See id. § 201.23(c). If a manufacturer does not comply with FDA's pediatric testing requirement, FDA asserts the authority to declare the offending product to be "misbranded or an unapproved new drug or

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[5] Indeed, FDA has long required manufacturers to disclaim pediatric uses in the absence of clinical testing. See 21 C.F.R. § 201.57(f)(9)(v), (vi) (1999).

unlicensed biologic." Id. § 201.23(d); 21 U.S.C. § 355(d) (1994 & Supp. III 1997).[6] FDA claims this authority notwithstanding its necessary previous finding that precisely the same product is "safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof." 21 C.F.R. § 201.23(d); 21 U.S.C. § 355(d).

3. Summary of Argument

FDA should immediately revoke the regulations comprising the Pediatric Rule. The Pediatric Rule is fundamentally inconsistent with key purposes and provisions of FDAMA which encourage manufacturers to bring off-label uses on-label voluntarily – that is, in response to incentives rather than by FDA fiat. One of these incentives encourages manufacturers to seek approval for use of their drugs in pediatric populations by offering them an additional six months of exclusivity for their drugs under certain circumstances. 21 U.S.C. § 355a (Supp. III 1997). Another important FDAMA provision requires FDA to publish "standards for the prompt review of supplemental applications" to encourage manufacturers to seek approval for off-label uses of marketed drugs. See 21 U.S.C. § 371 note (Supp. III 1997). The Pediatric Rule, however, requires precisely the same type of studies that the statute only authorizes FDA to request. The mandatory nature of the Pediatric Rule also creates serious ethical problems associated with drug testing on children that are minimized under Congress's voluntary scheme. For a more detailed discussion of these points, see App. A, pp. A-2 to A-26.

The Pediatric Rule also conflicts with FDAMA's goal of reducing the inordinate amount of time that FDA consumes in approving new drug applications ("NDAs"). To effectuate this purpose, Congress included provisions in FDAMA designed to: (1) abbreviate and simplify the data necessary for FDA to conclude that a drug is safe and effective, 21 U.S.C. § 355(d); (2) streamline clinical research on drugs, id. § 355(i); and (3) institute a fast-track approval process for drugs to treat life-threatening illnesses, id. § 356. Yet the Pediatric Rule requires not only additional clinical studies but also the potential development of pediatric formulations of certain drugs. Thus, the Rule will render the already cumbersome drug approval process costlier, slower, and even more inefficient. For a more detailed discussion of this point, see App. A, pp. A-26 to A-39.

In addition to conflicting with key FDAMA goals, the Pediatric Rule contravenes the long-standing and universal understanding of Congress, the courts, and FDA concerning the nature of the "intended uses" of drug products that are subject to FDA's regulatory authority. From the 1906 inception of national food and drug law to the present, drug manufacturers have always determined the "intended uses" for which they sought approval to market their drug

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[6] In the vast majority of cases, however, FDA does not actually intend to seize the offending drugs and remove them from the market as provided in 21 U.S.C. § 334 (1994 & Supp. III 1997). Rather, FDA intends to seek court injunctions requiring manufacturers to conduct the testing required by the Pediatric Rule. See 63 Fed. Reg. at 66,655.

products by virtue of the promotional claims they made in their product's labeling. Any other uses – no matter how foreseeable or desired – were considered to be "off-label" and, thus, outside of FDA's jurisdiction.

FDA's promulgation of the Pediatric Rule, by contrast, would overturn this long-standing and universally understood balance of power by purporting to allow FDA – rather than the manufacturer – to determine the uses to which the manufacturer's product would be put. Specifically, FDA has asserted the right to require manufacturers of both new and marketed drugs to seek approval for use of their drugs on pediatric populations – even though the manufacturer may only desire to market its drug to adult populations. See 21 C.F.R. §§ 201.23, 314.55. Under the Pediatric Rule, FDA may now even force a manufacturer to develop new formulations of a drug for uses for which the manufacturer never intended to seek approval. See 21 C.F.R. §§ 201.23, 314.55. Not only has FDA far exceeded its congressional mandate in treating foreseeable uses as "intended uses," but it has also gone farther afield by creating a per se presumption that certain uses are foreseeable even where (1) the drug has not actually been marketed, and (2) the manufacturer has affirmatively disclaimed the allegedly "foreseeable" use at issue. FDA should immediately cease such unwarranted intrusion into determining the uses for which drugs will be marketed, which Congress historically has made the manufacturers' exclusive province. For a more detailed discussion of these points, see App. B, pp. B-1 to B-15.

If taken to its logical conclusion, the theory underlying the Pediatric Rule would render the drug approval and misbranding mechanisms of the Food, Drug, and Cosmetic Act ("FDCA"), Pub. L. No. 75-717, 52 Stat. 1040 (1938), virtually inoperable. For example, requiring manufacturers to conduct clinical studies to establish the safety and efficacy of all arguably foreseeable uses of each new drug that they seek to market would dramatically delay the necessary approvals for marketing those drugs. Moreover, the "Abbreviated New Drug Application" ("ANDA") process for generic follow-on drugs – which requires the ANDA to contain substantially identical labeling to the pioneer label – would cease to function if ANDA applicants were required to claim, on their labeling, foreseeable uses that were unforeseen when the pioneer drug's label was approved. Further, considering foreseeable uses to be "intended" would render the overwhelming majority of marketed drugs "misbranded" because their labels would not contain adequate directions for each "intended use" of the drug as required by law. See 21 U.S.C. § 352 (1994 & Supp. III 1997); 21 C.F.R. §§ 201.5, 201.100 (1999). FDA cannot avoid these harsh consequences by selectively enforcing its newly created foreseeability theory, which would be impermissible in any event. For a more detailed discussion of these points, see App. B, pp. B-15 to B-22. Thus, FDA's per se "foreseeability" theory, and consequently the Pediatric Rule, are untenable.

In addition to conflicting with key purposes of FDAMA and flying in the face of well-settled understanding of the types of intended uses subject to FDA's regulatory authority, the Pediatric Rule finds no statutory support in any other provision of the food and drug laws. Indeed, none of the statutory bases upon which FDA relies authorize the agency to venture so far afield from its mission of ensuring that drugs are safe and effective for their labeled indications

and into the realm of direct control over manufacturer research and development of formulations. For a more detailed discussion of this point, see App. D.

In sum, FDA should revoke the regulations comprising the Rule in light of:

(1) the stark contrast between key goals of recent food and drug legislation and the Pediatric Rule's effect, see App. A;

(2) FDA's abrogation of the well-settled "intended use" principle in purporting to dictate manufacturer decisions concerning appropriate labeled indications for their drug products, see App. B, pp. B-1 to B-15;

(3) the disruption of Congress's drug approval and misbranding mechanisms that would ensue if FDA's per se "foreseeability" theory underlying the Rule is consistently applied, see App. B, pp. B-15 to B-22;

(4) the lack of statutory support for the Rule, see App. C; and

(5) the unconstitutional taking that results from enforcement of the Rule, see App. D.

C. Environmental impact

The subject matter of this petition is not within any of the categories of action for which an environmental assessment is required pursuant to 21 C.F.R. § 25.22 (1999), and is exempt pursuant to 21 C.F.R. § 25.30(h) (1999) in that it is concerned with FDA's procedures in administering the Act.

D. Economic impact

Not requested.

E. Certification

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition, including all appendices attached hereto, 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.

Respectfully submitted,

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