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APPENDIX A:

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Perhaps the most striking deficiency of the Pediatric Rule ~~is~~ that it clashes with fundamental policies embodied in Congress's ~~most~~ recent food and drug legislation, the Food and Drug Administration Modernization and Accountability Act ("FDAMA"), which was enacted barely one year before FDA promulgated the regulations comprising the Pediatric Rule. Compare Pub. L. No. 105-115, 111 Stat. 2296 (1997) with Regulations Requiring Manufacturers To Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients: Final Rule, 63 Fed. Reg. 66,632 (1998).

It is a fundamental principle of administrative law that:

The rulemaking power granted to an administrative agency charged with the administration of a federal statute is not the power to ~~make~~ law. Rather, it is the power to adopt regulations to carry into effect the will of Congress as expressed by the statute.

v. Hochfelder, 425 U.S. 185, 213-14 (1976) (internal quotations omitted). The "regulations, in order to be valid[,] ~~must~~ be consistent with the statute under which they are promulgated." United States v. Larrison, 431 U.S. 864, 873 (1977) (invalidating regulations that were "contrary to the manifest purposes of Congress"); accord States v. Vogel Fertilizer Co., 455 U.S. 16, 26 (1982) ("This Court has firmly rejected the suggestion that a regulation is to be sustained simply because it is not technically inconsistent with the statutory language, when that regulation is fundamentally at odds with the manifest congressional design." (internal quotations omitted)).

Far from reflecting and enforcing the congressional policies and purposes underlying FDAMA, the Pediatric Rule contravenes key FDAMA goals in at least two respects, as set forth below.

I. THE RULE CONFLICTS WITH CONGRESS'S GOAL OF ENCOURAGING MANUFACTURERS TO BRING ADDITIONAL USES OF A DRUG ON-LABEL VOLUNTARILY.

One major goal of FDAMA is to encourage manufacturers, through various incentive provisions, to bring off-label uses of their drugs on-label on a voluntary basis. In making these provisions voluntary rather than mandatory, Congress recognized the value of off-label uses by ensuring that cumbersome regulatory restrictions would not interfere with physicians' ability to prescribe cutting-edge medical treatments.¹ The Pediatric Rule, however, which requires that off-label pediatric uses be brought on-label, rejects the very notion that off-label uses represent a beneficial treatment option (as FDA has long acknowledged), and upsets Congress's carefully crafted balance concerning the appropriate circumstances for bringing off-label uses on-label.

A. As Congress Has Recognized, Off-Label Uses Are A Common, Well-Recognized, And Essential Part Of Medical Practice.

The label for an approved drug "identifies only those uses for which the manufacturer has conducted studies and has demonstrated, to FDA's satisfaction, substantial evidence of safety

¹ Indeed, it is precisely the voluntary nature of the pediatric exclusivity provisions that is essential to keeping FDA within its statutory **mandate**. If manufacturers were instead required to bring off-label uses of a drug on-label, this would interfere even **more** with the practice of medicine than would barring physicians from prescribing drugs off-label, which is indisputably outside FDA's jurisdiction. Forbidding physicians from prescribing drugs off-label would merely eliminate certain uses of the drug. Requiring manufacturers to bring off-label uses on-label, by contrast, could cause the drug to be withdrawn from the market altogether as a "misbranded" product until the manufacturer could comply.

and effectiveness."² Nevertheless, once "a drug or device is approved by the agency as safe and effective for one purpose, no FDA regulations prevent doctors from prescribing it for any other purpose." Such use is called "off-label use" and includes treating a condition not indicated on the label, or treating the indicated condition but varying the dosing regimen or the patient population." 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).⁴

As **FDA's** former Deputy Commissioner for Policy, William B. Schultz, has acknowledged, "**FDA** knows that there are important off label uses of approved drugs." The agency has even gone so **far** as to state that:

There is no **FDA** policy that seeks to limit physician prescribing of prescription drugs to only **FDA** approved indications. Such a policy would . . . be an unwarranted intrusion into the physician-patient relationship and have detrimental public health consequences. . . . We, too, recognize that the physician in clinical

² U.S. General Accounting Office, Off-Label Drugs: Reimbursement Policies Constrain Physicians in Their Choice of Cancer Therapies, Pub. No. GAO/PEMD-91-14, at 10 (1991) [hereinafter "**GAO Report**"].

³ Michael I. Krauss, Loosening the FDA's Drug Certification Monopoly: Implications for Tort Law and Consumer Welfare, 4 Geo. Mason L. Rev. 457, 470 (1996).

Accord James M. Beck & Elizabeth D. Azari, FDA, Off-Label Use, and Informed Consent: Debunking Myths and Misconceptions, 53 Food & Drug L.J. 71, 104 (1998) (describing off-label uses as "using an approved drug to treat a disease that is not indicated on its label, but is closely related to an indicated disease, treating related, unindicated diseases, and treating the indicated disease but varying from the indicated dosage, regimen, or patient population").

⁵ More Information for Better Patient Care: Hearing Before the Senate Comm. on Labor and Human Resources, 104th Cong. 81 (1996) (statement of William B. Schultz, FDA Dep. Comm'r for Policy); see Beck & Azari, supra note 4, at 84 ("Nothing in the FDCA . . . suggests that FDA is to conduct its own evaluations of uses other than those proposed by a manufacturer.").

practice is well-equipped to make responsible prescribing choices for both approved and unapproved uses.⁶

Even this is an understatement. Off-label uses of drugs and medical devices constitute a "common and integral feature" of many, if not most, areas of medical practice.⁷ Estimates of the number of prescriptions for off-label uses of drug products range from twenty to sixty percent of the approximately 1.6 billion prescriptions written each year.⁸ As Michael R. Taylor, a former FDA Deputy Commissioner for Policy, has stated, "off-label use is often essential to good medical practice, and in some areas – oncology and pediatrics among them – off-label uses constitute a significant portion of standard therapy. FDA recognizes and accepts this reality."⁹ William Hubbard, **FDA's** Senior Associate Commissioner for Policy, Planning, and Legislation, has likewise affirmed that "[a]ll of [FDA's] physicians and scientists . . . strongly believe in the concept of physicians being able to prescribe for off-label uses based on their own experience, knowledge, consultation with colleagues and other sources of information."¹⁰

⁶ Letter from Ann Witt, Acting Director of FDA Division of Drug Marketing, Advertising and Communications, Office of Drug Standards, to A. John Rush, M.D., Director, Mental Health Clinical Research Center, University of Texas at Dallas, at 1 (Jan. 17, 1991).

Beck & Azari, supra note 4, at 79.

See id. at 80; accord Krauss, supra note 3, at 472 (observing that twenty to sixty percent of all prescriptions written each year prescribe drugs for an off-label use).

⁹ Michael R. Taylor, Speech of FDA Deputy Commissioner for Policy at the Food and Drug Law Institute Seminar on Drug Advertising and Promotion (Feb. 26, 1992); see Use of Approved Drugs for Unlabeled Indications, 12 FDA Drug Bulletin 4, 5 (Apr. 1982) ("'Unlabeled' uses may be appropriate and rational in certain circumstances, and may, in fact, reflect approaches to drug therapy that have been extensively reported in medical literature.") [hereinafter "Unlabeled Indications"].

¹⁰ Pl.'s Mem. in Supp. of Summ. J. at 9, Washington Legal Found. v. Friedman, 13 F. Supp. 2d 51 (D.D.C. 1998) (No. 1:94CV01306) (hereinafter "WLF Mem.") (citing Hubbard Tr. 72).

In certain fields, rates of off-label use are particularly high. For example, “[o]ff-label use is common, and even predominant, in the treatment of cancer patients.”¹¹ A government study that collected data from the spring of 1990 found that, of the seventeen most commonly used anti-cancer drugs, five had been used off-label at least 70% of the time.” Similarly, Carl Dixon, the President of the Kidney Cancer Association, recently stated that the “most widely prescribed medication for kidney cancer is off-label.”¹²

Some off-label uses define “state of the art treatment.”¹³ In the case of AIDS, for example, experts report that between 90% and 100% of applications are off-label.” According to a representative of the American Medical Association, “[i]n some cases, if you didn’t use the drug in the off-label way, you’d be guilty of malpractice.”¹⁴ As one author bluntly stated,

¹¹ GAO Report, *supra* note 2, at 40; *id.* at 3, 11 (“A third of all drug administrations to cancer patients were off-label, and more than half of the patients received at least one off-label drug. . . . [I]t is even possible that for a specific form of cancer, a drug given off-label may have been proven to be more beneficial than any drug labeled for that cancer.”).

¹² *Id.* at 21-22.

¹³ See FDA, Single Issue Focus Meeting, Section 401 of the FDA Modernization Act: Dissemination of Information on Unapproved/New Uses for Marketed Drugs, Biologics, and Devices, at 14 (July 8, 1998) <<http://www.fda.gov/ohrms/dockets/dockets/98n0222/tr00001.txt>>.

¹⁴ GAO Report, *supra* note 2, at 11.

¹⁵ See Kenneth P. Berkowitz et al., Congress Tries To Bridge the “Label Gap,” but Nobody Is Cheering, *Med. Mktg. & Media*, Jan. 1998, at 40, 42.

¹⁶ Beck & Azari, *supra* note 4, at 80 (citing Fran Kritz, FDA Seeks To Add Drugs’ New Uses to Labels, *Wash. Post*, Mar. 29, 1994, at Z11 (quoting American Medical Association vice-president)).

"[o]bviously, many more people would die, and the clamor about FDA-induced 'drug lag' would be more intense, if off-label prescriptions were suppressed."

Through off-label use, physicians discover new, more effective means of treating their patients. The **FDX** Drug Bulletin reported that when physicians resort to off-label use of drug products, they often discover "[v]alid new uses for drugs already on the market . . . through [their] serendipitous observations and therapeutic innovations."¹⁸ The great majority of breakthroughs in treating depression and schizophrenia come through unapproved uses, as have nearly all curative anti-cancer therapies."

Off-label uses are especially common in pediatric populations. See Washington Legal Found., 13 F. Supp. 2d at 56 (observing that off-label uses are important to pediatrics). In fact, **FDA** recognizes that many off-label uses are the norm in pediatrics, often because testing in children can be prohibitively expensive and because involving children in clinical trials raises special concerns not present with respect to adult testing—" **As** a result of the costs, risks, and unique difficulties involved in bringing pediatric uses on-label for a drug only approved for uses

¹⁷ Krauss, supra note 3, at 473.

¹⁸ Off-Label Indications, supra note 9, at 5.

¹⁹ See Robert M. Goldberg, Breaking up the FDA's Medical Information Monopoly, 1995 Regulation: Cato Rev. of Bus. & Gov't No. 2 at 48.

²⁰ See WLF Mem., supra note 10, at 7 (citing Temple ¶ r. 54; David Kessler, Speech of FDA Commissioner to the American Academy of Pediatrics (Oct. 14, 1992); Hubbard Tr. 164. 11-181: infra pp. A-23 to A-25 (discussing unique problems associated with pediatric testing, including separation from parents, discomfort, fear, and difficulty in obtaining blood samples).

in adult populations. most drugs carry a disclaimer stating that safety and effectiveness have not been tested in children."

FDA has attempted to justify the Pediatric Rule by saying that "the absence of pediatric labeling information poses significant risks for children." 63 Fed. Reg. at 66.633. Yet off-label pediatric uses, like other off-label uses, are not unduly risky. "Off-label" merely means that the label is "silent" as to that particular use. Such uses pose no great safety hazard because "FDA premarket review of drugs involves [such] extensive scrutiny [that] the agency ordinarily has reasonable assurances that marketed products are safe, both for their labeled uses and for general use."²² Neither does any correlation necessarily exist between the off-label versus on-label status of a use and the benefits of that use." As the GAO Report stated. "[t]he category 'off-label use' runs from clearly experimental use to standard therapy and even to state-of-the-art treatment."²³

²¹ See Lawrence Bachorik, Why FDA Is Encouraging Drug Testing in Children, FDA Consumer, July-Aug. 1991, at 15 (interview with Paula Botstein, M.D., Deputy Director of FDA's Office of Drug Evaluation I) (stating that because population of children is small, financial return of studying drugs in children is small); 21 C.F.R. § 201.57(f)(9)(v) (1999) (requiring explicit disclaimer on label of drugs not approved for pediatric populations); Reauthorization of the Prescription Drug User Fee Act and FDA Reform: Hearings Before the Subcomm. on Health and Environment of the House Commerce Comm., 105th Cong. (Apr. 23 1997) (statement of Sanford N. Cohen, American Academy of Pediatrics ("Eighty percent of more of drugs approved since 1962 have been approved and labeled for use in adults with a disclaimer that they are not approved for use by children.") [hereinafter "Cohen Testimony"]).

²² Beck & Azari, *S* i note 4, at 82.

²³ See *id.* at 72 ("All medical treatments, including off-label treatments, have medical risks. . . . The mere fact of off-label use . . . is a matter solely of FDA regulatory status and cannot logically be considered a medical risk of a drug or medical device. Nor is off-label use inherently experimental or investigational." (citation omitted)).

²⁴ GAO Report. *supra* note 2, at 11.

If anything, off-label pediatric uses arguably represent a less risky alternative for children than does FDA's Pediatric Rule. Drugs used off-label in pediatric populations have already been established to be safe and effective for use in adult populations. See 21 U.S.C. § 355(d) (1994 & Supp. III 1997) (requiring that drug be safe and effective "for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof"). Moreover, doctors prescribing drugs off-label to children will do so on a one-on-one basis, in the context of a doctor-patient relationship. The Pediatric Rule, by contrast, pressures manufacturers in the context of clinical studies – which involve groups of patients rather than the highly individualized setting of a doctor-patient relationship – to administer those same drugs to children before they are approved for use on adults. See 21 C.F.R. § 314.55(a) (1999) (requiring new drug sponsors 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"). Common sense dictates that the individualized administration to children in the context of a doctor-patient relationship of drugs already established to be safe and effective for adults represents an alternative that is at least as safe – if not far safer – than forcing manufacturers to test unapproved drugs on groups of children in the context of clinical studies:

Congress has recognized the well-established benefits of off-label uses. Specifically, it has expressly forbidden FDA from interfering with those uses, thus enabling physicians to take advantage of the latest advances in medical technology in treating their patients:

[I]t has been the long held view of Congress that the FDA should not regulate the practice of medicine. In general, the FDA has no authority to regulate how physicians prescribe approved drugs in the context of their medical practice. Physicians prescribing off-label uses of approved drugs is not within the jurisdiction of the FDA.

H.R. Rep. So. 105-310, at 60 (1997); see also 21 U.S.C. § 396 (Supp. III 1997) (exempting practice of medicine from Food, **Drug**, and Cosmetic Act); H.R. Conf. Rep. No. 105-399, at 97, reprinted in 1997 U.S.C.C.A.N. 2880, 2887 (warning that "the FDA should not interfere in the practice of medicine" and that physician-prescribed off-label use of medical devices "is not the province of the FDA"). Likewise, Congress allows **reimbursement under the Medicare and Medicaid programs for off-label prescriptions. See** 42 U.S.C. §§ 1396b, 1396r-8 (1994 & Supp III 1997).²⁵

At the same time, Congress recognizes that there is some benefit in encouraging manufacturers to seek FDA approval for off-label uses to **keep the drug label up to date – so long as the FDA approval process does not obstruct the availability of effective treatments to prescribing physicians and their patients:**

Although the use of **an** approved product for **an** unapproved use does not violate the law, it is **important to encourage the addition of new uses to the FDA-** approved product labeling in order to keep that **labeling current with medical practice.**

H.R. Rep. No. 105-310, at 63; see also S. Rep. No. 105-43, at 42 (1997). To encourage manufacturers voluntarily to seek approval for off-label indications – while at the same time ensuring that **FDA** did not exceed its statutory authority – Congress included various incentives in FDAMA. The Pediatric Rule undercuts that regime, substituting compulsion for cooperation.

²⁵ See also FDA, Public Hearing on Pharmaceutical Marketing and Information Exchange in Managed Care Environments (Oct. 19, 1995) <<http://www.fda.gov/cder/ddmac/MANAGEDCAREPANEL2.htm>> (statement of Pharmacist Calvin Knowlton on behalf of American Pharmaceutical Association) (stating that Medicare and Medicaid statutes "provide payment for off-label use of drugs if these **uses are** recognized as accepted medical practice under the authoritative compendia listed in the Federal Medicare and Medicaid statutes").

B. The Pediatric Rule Is Inconsistent With FDAMA Provisions Designed To Encourage Manufacturers To Bring Off-Label Uses On-Label Voluntarily.

1. The Rule is Inconsistent with the Pediatric Exclusivity Provision.

In FDAMA, Congress enacted an elaborate voluntary incentive scheme whereby FDA may request pediatric studies for both new and marketed drugs if FDA determines that additional pediatric information concerning those drugs "may produce health benefits in the pediatric population." 21 U.S.C. § 355a (Supp. III 1997). If the manufacturer agrees to conduct, and FDA accepts, such studies, the manufacturer is entitled to an additional six months of marketing exclusivity under certain circumstances. *See id.* The statute also contains a sunset provision and a requirement that FDA report to Congress on this provision by January 1, 2001. *Id.* § 355a(j)-(k) (Supp. III 1997). Notably, FDA must discuss in its report (1) "the effectiveness of the program in improving information about important pediatric uses for approved drugs," (2) "the adequacy of the incentives provided under this section," and (3) "any suggestions for modification that the Secretary determines to be appropriate." *Id.* § 355a(k).

Although Congress only authorized FDA to request pediatric studies and to appropriate modifications after the incentive program had been tested, FDA has promulgated regulations, far beyond its statutory mandate, which require manufacturers to conduct those same studies. Compare 21 U.S.C. § 355a(a), (c) (Supp. III 1997) (authorizing FDA to "make[] a written request for pediatric studies" from manufacturers of new and marketed drugs) and S. Rep. No. 105-43, at 3 ("The legislation gives the Secretary authority to request pediatric clinical trials for new drug applications and provides 6 extra months of market exclusivity to drugs when the manufacturer voluntarily meet[s] certain conditions under the program.") with 21 C.F.R.

§ 201.23(a) (1999)(providing that manufacturer of marketed drug "may be required to submit an application containing data adequate to assess" safety and effectiveness of drug, including dosage and administration in some or all pediatric subpopulations and "may also be required to develop a pediatric formulation") and id. § 314.55 (1999)(requiring new drug manufacturers to conduct pediatric studies and develop pediatric formulations). It makes little sense for Congress to have enacted legislation that "~~gives the Secretary authority to request~~ pediatric clinical trials" - and provides substantial incentives to induce manufacturers to agree to conduct such studies - **if** all along the Secretary had authority to **require** those same studies, thus largely negating the elaborate congressional scheme.

It is particularly inappropriate for **FDA** to contradict these explicit congressional provisions in light of their obviously experimental nature. Not only did Congress include a sunset provision in the legislation, but it also expressly **required FDA to report to Congress** concerning the effectiveness of the legislation, including any suggestions that **FDA** could offer to improve the scheme. 21 U.S.C. § 355a(j)-(k). **Rather than heed these explicit directives by** giving Congress's scheme the benefit of the statutorily mandated trial run, however, **FDA** instead proclaimed that it "~~does not believe. . . that incentives alone will result~~ in pediatric studies of some of the drugs and biologics where the need is greatest." 63 Fed. Reg. at 66,639. Rather, **FDA** declared its "belief" that a mixture of incentives and requirements is most likely to result in real improvements in pediatric labeling." Id. **FDA provided no evidence to support this "belief.** Instead, it pointed out that, under **FDAMA**, incentives are not available for many products. See id.

Contrary to **FDA's** pessimistic view of the efficacy of the pediatric exclusivity provisions in **FDAMA**, many manufacturers have already **decided** to take advantage of these provisions. To

illustrate. as of October 1, 1999, manufacturers had already filed 159 proposed pediatric study requests with FDA.²⁶ Of those 159 requests, FDA had acted on 157.²⁷ Six active moieties, including six approved active moieties, have already received extended exclusivity as a result of pediatric testing.²⁸ Most of the drugs that are currently benefiting from the extended pediatric exclusivity provisions are approved, marketed drugs rather than new drugs. FDA has stated that it would require pediatric testing for approved drugs "only in compelling circumstances," which it estimates will exist for "approximately two marketed drugs per year." 63 Fed. Reg. at 66,654.

In light of this experience, FDA should reconsider its assertion that the FDAMA procedures will be insufficient to bring about pediatric testing and revoke the Pediatric Rule. 63 Fed. Reg. at 66,639; see Home Box Office, Inc. v. FCC, 567 F.2d 9, 36 (D.C. Cir. 1977) ("[A] regulation perfectly reasonable and appropriate in the face of a **given** problem may be highly capricious if that problem does not exist." (internal quotations omitted)); see also Texas v. EPA, 499 F.2d 289, 319 & n.49 (5th Cir. 1974) (observing that agency must rely upon data that is "the best that is feasibly available" and that agency has "duty to reconsider and revise its requirements as better data becomes available"). At a minimum, FDA should allow Congress's voluntary pediatric exclusivity scheme the congressionally mandated opportunity to prove its efficacy.

²⁶ See FDA, Center for Drug Evaluation and Research, Pediatric Exclusivity Statistics (last modified Oct. 1, 1999) <<http://www.fda.gov/cder/pediatric/wrstats.htm>>.

²⁷ See *id.*

²⁸ See FDA, Center for Drug Evaluation and Research, Approved Active Moieties to Which FDA Has Granted Exclusivity for Pediatric Studies Under Section 505A of the Federal Food, Drug, and Cosmetic Act (last modified Oct. 29, 1999) <<http://www.fda.gov/cder/pediatric/exgrant.htm>> (listing grants of pediatric extended exclusivity for six approved active moieties, including grants for ibuprofen to two different sponsors).

2. The Rule Conflicts with the Supplemental Application Provision.

A second provision demonstrating that Congress intended to encourage – not force – manufacturers to seek approval for off-label uses concerns supplemental applications for new uses of approved drugs. See 21 U.S.C§ 371 note (Supp. III 1997). The provision accomplishes this by, inter alia, establishing mechanisms by which **FDA** can “encourag[e] the prompt review of supplemental applications” and “work[] with sponsors to facilitate the submission of data to support supplemental applications.” Id. According to an accompanying House Report, the purpose of the legislation is to “encourage the regulated industry to submit supplemental applications whenever feasible” for new uses of approved products and to do so by “reducing the overall burden of submitting supplemental applications and obtaining their approval.” H.R. Rep. No. 105-310, at 64.

Congress had a compelling practical reason for structuring **FDAMA** to allow off-label uses to continue rather than to forcing those uses on-label immediately – medical discoveries happen faster than **FDA** can possibly track:

New uses for drugs are often discovered after **FDA** approves the package inserts that explain a drug's approved uses. Congress would have created havoc in the practice of medicine had it required physicians to follow the expensive and time-consuming procedure of obtaining **FDA** approval before putting drugs to new uses.

United States v. Algon Chem. Inc., 879 F.2d 1154,1163 (3d Cir. 1989).²⁹

²⁹ See William L. Christopher, Off-Label Drug Prescription: Filling the Regulatory Vacuum, 48 Food & Drug L.J. 247, 261 (1993) (stating that **FDA** “could not review drugs . . . at a pace equal to that at which physicians discover beneficial off-label uses”).

Many states have statutes endorsing the use of off-label drugs. For example, **N.J.Stat. Ann. § 26.1A-36.9(g)** (1996) contains the following statement:

(Continued...)

Despite Congress's clear intent to allow off-label uses to continue and merely encourage - rather than require - that those uses be brought on-label, the Pediatric Rule requires manufacturers of marketed drugs to seek approval for off-label pediatric uses. Moreover, although the goal of the supplemental application provision is to "reduc[e] the overall burden of submitting supplemental applications and obtaining their approval," the Pediatric Rule increases that burden by requiring manufacturers not only to conduct clinical studies to support pediatric uses, but also to develop entirely new formulations appropriate for various pediatric subpopulations. See 21 C.F.R. § 201.23(a) (requiring manufacturer of marketed drug "to

(... Continued)

"Off-label" use of FDA-approved drugs provides efficacious drugs at a lower cost. To require that all appropriate uses of a drug undergo approval by the FDA may substantially increase the cost of drugs and delay or even deny patients' ability to obtain medically effective treatment. FDA approval for each use would require substantial expenditure and time to undergo the clinical trials necessary to obtain FDA approval.

This widespread consensus that a drug regulatory scheme permitting off-label uses is superior to one that does not stems from the notion that market forces, rather than the government, can most efficiently determine the uses and the patient populations for which drugs should be marketed. As one commentator has observed, "the clinical judgment of the marketplace is more effective and quicker than the FDA regulatory scheme in making the comparisons required to determine what drugs work and for whom." Goldberg, *supra* note 19, at 42; see Doug Bandow, The FDA Can Be Dangerous to Your Health, Cato: This Just In (Jan. 29, 1997) <<http://www.cato.org/dailys/1-29-97.html>> ("[E]ffectiveness is best tested in the marketplace."). Indeed, economic studies, along with many years of FDA and drug manufacturer experience, demonstrate that market forces have provided manufacturers with the incentive to design and produce safe drugs, particularly if tort remedies are available as a disincentive. See Krauss, *supra* note 3, at 459 (citing A. Mitchell Polinsky, An Introduction to Law and Economics (1983)). Thus, private drug companies as market actors, and physicians and patients making individualized health decisions - rather than the government - are better able to respond to the medical, pharmaceutical, toxicologic, ethical, and resource considerations involved in deciding whether to market a drug to pediatric populations.

develop a pediatric formulation" in certain instances). In short, the Pediatric Rule contradicts the supplemental application provision.

C. Judicial Precedent Establishes That FDA Cannot Superimpose Its Own Conflicting Scheme Of Mandatory Pediatric Regulations On Congress's Voluntary Scheme.

Judicial precedent confirms that FDA may not superimpose its own mandatory system of regulations on Congress's dramatically different, voluntary scheme, addressing the identical area of law. As the Supreme Court has long recognized, it is "an elemental canon of statutory construction that where a statute expressly provides a particular remedy or remedies, a court must be chary of reading others into it. When a statute limits a thing to be done in a particular mode, it includes the negative of any other mode." Transamerica Mortgage Advisors, Inc. v. Lewis, 444 U.S. 11, 20 (1979) (internal quotations omitted). Applying this well-established canon in Transamerica Mortgage Advisors, the Supreme Court refused to recognize private causes of action for damages for violations of a statute that "nowhere expressly provides for a private cause of action." Id. at 14, 19-20. After observing that "Congress expressly provided both judicial and administrative means for enforcing compliance," the Court concluded that "it is highly improbable that Congress absentmindedly forgot to mention an intended private action." (internal quotations omitted).

The D.C. Circuit reached a similar conclusion in considering the propriety of the National Mediation Board's assertion of authority to investigate representation disputes among a carrier's employees. See Railway Labor Executives' Ass'n v. National Mediation Bd., 29 F.3d 655, 658-59 (en banc), amended by 38 F.3d 1224 (D.C. Cir. 1994). In light of a statute that provided for such investigations to be initiated "upon request of either party to the dispute," the court held that

the Board had exceeded its jurisdiction by initiating dispute investigations sua sponte given that "Congress effectively has provided a 'who, what, when, and how' laundry list governing the [agency's] authority." *Id.* at 665.667. The court further observed that "[t]he duty to act under certain carefully defined circumstances simply does not subsume the discretion to act under other, wholly different, circumstances, unless the statute bears such a reading." *Id.* at 671.

Applying this judicial reasoning to the context of the Pediatric Rule, where Congress **has** enacted a detailed statutory scheme granting **FDA** limited authority to request that manufacturers voluntarily conduct pediatric studies of certain drugs, **FDA** cannot assert the authority to require manufacturers to conduct those studies. Moreover, where, **as here**, Congress expressly **gave** **FDA** authority to request pediatric studies, "it is highly improbable that Congress absentmindedly forgot to mention" that it also intended to **grant** **FDA** authority to require those same studies.

D. The Serious Ethical Problems That Arise From The Mandatory Nature Of The Pediatric Rule Confirm The Superiority Of Congress's Incentive-Based Solution

The disturbing ethical problems that arise **from** the Pediatric Rule's requirement of mandatory testing of **drugs** in children – problems that are minimized by use of a voluntary pediatric testing scheme – further confirm the superiority of Congress's incentive-based scheme over the mandatory Pediatric Rule. First, **the** Pediatric Rule pressures manufacturers to conduct pediatric testing before a drug **has** been established **as safe for adults**. Second, by presuming that all drugs should be tested in children, the Pediatric Rule exacerbates the special risks involved in pediatric testing.

I. **The Pediatric Rule Increases the Risk of Pediatric Testing Before a Drug Is Shown To Be Safe for Adults.**

The domestic and international medical communities, as well as FDA, agree that pediatric testing generally should be deferred until Phase 2 or Phase 3 of the clinical research process. The American Academy of Pediatrics, for example, pointed out "without hesitation" in its response to FDA's proposed rulemaking that researchers should complete Phase 1 and part of Phase 2 before beginning pediatric testing.³⁰ The international community likewise acknowledges that "[w]hen pediatric patients are included in clinical trials, safety data from previous adult human exposure would usually represent the most relevant safety data and should generally be available before pediatric clinical trials."³¹ Acting together with parallel regulatory bodies in Europe and Japan, FDA co-sponsored and endorsed the international agreement that made this assertion.³² FDA

³⁰ Letter from American Academy of Pediatrics to FDA Dockets Management Branch re Docket No. 97N-0165, Regulations Requiring Manufacturers To Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients, at 1, 5 (Nov. 13, 1997) [hereinafter "AAP Comments"]; see Committee on Drugs for the American Academy of Pediatrics, Guidelines for the Ethical Conduct of Studies To Evaluate Drugs in Pediatric Populations, 95 Pediatrics 286, 287 (1995) (stating that "studies in children should be preceded by initial clinical trials in adults to provide preliminary pharmacokinetic, safety, and efficacy data") [hereinafter "Ethical Guidelines"]; see also FDA, Public Meeting on FDA's Proposed Regulation to Increase Pediatric Use Information for Drugs and Biologics (Oct. 27, 1997) <<http://www.fda.gov/cder/meeting/transcript/1027pedi.htm>> (remarks of Dr. McCarthy, senior research fellow at the Kennedy Center for Bioethics, Georgetown University) ("I would make sure that the studies are at least through Phase II in adults before you move to children, and I would like to see it in two or three phases – older children, then younger children, and finally infants.") [hereinafter "Public Meeting"]; *id.* (remarks of Dr. Spielberg) ("[P]ediatric studies in general should not be initiated with a new chemical entity prior to the establishment of the adult dose, serum concentration profile, and a clear 'go' decision for the drug development process.").

³¹ International Conference on Harmonisation, Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals, 62 Fed. Reg. 62,922, 62,925 (1997).

³² *Id.* at 62,922 (stating that FDA "is committed to seeking . . . harmonized technical procedures"). Similarly, the European Committee for Proprietary Medicinal Products ("CPMP") (Continued...)

also expressed its commitment to deferring pediatric testing in a 1977 report entitled General Considerations for the Clinical Evaluation of Drugs in Infants and Children when it stated that "[b]ecause of ethical considerations, reasonable evidence of efficacy generally should be known before infants and children are exposed to the agent."¹³

Congress's voluntary incentive scheme minimizes the risks arising from concurrent pediatric testing. Because adult drug approval does not hinge upon successful completion of pediatric testing, there is no pressure on manufacturers to rush pediatric testing. Rather, the manufacturers, after consulting with appropriate medical professionals, may determine the appropriate timing and circumstances under which to initiate pediatric testing, first ensuring that the product is safe for adults.

By contrast, the Pediatric Rule's mandatory approach exerts enormous pressure on manufacturers to conduct concurrent pediatric testing, given that their drug products cannot be approved and marketed until safety and efficacy testing is complete. See 21 C.F.R. § 314.55(a).

(... Continued)

determined that, "In general, safety studies should be conducted first in animals as a part of the routine pre-clinical development, then in adults, and subsequently in younger patients." European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, Note for Guidance on Clinical Investigation of Medicinal Products in Children, at 2 (Mar. 17, 1997). The age categories for pediatric testing also conflict with those set forth in the CPMP. See id. at 4-5. Such inconsistencies in timing requirements and age categories could force sponsors engaged in the international pharmaceutical market to conduct duplicative studies, thereby exposing more children than necessary to the risk of drug testing, resulting in what one drug manufacturer has called a "tremendously wasteful" allocation of resources. Letter from Glaxo Wellcome Research and Development to FDA Dockets Management Branch re Docket No. 97N-0165, Regulations Requiring Manufacturers To Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients, at 15 (Nov. 12, 1997) [hereinafter "Glaxo Wellcome Comments"].

¹³ FDA. General Considerations for the Clinical Evaluation of Drugs in Infants and Children, at 5 (1977) [hereinafter "General Considerations in Infants and Children"].

Manufacturers naturally will try to place valuable new treatments into the hands of adults who need them as expeditiously as possible. The Pediatric Rule, however, hinders manufacturers' efforts to do so by requiring that, before adults may have access to the new drug, it must first be approved as safe and effective for use in children. Thus, **FDA** has limited manufacturers to three undesirable choices:

- (1) test the drug on children sooner rather than later to minimize the delay in providing it to ailing adults, thus triggering the ethical concerns discussed above by prematurely testing a product on children;
- (2) test the drug on adults first to ensure that it is **safe and effective before testing it on children, thereby causing undesired, and potentially life-threatening, delays in making the treatment accessible to adults;** or
- (3) redirect research and development efforts away from diseases occurring in both adults and children and toward diseases occurring exclusively in adults to avoid this conundrum altogether, ultimately harming children by limiting the quantity and quality of available pediatric treatments, both off-label **and** on-label.

In light of these alternatives, **FDA's claim that "[n]othing in the rule requires concurrent testing in adults and pediatric patients, nor testing in infants and neonates before testing in older children."** 63 Fed. Reg. at 66,642, rings hollow.

Nor does **FDA's** reliance upon the Pediatric Rule's deferral provisions solve this dilemma. See *id.* ("[I]ndustry comments appear to have **misunderstood** the explicit deferral provisions of the rule and perceived them as **rare** exceptions to a usual requirement that adults and children be studied at the same time."); *id.* at 66,640 (arguing that "the rule will not require studies in settings where ethical or medical concerns militate against studies" and that the Rule's deferral provisions are "specifically designed to ensure that no pediatric study **begins** until there are sufficient safety and effectiveness data to conclude that the study is ethically and medically appropriate"). Those provisions are **merely exceptions** to the general rule that **all** pediatric

testing must be completed before a drug can be approved and marketed. See 21 C.F.R.

§ 314.55(a).

Moreover, FDA has indicated that deferral should rarely be granted. FDA, for **example**, refused one pharmaceutical company's request to recognize circumstances in which FDA would automatically grant deferral. Instead, FDA adopted rules that give FDA complete discretion to determine whether deferral is appropriate. See id. § 314.55(b) (1999); 63 Fed. Reg. at 66,643 ("The need for deferral must be considered case-by-case."). FDA has **further** warned that deferral is not "necessarily warranted where analytic tools and clinical methodologies cannot be easily adapted to pediatric patients," nor are "[d]ifficulties in developing an adequate pediatric formulation" likely grounds for obtaining a deferral. Id. at 66,644.

Even in the rare instances where deferral may be granted, the Pediatric Rule places a high premium on testing new drugs on children **as early as possible**. Applications for deferral must not only "provide a certification from the applicant of the grounds for delaying pediatric studies" and "a description of the planned or ongoing studies," but they **must** also include "evidence that the studies are being or will be conducted with due diligence and at the earliest possible time." 21 C.F.R. § 314.55(b).³⁴

In **sum**, FDA has done little to address legitimate concerns that the Pediatric Rule essentially mandates concurrent testing. Rather, it **has s u m a r i l y** dismissed these concerns, leaving ethical issues unanswered and raising additional concerns about how it will apply this

³⁴ In light of this substantial premium placed on early drug testing on children, FDA's oft proffered justification of the safety of the Rule – i.e., that "no pediatric study may go forward without the approval of an [Institutional Review Board] which is responsible for ensuring that the study is ethical and adequately protects the safety of the subjects" – provides little comfort. 63 Fed. Reg. at 66,640.

new mandate. This response is insufficient as a matter of law. See, e.g., Motor Vehicle Mfrs. Ass'n v. State Farm Mut. Auto. Ins. Co., 463 U.S. 29, 43 (1983) (holding that "agency must examine the relevant data and articulate a satisfactory explanation for its action").

It is particularly troublesome for **FDA** to subject children to the risk of concurrent testing where the vast majority of that testing will ultimately prove unnecessary. Only a tiny fraction of all new drugs actually obtain **FDA** approval to be marketed, and thus are ever used by children. Of the drugs that begin human clinical testing, "[o]nly 23% . . . eventually receive marketing approval." Drugs and Biologics – A Consumer's Perspective: Hearings Before the Subcomm. on Oversight and Investigations of the House Commerce Comm., 104th Cong. (May 25, 1995) (written testimony of Kenneth Kaitin) [hereinafter "Kaitin Testimony"].³⁵ As one commenter observed, "up to 50% of drugs are abandoned before phase 3." See 63 Fed. Reg. at 66,643.³⁶ Even for the drugs that successfully reach Phase III, **FDA** itself has estimated that "only about 63% of all [new molecular entities] that enter phase III trials are eventually approved." Pediatric Patients: Regulations Requiring Manufacturers To Assess the Safety and Effectiveness of New Drugs and Biological Products: Proposed Rule, 62 Fed. Reg. 43,900, 43,911 (1997); accord

³⁵ See Krauss, supra note 3, at 462 ("Only one out of 5,000 new drugs now complete [the drug approval] process successfully.").

³⁶ Accord David A. Kessler, The Regulation of Investigational Drugs, 320 New Eng. J. Med. 201, 202 (1989) ("The vast majority of preliminary drug studies do not lead to marketing applications,").

³⁷ FDA's position in the Pediatric Rule is that pediatric testing for products meant to cure serious diseases that are less than life-threatening should begin when data is available "from the initial well-controlled studies in adults" – i.e., at the end of Phase II. 63 Fed. Reg. at 66,643.

Kaitin Testimony. supra p. A-21 (stating that only 64% of the drugs that begin Phase III testing eventually receive market approval).

These "drug dropout" rates establish that the Pediatric Rule **will** subject children to risky testing of products **that will** never even be marketed in the U.S.³⁸ Indeed, by FDA's own calculations, fully thirty percent of the children who would be exposed to drug testing under the Pediatric Rule would be needlessly put at risk. 62 Fed. Reg. at 43,911 (increasing estimate of pediatric studies required by 30% to account for testing of "drugs that ultimately fail to gain regulatory approval"): accord 63 Fed. Reg. at 66,662-63 (affirming prior calculations).³⁹ FDA's estimate conservatively assumes that manufacturers would conduct **no** pediatric testing until Phase III or later. See 62 Fed. Reg. at 43,911. If some pediatric testing occurred before Phase III, the number of children needlessly put at risk would be even higher than FDA's 30% estimate.

To expose children to huge risks unnecessarily, even before **minimal** safety and efficacy of drugs for adults has been established, violates the whole purpose of the Pediatric Rule, which is purportedly to make treatments safer for children. In addition, this potential exposure highlights the superiority of Congress's voluntary approach to pediatric testing. That approach

³⁸ See Public Meeting, supra note 30 (statement of Dr. Walson, Division Head, Clinical Pharmacology/Toxicology, at Children's Hospital in Columbus, Ohio) (referring to "negative guinea pig image of [pediatric] research").

³⁹ FDA's assumption that **only** 30% of pediatric testing will be unnecessary is inconsistent with its position that "[p]ediatric studies of **drugs** and biologics for life-threatening diseases may in some cases be appropriately begun as early as the initial safety data in adults becomes available." 63 Fed. Reg. at 66,643.

allows for maximum flexibility in ensuring that such testing is both necessary and safe before its Initiation.”

2. The Pediatric Rule Exacerbates the Special Risks and Difficulties Involved in Pediatric Testing.

The Pediatric Rule's requirement that new drugs be universally tested on children unless FDA affirmatively waives the requirement also unnecessarily aggravates the special problems involved in conducting pediatric testing. As Dr. Clemente, founder and Chairman of the Board of Ascent Pediatrics, explained during hearings on the Pediatric Rule, “[t]esting in children is different and it is also very demanding and expensive for a number of reasons, such as the limitation of qualified study sites, the identification of appropriate patients, [and] parents['] reluctan[ce] to enroll their children in a clinical study.”⁴⁰ Additionally, “[t]here are practical considerations, such as obtaining blood and urine samples, [and] difficulty in obtaining outcome data as children may not be able to describe symptoms or side effects.”⁴¹ These practical considerations can make it difficult to develop appropriate methodologies to assess a drug's safety and effectiveness in children as well as to implement adequate behavioral safeguards for studies. Other problems include obtaining informed consent,⁴² the limited number of

⁴⁰ This potential for harm undercuts FDA's former position that “[a] prime requirement [of clinical investigation] is that the subjects (patients) are exposed to the least possible risk consistent with anticipated benefit.” FDA, General Considerations for the Clinical Evaluation of Drugs (1977), at ii; accord id. at 1.

⁴¹ Public Meeting, supra note 30 (remarks of Dr. Clemente).

⁴² Id.

⁴³ See Ethical Guidelines, supra note 30, at 292 (observing that “obtaining truly informed consent may be difficult [in children with chronically progressive or potentially fatal diseases] because of the child's debilitated condition or the mental and emotional state of the parents”).

investigators who have expense to conduct trials in young children, and determining appropriate timing of clinical trials in light of the child's maturation." Additionally, special risk factors apply to children, including "discomfort, inconvenience, pain, fright, separation from parents or familiar surroundings [and] effects on growth or development of organs."⁴⁵

Yet another barrier to conducting clinical trials in pediatric patients is the difficulty in enrolling sufficient numbers of children. Traditionally, studies of drug products in pediatric populations have involved sick children." Without the prospect of a medical advance for their child, parents may have no incentive to enroll their children. In fact, at least one pediatric medical journal has declared that "[s]tudies that promise no demonstrable benefits to the child participating in the study or to children in general should not be conducted, irrespective of the minimal nature of the attendant risks."⁴⁶

The scheme that Congress established in FDAMA minimizes such problems. Because pediatric testing is encouraged but not required, manufacturers can determine when, and whether, to conduct such testing. Manufacturers are therefore likely to defer testing until they are sure that the product will gain approval for use in adults and there is demonstrated pediatric interest, thus producing a potential "sick child" population for testing. This winnowing process will eliminate

Letter from Novartis Pharms. Corp. to FD.4 Dockets Management Branch re Docket No. 97N-0165, Pediatric Patients: Regulations Requiring Manufacturers To Assess the Safety and Effectiveness of New Drugs and Biological Products: Proposed Rule, at 3-4 (Nov. 13, 1997).

⁴⁵ Ethical Guidelines, *supra* note 30, at 288.

⁴⁶ See General Considerations in Infants and Children, *supra* note 33, at 5 ("Based on ethical considerations, sick children rather than well ones will be the principal source of the experimental population . . .").

⁴⁷ Ethical Guidelines, *supra* note 30, at 288.

a large number of products from consideration for testing on children. The Pediatric Rule, by contrast, exacerbates these problems by virtue of its universal mandatory approach to pediatric testing.

E. Section 355a(i) Of FDAMA Does Not Allow FDA To Bootstrap Its Authority To Promulgate The Pediatric Rule.

Contrary to FDA's claims, 21 U.S.C. § 355a(i) does not support its position that the Pediatric Rule is statutorily permissible and consistent with FDAMA. That provision awards extended market exclusivity to a drug for which a manufacturer has conducted pediatric studies that were "required pursuant to regulations promulgated by the Secretary" and that comply with the requirements of § 355a. See 21 U.S.C. § 355a. The provision, however, does not constitute an independent grant of statutory authority for FDA to require pediatric studies. See H.R. Rep. No. 105-310, at 54 (acknowledging that regulations requiring pediatric studies must be "promulgated under other authorities of law"); National Pharm. Alliance v. Henne, 47 F. Supp. 2d 37, 41 (D.D.C. 1999) (acknowledging that, apart from congressionally enacted legislative incentives for pediatric testing, such testing "is not otherwise required of drug manufacturers"). Rather, it recognizes that there may be situations where FDA properly may require pediatric testing under preexisting statutory authorities, such as where a manufacturer declines to disclaim pediatric uses. As discussed in Appendices B and C below, FDA's rule goes far beyond its preexisting authorities. Section 355a(i), which deals with the consequence of properly required testing, cannot expand these authorities. See 21 U.S.C. § 355a(i) (Supp. III 1997).

* * *

in sum, the Pediatric Rule is inconsistent with FDAMA's voluntary pediatric exclusivity and supplemental application provisions. It is, accordingly, an impermissible exercise of FDA's regulatory authority.

II. THE RULE CONFLICTS WITH CONGRESS'S GOAL OF STREAMLINING AND ACCELERATING THE DRUG APPROVAL PROCESS.

Another of Congress's primary concerns in enacting FDAMA was the unreasonably long delay between a manufacturer's submission of a new drug application ("NDA") and FDA's approval of the application, as well as the substantial expense associated with that process. Since 1962, regulation by FDA has more than doubled the development costs for drugs and has significantly delayed the introduction of new drugs to the United States market.⁴⁸ A study that was reported in 1992 estimated that "the cost of bringing a new drug to market" had increased 230% over a fifteen-year time period.⁴⁹ From 1963 to 1975, the average cost of developing a new drug was \$125 million. From 1981 to 1990, the cost averaged \$394 million.⁵⁰ Average drug review time has almost doubled from two years in 1962 to more than three years in 1989, and the time required to gather data has more than doubled from three years to between six and seven years.⁵¹

⁴⁸ See Sam Kazman, Deadly Overcaution: FDA's Drug Approval Process, J. Reg. & Soc. Costs, Sept. 1990, at 35-36.

⁴⁹ See Michael R. Ward, Drug Approval Overregulation, 1992 Regulation: Cato Rev. of Bus. & Gov't, No. 4, at 49; see also The Cato Institute, Handbook for Congress (105th Congress), at 342 (1998) (stating that cost of drug development has increased by over 400% in less than two decades).

⁵⁰ See Goldberg, supra note 19, at 45.

⁵¹ See Ward, supra note 49, at 49.

While cost and delay have dramatically increased, the number of unsafe drugs has not declined correspondingly.⁵² Moreover, the number of new drugs introduced in the U.S. has declined by fifty percent relative to other industrialized countries. Although the United States leads the world in researching, developing, and patenting valuable new drug treatments – from 1979 to 1989, the United States Patent and Trademark Office granted between 2,000 and 4,200 drug patents annually – increasingly onerous FDA regulation has significantly hampered the marketing of these products.⁵³ For example, for each year from 1964 to 1989, “pharmaceutical firms filed between 800 to 2,200 investigational new drugs with the FDA. . . . Of the 80 to 250 new drug applications firms file annually, the FDA approves only 20 to 60.” and “[m]any of those represent reformulations of existing products.”⁵⁴ Similarly, “[o]nly 27% of recently approved new drugs in the U.S. were first marketed in this country; 54% were available one or more years in a foreign market prior to U.S. approval. . . . For biopharmaceutical products approved in the U.S., Europe, and Japan, 58% originated in the U.S., 47% began clinical testing in this country, but only 18% were first marketed here.” Kaitin Testimony, *supra* p. A-21. “In contrast, 57% were first marketed in Europe and 25% were first marketed in Japan.” *Id.*

⁵² See *id.*; see also Goldberg, *supra* note 19, at 43 (“[T]he FDA’s regulation of new drug approvals yields little in the way of additional safety. In fact, over the past 20 years the number of drugs that the FDA or manufacturers pulled from the market because of safety concerns has been insignificant both here and abroad. Worldwide only a handful of drugs have been discontinued for safety reasons, and little difference exists in the rate that unsafe drugs have been pulled from the market in the United States and the United Kingdom.”).

⁵³ See Ward, *supra* note 49, at 48.

⁵⁴ *Id.*

Unsurprisingly, FDA's onerous regulations have caused Britain to overtake the C.S. as the world leader in introducing new drugs to the market."

Doctors are also highly dissatisfied with FDA's lengthy drug approval process. Recent polls commissioned by **CETI** revealed that "67% of the neurologists and neurosurgeons surveyed believe that the FDA takes too much time to approve new drugs and medical devices, and 58% agree that such delays cost lives."⁵⁶ Sixty-five percent of cardiologists and 77% of oncologists agree that FDA is too slow in approving new drugs and medical devices, and 57% of cardiologists and 47% of oncologists also agree that FDA's delay in approving drugs costs lives.⁵⁷ Eighty percent of neurologists and neurosurgeons "claim that the approval process, on at least one occasion, prevented them from treating their patients with the best possible care," while 71% of cardiologists and 63% of oncologists agree that "FDA's approval process has hurt [their] ability to treat [their] patients with the best possible care" on one or more occasions.⁵⁸

⁵⁵ See Kazman, *supra* note 48, at 40 ("From 1977 to 1987, 204 new drugs were introduced in the US; of these, 114 were available in Britain, with an average lead-time of more than five years per drug. On the other hand, of the 186 new drugs introduced into Britain during this period, only 41 were already available in the U.S. and then only by an average lead-time of two and a half years. As for exclusively available drugs, there were 70 in Britain but only 54 in the U.S."). Similarly, a Competitive Enterprise Institute publication reveals that it took FDA nearly two years to approve taxotere, a drug designed to treat advanced cases of breast cancer, while the Canadians had approved the drug in a year and the Europeans in 16 months. See Julie C. Defaico, Competitive Enterprise Institute, *Treatment Delayed, Treatment Denied: Therapeutic Lag and FDA's Performance*, at 2-3 (Feb. 1997).

⁵⁶ Competitive Enterprise Institute, *A National Survey of Neurologists and Neurosurgeons Regarding the Food and Drug Administration*, at 1 (Oct. 1998).

⁵⁷ *Id.* at 12 (citing surveys of oncologists and cardiologists commissioned by **CETI** in July 1996 and August 1995, respectively).

⁵⁸ *Id.* at 2, 14.

Congress recognized all of this. As a House Report discussing the proposed drug modernization legislation notes:

Currently, it takes nearly 15 years to develop a new drug – twice the time required in the 1960s. New scientific knowledge can produce effective new treatments for uncured diseases, but a drug development process slowed by outmoded regulation may mean that cures come too late for many patients.

...

Unfortunately, many patients do not have the time to wait the nearly 15 years it now takes to bring a new drug or biologic from the laboratory to the pharmacy shelf. . . .

Part of the reason for this growing development time is the increasing complexity of the diseases researchers are targeting. But an undeniable part of the delay in getting medicines to patients lies in the rules and regulations imposed by the FDA – requirements that add to development and approval time without enhancing the safety and effectiveness of new drugs and biologics.

H.R. Rep. No. 105-310, at 34-35. The Senate noted similar problems concerning the protracted, complex, and expensive nature of obtaining FDA approval to market a new drug:

Over the years, and particularly with the enactment of requirements that the FDA determine that drugs and devices are effective as well as safe, the FDA's requirements for clinical testing and its premarket reviews of new products have grown increasingly complex, time-consuming, and costly. From the 1960's to the 1990's, for example, the time required to complete clinical trials for new drugs has grown from 2.5 to nearly 6 years. Applications for the approval of new drugs typically run to hundreds of thousands of pages in length. According to a recently published study, from the beginning of the process to the end, it takes an average of 15 years and costs in the range of \$500 million dollars to bring a new drug to market.

S. Rep. No. 105-43, at 6.

To address this problem, Congress included a number of provisions in FDAMA intended to streamline and accelerate the drug approval process. For example, Congress enacted a fast-track approval process to "expedit[e] the approval of drugs and biological products that demonstrate the potential to address unmet medical needs for serious and life-threatening

conditions." H.R. Rep. No. 105-310, at 54; 21 U.S.C. § 356 (1994 & Supp. III 1997). Likewise, Congress adopted provisions designed to "[s]treamlin[e] clinical research on drugs." H.R. Rep. **So.** 105-310, at 69; 21 U.S.C. § 355(i) (1994 & Supp. III 1997). Further, Congress allowed **FD.4** to approve an NDA based on only "one adequate and well-controlled clinical investigation and confirmatory evidence," rather than the two investigations that FDA often had required. Id. 6 355(d); see H.R. Rep. No. 105-310, at 67. Primary purposes underlying this latter provision were to:

reduce the number of patients required to undergo clinical trials and the possibility of receiving a placebo; reduce the cost of drug development, and thus, the ultimate cost of a new drug to the public; reduce the total time needed to obtain FDA approval of a new drug; increase the number of new drugs that can be investigated; and thus speed the development and availability of important new drugs to help improve the public health.

at 68.

Far from making the drug approval process simpler, speedier, and less costly, however, the Pediatric Rule instead renders the process more expensive, protracted, and inefficient, as discussed in more detail below.

A. The Pediatric Rule Further Delays Bringing Drugs To Market.

The increased testing and formulation requirements of the Pediatric Rule will delay the drug approval process, directly contravening FDAMA's goal of accelerating drug approvals. For example, one survey of drug manufacturers showed that it takes ~~from~~ five months to four years to develop a pediatric formulation.⁵⁹ Moreover, requiring additional clinical studies can only

⁵⁹ See Letter from Pharmaceutical Research and Manufacturers of America to FDA Dockets Management Branch re Docket No. 97N-0165, *Pediatric Patients: Proposed Rule Requiring Manufacturers To Assess the Safety and Effectiveness of New Drugs and Biological Products*, at (Continued...)

hinder even further a drug approval process that is already subject to sharp congressional criticism for its protracted nature. *See supra* pp. A-26 to A-30.

Substantial social harm results from this unwarranted delay. Even "[b]y a conservative estimate, **FDA** delays in allowing US . marketing of drugs used safely and effectively elsewhere around the world have cost the lives of at least 200,000 Americans over the past 30 years.'" In the pediatric context, **FDA'S** extensive new testing and formulation requirements will further delay the access of new drugs to the market. This denial to the general population of these beneficial treatments will harm patients who are unable to obtain potentially lifesaving medication. Indeed, it will not only be adults who suffer because they are denied access to safe and effective treatments. Even the children that the Pediatric Rule purports to help will instead be harmed because they will no longer be able to obtain beneficial drugs on an off-label basis. As one commentator pointedly asked, "if a new drug will save lives after its approval, then how many lives were lost while it was being reviewed?"

The difficulty of detecting the victims of FDA's "drug lag" renders the harm even more insidious. When FDA approves a harmful drug too quickly, the political outcry of newspaper

(... Continued)

8 (Nov. 13, 1997) (citing informal survey of PhRMA member companies) [hereinafter "PhRMA Comments"].

⁶⁰ Bandow, *supra* note 29, at 1 (quoting Robert Goldberg of Brandeis University); see Gregory Conko, Slowing Down Drug Approval Could Prove Costly, USA Today, July 21, 1998, at 10A ("While the FDA approval process is intended to keep unsafe drugs off the market, its overcaution in reviewing new drug applications often keeps potentially life-saving therapies out of the hands of people who need them."). For specific examples of lives lost due to overcaution, see Krauss, *supra* note 3, at 467-68.

⁶¹ Kazman, *supra* note 48, at 47.

headlines, television coverage, and congressional hearings creates pressure on FDA. When FDA delays approval of a beneficial drug, however, the victims are "invisible." The victims of drug lag and their families rarely know of the error and therefore cannot complain. The Pediatric Rule has only reinforced this harmful political incentive for FDA to be overcautious in approving drugs." Thus, despite FDA's best intentions, the Rule, as a practical matter, may largely ignore the following admonition of even one of the Rule's most ardent supporters:

Remedies should avoid impeding availability of a necessary drug to non-pediatric populations [because t]he goal is to accomplish pediatric studies so the drug may be labeled for infants and children, not to deprive a non-pediatric population of an important drug.⁶⁴

B. The Pediatric Rule Increases The Costs Of Drug Approval.

The Pediatric Rule also will lead to increased research and development costs, which will be borne by manufacturers and consumers alike.

⁶² See Walter E. Williams, The Argument for Free Markets: Morality vs. Efficiency, 15 Cato J. Nos. 2-3, at 183 (Fall/Winter 1995/96) ("In all interventionist policy there are those who are beneficiaries and those who are victims. In most cases, the beneficiaries are highly visible and the victims are invisible."); Kazman, supra note 48, at 41 ("As former FDA Commissioner Alexander Schmidt once stated, 'In all of FDA's history, I am unable to find a single instance where a Congressional committee investigated the failure of FDA to approve a new drug. But the times when hearings have been held to criticize our approval of new drugs have been so frequent that we aren't able to count them. The message to FDA staff could not be clearer.'" (quoting H.G. Grabowski & J.M. Vernon, The Regulation of Pharmaceuticals, at 5 (1983))); Kazman, supra note 48, at 41-43 (contrasting reaction to erroneous approval with reaction to erroneous delay).

⁶³ See Ward, supra note 49, at 47 ("Drug approval stringency... exceed[s] what is socially optimal because the FD.4 is more adversely affected by approving harmful drugs than by denying approval of beneficial drugs."); Kazman, supra note 48, at 42 ("The political invisibility of drug lag's victims is the major reason for FDA's inherent overcaution in approving new drugs.").

⁶⁴ AAP Comments, supra note 30, at 6.

1. The Pediatric Rule Increases Manufacturer Costs.

FDA has substantially underestimated the monetary cost of the studies that manufacturers must now conduct. In its Final Rule, FDA estimated the cost of the Rule to be \$46.7 million, a figure that was reached only after reducing the total cost of testing by 42% to account for costs that manufacturers purportedly would have incurred voluntarily. See 63 Fed. Reg. at 66,661. This estimate, however, does not accurately assess the number of children who must be studied for each drug. According to one prominent drug manufacturer, the Pediatric Rule will require testing of 34,000 patients per year, in contrast to FDA's extremely low estimate of 10,860.⁶⁵

In addition to the increased manufacturer research costs, the Pediatric Rule will also lead to increased manufacturer development costs associated with the now-required development of pediatric formulations. Drug manufacturers who responded to FDA's proposal of the Pediatric Rule showed that FDA "grossly underestimated the number of drugs for which new formulations would be required."⁶⁶ Moreover, one survey showed that developing a pediatric formulation for a single drug product now costs between \$500,000 and 33.5 million.⁶⁷ Taken together, the

⁶⁵ Compare Letter from Wyeth, *supra* note 32, at 2 (citing FDA Dockets Management Branch re Docket No. 97N-0165, Regulations Requiring Manufacturers To Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Populations: Proposed Rule, 6-7 (Nov. 13, 1997) with 63 Fed. Reg. at 66,663.

⁶⁶ See, e.g., Glaxo Wellcome Comments, *supra* note 32, at 2 (The impact on the industry of the Pediatric Rule is far greater than FDA has estimated").

⁶⁷ See PhRMA Comments, *supra* note 59, at 8 (citing informal survey of member companies); *id.* at 25 ("Some companies have spent millions of dollars in efforts to develop a pediatric formulation and some have given up the pursuit after multiple efforts to develop a pediatric formulation have failed."); see also Public Meeting, *supra* note 30 (remarks of Dr. Clemente) ("[T]he formulation question is a very important one . . . a formulation for a child is truly a daunting avenue to approach").

substantial number of products for which pediatric formulations likely will be necessary and the enormous development costs for each of those products equal a staggering increase in manufacturer expenditures to bring a new drug to market.

2. The Pediatric Rule Increases Consumer Costs,

Drug companies will not be the only ones who suffer economic burdens as a result of the Pediatric Rule. Consumers also will pay an additional price because manufacturers will pass on at least some of their increased research costs to purchasers. By requiring the development of pediatric formulations, "the cost of some, if not most, adult formulations [will increase] due to the need to allow for the incremental and potentially high cost of development of such pediatric formulations."¹¹

C. The Pediatric Rule Exacerbates The Inefficiencies Of The Drug Approval Process.

Many drugs are of little or no use to pediatric populations. Moreover, creating pediatric formulations is difficult. Accordingly, establishing a presumption that manufacturers must test drugs on children and develop pediatric formulations will lead to an inefficient use of both FDA's and drug manufacturers' resources.

FDX, the American Academy of Pediatrics, and sponsors of drug development all agree that a large number of drugs, probably the majority, are of limited or no benefit to pediatric patients.¹² Yet despite these limited or nonexistent benefits for many drugs, the Pediatric Rule

¹¹ Glaxo Wellcome Comments, *supra* note 32, at 11-12.

¹² See Cohen Testimony, *supra* note 21 (noting that "pediatric use represents a relatively small segment of the total market for a drug"); Pediatric Patients: Regulations Requiring Manufacturers To Assess the Safety and Effectiveness of New Drugs and Biological Products: Proposed Rule, 62 Fed. Reg. 43,900, 43,902 (1997) (observing that "[n]ot all [New Molecular

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presumptively requires pediatric testing and formulation development on all new drugs - and even some marketed drugs - and for "all relevant pediatric subpopulations." including neonates, infants, children, and adolescents. 21 C.F.R. §§ 314.55(a), 201.23(a).

FDA's reliance on the Rule's waiver provisions in response to concerns that many drugs do not have pediatric uses is not reassuring. See 63 Fed. Reg. at 66,644-45. Although FDA asserts that the "rule is designed to require studies only in those settings in which there is a significant medical need or where usage among pediatric patients is likely to be substantial." at 66.640, FDA continues to ignore that, by requiring all manufacturers to conduct testing absent a waiver, FDA creates a broad presumption that it will require such testing, not that it will limit such testing." Even if FDA were to waive the requirement for most drugs, the mere process of requiring all manufacturers to compile data to support waiver requests and considering each request would largely be a wasted effort, resulting in a significant and unnecessary drain on both public and private resources.

Nor was FDA's response to concerns that required testing in each pediatric age group would be excessive and unnecessary any more reassuring. Rather than addressing these concerns or providing further guidance in the preamble to the Pediatric Rule, FDA instead insisted that it

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Entities] have usefulness in pediatric patients"); Letter from Merck Research Laboratories to FDA Dockets Management Branch re Docket No. 97N-0165, Regulations Requiring Manufacturers To Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients, at 9 (Nov. 12, 1997) ("FDA and sponsors agree with the American Academy of Pediatrics that there are substantial numbers of drugs, probably the majority of those developed, which would be of limited or no benefit to pediatric patients."); PhRMA Comments, supra note 59, at 20 ("Physicians caring for children use relatively few of the hundreds of drugs and biologics currently marketed.").

⁷⁰ See, e.g., AAP Comments, supra note 30, at 4 ("Waivers should be granted RARELY.").

still believed that "studies in more than one age group may be necessary." ⁷¹ FDA's Final Rule gives it absolute discretion to decide whether to waive testing requirements in particular pediatric age groups "if data from one age group can be extrapolated to another." 21 C.F.R. § 314.55(a). This response is insufficient as a matter of law. See, e.g., State Farm, 463 U.S. at 43 (holding that "agency must examine the relevant data and articulate a satisfactory explanation for its action").

The detrimental effects of this inefficient allocation of limited **manufacturer drug** development resources extend beyond mere economic inefficiencies. The regulations **also** will hamper valuable new drug innovation.⁷² Requiring that drugs be tested concurrently in adults **and** children will further discourage sponsors from pursuing high risk projects.⁷³ The Pediatric

⁷¹ FDA's statement is even less assuring in light of the limited resources that it has to implement the rule. See Public Meeting, supra note 30 (statement of Dr. Temple, Executive Director of Medical Affairs at McNeil Consumer Products Company) ("Unless additional resources are provided, and unless additional help is available, the challenges to [FDA] to implement this proposed rule will be enormous. [FDA] will need much outside assistance.").

⁷² See Goldberg, supra note 19, at 40 ("[T]he FDA's approval procedures have short-circuited the natural process of incorporating . . . information in the development of new products. The FDA in effect forces pharmaceutical companies to reinvent the wheel, thus driving up development costs."); Handbook for Congress, supra note 49, at 342 ("Just as control of information in despotic countries destroys creativity and innovation, the FDA's monopoly on the research, development, and use of new medical knowledge is choking off the next medical revolution."); Krauss, supra note 3, at 462 (observing that "substantial increases in the cost of developing a drug for the United States market," largely caused by FDA's "involvement in testing" . . . will "affect both the number of new drugs developed and the market price of developed drugs during their patent monopoly").

⁷³ See Glaxo Wellcome Comments, supra note 32, at 11-12 ("[S]uch a requirement during the investigational phases would necessitate diversion of resources from concurrent competing programs (e.g., development and testing of adult formulations). If resources are diverted from development of an adult formulation, the larger patient population would not be served and the sponsor would be less prepared to generate the pharmaceutical data necessary to achieve approval of the adult formulation.").

Rule will divert limited company resources from the research of new therapies to pediatric trials that explore limited, and possibly inappropriate, uses of existing products. By diverting resources, the Rule will hurt patients who await new life-saving discoveries. It may even give companies an incentive to focus their research on diseases that almost exclusively affect adults.

* * *

Although FDA claims the Rule is necessary to address the lack of adequate drugs approved for pediatric uses and to ensure that children will have safe and appropriate treatments available, the above discussion demonstrates that the Rule creates, rather than solves, problems. Moreover, the evidence that FDA cites in justifying the need for the Rule is scant and/or questionable. FDA has failed to demonstrate that pediatric populations are being denied needed treatments, or that off-label uses of adult-use drugs are any less safe or effective than they would be if those uses were on-label. See Home Box Office, 567 F.2d at 36 (“[A] regulation perfectly reasonable and appropriate in the face of a given problem may be highly capricious if that problem does not exist.” (internal quotations omitted)); see also Northwest Airlines, Inc. v.

⁷⁴ See Handbook for Congress, *supra* note 49, at 342 (observing that FDA’s drug approval process “is raising the cost of essential drugs and denying sick people access to lifesaving medicines”); Krauss, *supra* note 3, at 458 (observing that FDA’s “certification monopoly” over drugs “has arguably cost thousands of American lives”); *id.* at 471 (noting that “efforts to extend the FDA’s certification monopoly to off-label prescriptions have cost lives and money”).

⁷⁵ For example, FDA’s assertion in its Proposed Rule that the ten drugs most prescribed for children all lack adequate pediatric labeling is simply inaccurate. See 62 Fed. Reg. at 43,900. As the Pharmaceutical Manufacturers Association of America has explained: five of the ten drugs cited by FDA already contain pediatric labeling; one is in the midst of FDA’s approval process; one does not have labeling, but extensive dosage information about it is available in pediatric and standard medical texts; one does not have an NDA on file to amend because it has an exemption under the grandfather clause; and one states on its label that it is not approved for diaper dermatitis. PhRMA Comments, *supra* note 59, at 4-5.

Goldschmidt, 645 F.2d 1309, 1317 (8th Cir. 1981) (same). Instead, FDA relies on nothing more than a handful of anecdotes documenting adverse reactions in children from off-label drug uses. See 62 Fed. Reg. at 13,901.

Adverse drug reactions, however, regularly occur from on-label uses as well.⁷⁶ Thus, identification of a few adverse reactions from off-label drug use in pediatric populations is an insufficient justification for the Rule. Rather, FDA must establish that a significant number of those reactions could have been prevented if those same products had been tested and approved for use in children, taking into account, of course, the likelihood of adverse drug reactions that might occur as a result of the clinical testing itself.

Even if the articles describing these scattered instances of adverse reactions did suggest that pediatric testing of an unapproved product might lead to fewer adverse drug reactions than would waiting to prescribe that product in children until after it has been approved as safe and effective for adults, isolated anecdotes cannot suffice to support the sweeping regulations embodied in the Pediatric Rule. See, e.g., 5 U.S.C. § 557(c) (1994) ("All decisions, including initial, recommended, and tentative decisions, . . . shall include a statement of . . . findings and conclusions, and the reasons or basis therefor, on all the material issues of fact, law, or discretion presented on the record . . ."); State Farm, 463 U.S. at 43 (holding that "agency must examine the relevant data and articulate a satisfactory explanation for its action"); Burlington Truck Line Inc. v. United States, 371 U.S. 156, 167 (1962) (rejecting agency decision where "[t]here are no

⁷⁶ See Beck & Azafi, *supra* note 4, at 82 (emphasizing that "previously unknown safety concerns can arise with labeled as well as unlabeled indications").

findings and no analysis . . . to justify the choice made[] [and] no indication of the basis on which the Commission exercised its expert discretion").--

In **sum.** the Pediatric Rule is not only inconsistent with FDAMA, it is also bad policy. Far from streamlining and accelerating the drug approval process, the Rule complicates and hinders that process. Moreover, instead of encouraging manufacturers to seek approval for off-label uses of a **drug** on a voluntary basis, the Rule ~~forces~~ **urges** manufacturers to seek approval for uses of their product that they did **not** intend to pursue. **FDA should effectuate the g** ai of bringing pediatric indications on-label through the incentive scheme established by Congress in FDAMA.

77 **To the extent that there remains some lingering concern over the availability and safety of current pediatric treatments, Congress has already addressed the problem by enacting the FDAMA. FDAMA is the best means to address Congress's policy choice concerning the most appropriate means of addressing this issue. See supra pp. A-10 to A-12.**