



Wiley Rein & Fielding LLP

ORIGINAL

1776 K STREET NW  
WASHINGTON, DC 20006  
PHONE 202.719.7000  
FAX 202.719.7049

Virginia Office  
7925 JONES BRANCH DRIVE  
SUITE 6200  
McLEAN, VA 22102  
PHONE 703.905.2800  
FAX 703.905.2820

www.wrf.com

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Food and Drug Administration  
Department of Health and Human  
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5630 Fishers Lane, Rm. 1061  
Rockville, MD 20852

**Re: Docket No. 02N-0152; Comments re Intersection of the BPCA and the Pediatric Rule**

Dear Madam or Sir:

The Association of American Physicians and Surgeons, Inc. ("AAPS"), the Competitive Enterprise Institute ("CEI"), and Consumer Alert, by their undersigned attorneys, submit the following comments in response to FDA's advanced notice of proposed rulemaking seeking comments on the intersection of FDA's 1998 "Pediatric Rule"<sup>1</sup> and the Best Pharmaceuticals for Children Act ("BPCA"), enacted in January 2002. See Obtaining Timely Pediatric Studies of and Adequate Pediatric Labeling for Human Drugs and Biologics: Advanced Notice of Proposed Rulemaking, 67 Fed. Reg. 20070 (Apr. 24, 2002). Specifically, FDA has requested comments, *inter alia*, on "what present authorities [in the Pediatric Rule], if any, have not proven effective, are now redundant, or need to be updated because of the BPCA." *Id.* at 20071.

As FDA is aware, AAPS, CEI, and Consumer Alert have challenged FDA's legal authority to issue the Pediatric Rule, pointing out that FDA had no statutory authority to mandate the pediatric testing and formulation requirements embodied in the Rule and that FDA's action was arbitrary, capricious, and an abuse of FDA's discretion. See Complaint, Ass'n of Am. Physicians & Surgeons, Inc. v. FDA, Civil Action No. 1:00CV02898 (HHK) (D.D.C. Dec. 4,

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<sup>1</sup> See Regulations Requiring Manufacturers To Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients, 63 Fed. Reg. 66632 (1998) (codified in 21 C.F.R. Parts 201, 312, 314, and 601).

2000) (“Complaint”) (App. Exh. 1).<sup>2</sup> As only one of the bases for our challenge, we pointed out the conflict between the voluntary pediatric testing incentives that Congress enacted in the FDA Modernization Act (“FDAMA”) and the mandatory testing and formulation provisions that FDA issued as part of its Pediatric Rule. See Mem. in Supp. of Pls.’ Mot. for Summ. J., Part II.C, Ass’n of Am. Physicians & Surgeons, Inc. v. FDA, Civil Action No. 1:00CV02898 (HHK) (D.D.C. Feb. 26, 2001) (“Pls.’ SJ Mot.”) (App. Exh. 2). Congress’s renewal and expansion of those voluntary testing incentives in the BPCA despite FDA’s request that Congress instead authorize the mandatory testing approach taken in the Rule provides further confirmation of FDA’s lack of statutory authority to issue the Rule. We remain concerned that FDA’s adherence to the Pediatric Rule is both unlawful and unnecessarily distracts FDA from focusing on the best possible implementation of the BPCA.

Our comments: (1) provide background procedural information concerning our challenge to the Pediatric Rule; (2) summarize some key legal bases for our challenge; (3) identify numerous conflicts between the BPCA and the Pediatric Rule; and (4) conclude that the only way that FDA can reconcile these two irreconcilable regimes is to revoke the Rule in its entirety.

### **The Commenters**

*AAPS* is a not-for-profit membership organization representing approximately 4,000 physicians nationwide in all practices and specialties, including physicians who practice and specialize in pediatric medicine. *AAPS* was established to preserve the practice of private medicine and has remained dedicated to the sanctity of the patient-physician relationship, which *AAPS* believes must be protected from all forms of third-party intervention. *AAPS* opposes the Pediatric Rule because it limits the availability to *AAPS*’s physician members of the most effective pediatric and non-pediatric drug treatments for their patients.

*CEI* is a not-for-profit public policy organization dedicated to the principles of free enterprise and limited government. It 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* 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 takes its arguments to court to ensure that the law is upheld. *CEI* has been involved in

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<sup>2</sup> Materials referred to or relied upon in these comments and required to be submitted to FDA pursuant to 21 C.F.R. § 10.20 are included in the accompanying Appendix to these comments and cited to as “App. Exh. \_\_\_\_.”

analyzing, and advocating reform of, the FDA drug and device approval process for over a decade. CEI opposes FDA's Pediatric Rule because it is an invasive governmental regulation that interferes with private choices made by pharmaceutical companies concerning how best to allocate their finite research and development funds. By forcing pharmaceutical companies to divert research and development funds away from valuable new drug treatments and toward testing of products for uses that companies do not wish to promote, the Rule will restrict access by both doctors and patients to the most effective drug treatments. CEI is also concerned that the Pediatric Rule will add yet another impediment to the approval of new drugs. As a poll of oncologists released by CEI on April 30, 2002, demonstrates, FDA approval delays are already viewed by these specialists as a serious impediment to the practice of medicine. CEI, [A National Survey of Oncologists Regarding The Food and Drug Administration](http://cei.org/gencon/025,02987.cfm), <http://cei.org/gencon/025,02987.cfm> (Apr. 30, 2002) (App. Exh. 12).

Plaintiff Consumer Alert is a national, non-partisan, not-for-profit organization whose mission is to enhance understanding and appreciation of the consumer benefits of a free market and to promote sound economic, scientific, and risk data in public policy decisions. Consumer Alert opposes the Rule because it impedes access to valuable pediatric and nonpediatric drug treatments. Because the Rule forces pharmaceutical companies to divert research and development funds away from valuable new drug treatments and toward testing of products for uses that companies do not wish to promote, the Rule hinders Consumer Alert's members from receiving the most effective pharmaceuticals for the treatment of disease, illness, or other afflictions.

### **Background to Commenters' Challenge of the Pediatric Rule**

For more than two decades preceding FDA's issuance of the Pediatric Rule, FDA required manufacturers seeking approval of a new drug for use in pediatric populations either (1) to establish the safety and effectiveness of that product in pediatric populations, typically through testing separate from that conducted on adults, or (2) to state expressly on the label that "Safety and effectiveness in pediatric patients have not been established." 21 C.F.R. § 201.57(f)(9)(vi).<sup>3</sup> If manufacturers tested their drugs for some, but not all,

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<sup>3</sup> FDA has determined that tests demonstrating safety and effectiveness in adults do not necessarily establish safety and effectiveness in children – *i.e.*, people 16 years old and under. FDA recognizes four subgroups of the pediatric population, each of which may require separate testing. See 21 C.F.R. § 201.57(f)(9)(i) - (iv) (defining "pediatric population(s)" and "pediatric patient(s)" as "the pediatric age group, from birth to 16 years, including age groups often called neonates, infants, children, and adolescents" and discussing

pediatric age groups, the labeling had to state that “Safety and effectiveness in pediatric patients below the age of (--) have not been established.” Id. § 201.57(f)(9)(v). Manufacturers who opted to use such a disclaimer could not claim that their products were FDA-approved for pediatric uses and could not promote their products for such uses. See generally 21 U.S.C. §§ 355(d)(7) (prohibiting approval of products with false or misleading labeling), 360aaa(b), 360aaa-4 (allowing dissemination of information concerning off-label uses only where supplemental application has been or will be filed to bring use on-label). While this regulatory regime was in effect, FDA’s Commissioner, David Kessler, expressly and publicly recognized that “[w]e do not have the authority to require manufacturers to seek approval for indications which they have not studied. Thus, as a matter of law, if an application contains indications only for adults, we’re stuck.” David Kessler, Speech of FDA Commissioner to the American Academy of Pediatrics (Oct. 14, 1992) (App. Exh. 3).

In 1997, Congress, in an attempt to increase pediatric use information, established a five-year experimental program giving manufacturers incentives to engage in voluntary pediatric testing. See FDA Modernization Act (“FDAMA”), Pub. L. No. 105-115, 1997 U.S.C.C.A.N. (111 Stat.) 2296 (App. Exh. 4). Specifically, FDAMA extended existing market exclusivity for six months where the manufacturer submitted, and FDA accepted, pediatric tests for drugs that “may produce health benefits in the pediatric population.” 21 U.S.C. § 355a(a), (c) (2000). FDAMA provided that FDA could “request” pediatric studies, but FDA and manufacturers had to agree to conduct them – the Act did not allow FDA to require pediatric studies on its own initiative. See id. § 355a(a), (c), (d). Moreover, FDA could not unilaterally alter the incentive scheme established in FDAMA; rather, FDAMA permitted FDA to “suggest” modifications in its status report to Congress, which was filed in early January, 2001. See id. § 355a(k).

On December 2, 1998, despite Congress’s express legislation to encourage pediatric testing through voluntary means, FDA promulgated the mandatory pediatric testing and formulation regulations at issue here. See Regulations Requiring Manufacturers To Assess the Safety and Effectiveness of New Drugs and Biological Products, 63 Fed. Reg. 66632 (1998) (“the Pediatric Rule” or “the Rule”) (App. Exh. 1 tab 3). In conjunction with issuing the Rule, FDA expressly discounted Congress’s chosen method of accomplishing the goal of increased pediatric labeling, proclaiming that it “does not believe . . . that incentives alone will result in pediatric studies on some of the drugs and biologics where the need is greatest.” Id. at 66639. Rather, FDA declared its “belie[f] that a mixture of incentives and requirements is most likely to result in

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specific requirements for inclusion of pediatric indications and use data in labeling).

real improvements in pediatric labeling” and proceeded to regulate by administrative fiat to correct this perceived (but unsubstantiated) problem. Id.

The Rule requires manufacturers of new drugs and biological products to conduct safety and effectiveness testing, in four separate pediatric subpopulations, for all drug and biological product applications “for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration.” See 21 C.F.R. § 314.55(a) (drugs); id. § 601.27(a) (biological products). Regardless of the proposed labeling of such applications, the Rule precludes approval of such applications absent pediatric testing unless FDA waives or defers that requirement. See id. §§ 314.55(a) - (c), 601.27(a) - (c). The Rule also requires manufacturers to create entirely new pediatric formulations if the proposed formulations are not suitable for (and could thus not foreseeably be used by) children. Id. § 314.55(a) (drugs); id. § 601.27(a) (biological products). The Rule also allows FDA to require manufacturers to conduct pediatric testing and develop new formulations for certain previously approved drugs and biological products. See id. § 201.23(a). If the manufacturer refuses to comply, FDA asserts the authority to declare the product to be misbranded or unapproved/unlicensed. See 63 Fed. Reg. at 66657.

AAPS, CEI, and Consumer Alert first challenged the wisdom and legal authority of FDA’s December 2, 1998 Pediatric Rule in a December 2, 1999 Citizen Petition that pointed out the many legal infirmities of the Rule and requested that FDA revoke it. See Letter of Bert W. Rein to FDA of 12/02/99, Docket No. 99P-5215/CPI (App. Exh. 1 tab 1). FDA reviewed the petition for just under one year and then rejected it. See Letter from FDA to Bert W. Rein of 11/1/00, Docket No. 99P-5215/CPI (App. Exh. 1 tab 2). On December 4, 2000, AAPS, CEI, and Consumer Alert sued FDA in the U.S. District Court for the District of Columbia, requesting that the Court (1) declare that FDA’s issuance of the Pediatric Rule contravenes FDA’s statutory mandate and is arbitrary and capricious and (2) permanently enjoin FDA from enforcing the Rule. Complaint at 17 (App. Exh. 1). The parties filed cross-motions for summary judgment. Briefing was completed on December 21, 2001, and the case has been awaiting the Court’s decision since then.

Shortly after we filed suit, FDA reported to Congress on the voluntary incentive program established in FDAMA. It pronounced the program successful and sought to renew and strengthen it. See FDA, The Pediatric Exclusivity Provision: January 2001 Status Report to Congress 8, 18-22 (2001) (“FDAMA Report”) (App. Exh. 6). Simultaneously, FDA asked Congress for an express grant of the mandatory testing authority it had already asserted under the Pediatric Rule. Id. at 21.

On January 4, 2002, Congress enacted the BPCA, which reauthorized and expanded the voluntary pediatric testing incentives in FDAMA but did not give FDA the grant of mandatory testing authority it sought. See Best Pharmaceuticals for Children Act, Pub. L. No. 107-109, 2001 U.S.C.C.A.N. (115 Stat.) 1408 (App. Exh. 5). The BPCA contained many carryover provisions from FDAMA, as well as some new provisions, designed to achieve the same goals of increasing pediatric labeling and pediatric formulations that the Rule purported to accomplish, but in ways totally at odds with the methodology chosen by FDA in the Rule. On January 23, 2002, AAPS, CEI, and Consumer Alert submitted a summary to the Court of these conflicting provisions.

### Basis for Challenge

#### **1. The Rule's Disregard of the FDCA's Mandate That FDA Must Approve Products Established To Be Safe And Effective For Their Labeled Uses**

Our central claim in the lawsuit was that in issuing the Rule, FDA exceeded its statutory drug approval mandate. Under the Food, Drug and Cosmetic Act ("FDCA"), 21 U.S.C. § 321 et seq., FDA must approve a new drug for marketing if it is shown to be safe and effective for the conditions of use determined by the manufacturer and "prescribed, recommended, or suggested in the proposed labeling thereof" and if the drug meets certain other statutory requirements not at issue in our challenge.<sup>4</sup> 21 U.S.C. § 355(c)(1)(A), (d); see also id. § 355(j)(2), (j)(4) (setting forth additional requirements (not at issue) for a generic manufacturer who files an Abbreviated New Drug Application ("ANDA")).<sup>5</sup> If the manufacturer's labeling of a drug does not prescribe, recommend, or suggest use of the product in pediatric populations, approval may not be conditioned on pediatric testing.

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<sup>4</sup> The manufacturer also must show that (1) "the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug are [i]adequate to preserve its identity, strength, quality, and purity," (2) the labeling is not false or misleading, and (3) the New Drug Application ("NDA") includes required patent information. 21 U.S.C. § 355(c)(1)(A), (d).

<sup>5</sup> The Public Health Service Act ("PHSA"), 42 U.S.C. § 201 et seq., allows FDA to license new biological products under similar standards to those applicable to new drugs. See 42 U.S.C. § 262(a)(2)(B), (d)(1); 21 C.F.R. § 601.5(b)(1)(vi). Although biological products are licensed under the PHSA and therefore do not require an approved NDA to be marketed, they are subject to all of the other requirements of the FDCA. See 42 U.S.C. § 262(j).

We argued that despite FDA's mandate to approve products that fulfill the listed statutory criteria, FDA has impermissibly augmented those criteria in the Pediatric Rule. Specifically, FDA asserts authority to withhold approval for products that are safe and effective for their labeled uses until they have been tested for unlabeled pediatric uses. FDA even asserts that it may treat a previously approved drug as misbranded or as an unapproved new drug if its safety and effectiveness for unlabeled pediatric uses have not been established. See 63 Fed. Reg. at 66657; 21 C.F.R. § 201.23. Such findings would render marketing illegal. See 21 U.S.C. § 331(a) (outlawing marketing of misbranded drugs); id. § 355(a) (outlawing marketing of unapproved new drugs); 42 U.S.C. § 262(a)(1) (outlawing marketing of unlicensed biological products).

We also pointed out that FDA asserted the authority to bar sale of such products even though their labeling must disclaim pediatric uses absent appropriate safety and effectiveness information. See 21 C.F.R. § 201.57(f)(9)(v), (vi). Even assuming (incorrectly) that allegedly "foreseeable" pediatric uses nowhere mentioned on a product's labeling somehow could be considered to be prescribed, recommended, or suggested in that labeling, disclaimed uses cannot. Therefore, we concluded that FDA cannot, consistent with the exhaustive list of approval criteria set forth in the FDCA, refuse to approve a product, or treat an approved product as misbranded or unapproved, as a means of compelling pediatric testing.

In addition, we discussed well-settled case law that establishes that FDA is prohibited from imposing an extra-statutory "requirement [that] cannot be reconciled with the literal language of the statute, and [which] alters the statutory scheme in a number of ways that do not clearly serve congressional intent." Mova Pharm. Corp. v. Shalala, 140 F.3d 1160, 1074 (D.C. Cir. 1998); see also Nat'l Wildlife Fed'n v. EPA, 980 F.2d 765-771 (D.C. Cir. 1992) (rejecting agency's attempt to ignore statutory mandate to withdraw state's primary enforcement responsibility for public water systems where certain conditions are met, and instead treat mandate as a discretionary matter, where attempt could not "be squared with the language of the statute"). We further pointed out that the U.S. Court of Appeals for the D.C. Circuit has "categorically reject[ed]" "the bare suggestion that [an agency] possesses plenary authority to act within a given area simply because Congress has endowed it with some authority to act in that area." Ry. Labor Executives' Ass'n v. Nat'l Mediation Bd., 29 F.3d 655, 670 (en banc) (emphasis removed), amended by 38 F.3d 1224 (D.C. Cir. 1994).

There is a reason why Congress and the courts have restricted FDA's regulatory authority to those uses "prescribed, recommended, or suggested" in the product's labeling. By limiting FDA's authority to "claimed" uses, Congress has prevented FDA from delaying market access for many valuable products based on FDA's determination that certain unlabeled uses are "foreseeable" and

must be tested before the product can be approved for marketing. This “claimed” use approach also ensures that pharmaceutical companies, rather than FDA, may decide what uses they will and will not try to claim, justify, and promote. Any other approach would permit FDA rather than drug manufacturers – which are largely research and development companies – to determine how private research dollars will be expended.

## **2. Conflict Between FDAMA’s Pediatric Testing Incentives and the Mandatory Testing and Formulation Provisions of the Rule**

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We also based our challenge on the fact that the mandatory approach taken in the Pediatric Rule clashed with the voluntary approach to encourage pediatric testing in the BPCA’s predecessor Act, FDAMA. See *supra* pp. 4-5. At the time Congress enacted FDAMA, it was well aware of the interest in more pediatric labeling. Congress addressed this issue in FDAMA by giving manufacturers incentives to conduct voluntary pediatric testing for certain products. Only one year later, FDA ignored Congress’s choice of voluntary measures to increase pediatric labeling and instead adopted the mandatory command-and-control regulations at issue.

In our challenge, we pointed to longstanding case law stating that 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, 19-20 (1979) (internal quotations omitted) (emphasis removed). Applying this well-established canon in *Transamerica Mortgage Advisors*, the Supreme Court refused to recognize private causes of action for violations of a statute that “nowhere expressly provides for a private cause of action.” *Id.* at 14, 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.” *Id.* (internal quotations omitted).

The United States Court of Appeals for the D.C. Circuit also has applied this *expressio unius* canon in considering the propriety of the National Mediation Board’s assertion of authority to investigate representation disputes among a carrier’s employees. See *Ry. Labor Executives’ Ass’n*, 29 F.3d at 658-59. 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; accord Chevron, U.S.A., Inc. v. Natural Resources Def. Council, Inc., 467 U.S. 837, 842-43 (1984) (observing that where “Congress has directly spoken to the precise question at issue,” a court “must give effect to the unambiguously expressed intent of Congress” without regard to agency’s regulation); FDA v. Brown & Williamson Tobacco Corp., 529 U.S. 120, 155 (2000) (rejecting FDA’s assertion of jurisdiction over tobacco where “Congress has enacted several statutes addressing the particular subject”); see also Am. Pharm. Ass’n v. Weinberger, 377 F. Supp. 824, 830-31 (D.D.C. 1974) (ruling that FDA exceeded its authority by issuing a regulation restricting the distribution of methadone in a manner inconsistent with Congress’s distribution scheme), aff’d sub. nom. Am. Pharm. Ass’n v. Mathews, 530 F.2d 1054 (D.C. Cir. 1976).

In light of this substantial precedent, we argued that Congress had “directly spoken to the precise question” of increasing pediatric labeling by enacting a voluntary incentive scheme. Moreover, Congress provided in FDAMA a “‘who, what, when, and how’ laundry list” setting forth which drugs are eligible for the incentives and how FDA may request that the manufacturer voluntarily conduct pediatric testing (i.e., by written request, based on a finding that the product “may produce health benefits” in the pediatric population). See 21 U.S.C. § 355a (2000). Indeed, earlier this year in an analogous context, the U.S. District Court for the District of Columbia held that an executive order that “sets a different standard of conduct” from that set by a federal statute presented a “clear conflict.” UAW-Labor Employment & Training Corp. v. Chao, No. 01CV00950 (HHK), 2002 WL 21720, at \*7-\*8 (D.D.C. Jan. 2, 2002) (addressing preemption of executive order by NLRA) (App. Exh. 13). Based on this conflict, the court granted plaintiffs’ motion for summary judgment by declaring the order to be invalid and permanently enjoining its enforcement. Id. at \*9-\*10. We argued that this case law demonstrated that Congress’s choice in FDAMA of a voluntary approach for increasing pediatric labeling signified that FDA may not second-guess Congress’s wisdom by mandating pediatric testing where the manufacturer does not claim a pediatric use.

### **Conflict Between the BPCA and the Pediatric Rule**

FDA’s current request for comments was triggered by Congress’s reenactment and expansion of its pediatric incentive scheme in the BPCA. In apparent recognition of the many voluntary provisions in the BPCA that conflict with FDA’s mandatory approach in the Pediatric Rule, FDA now seeks comments, inter alia, on “what present authorities [in the Pediatric Rule], if any,

have not proven effective, are now redundant, or need to be updated because of the BPCA.” 67 Fed. Reg. at 20071.

In fact, however, the Pediatric Rule is beyond “updating” or reconciling with the BPCA – the two regimes are irreconcilable. After FDA issued the mandatory Rule in the face of the voluntary FDAMA provisions, it attempted to justify the Rule by claiming that it fills gaps in FDAMA’s “temporary and partial attempt to address a problem” and thereby constitutes a “permanent, comprehensive solution.” See Defs.’ Mem. in Supp. of Their Mot. for Summ. J. at 33 n.11, *Ass’n of Am. Physicians & Surgeons, Inc. v. FDA*, Civil Action No. 1:00CV02898 (HHK) (D.D.C. Nov. 9, 2001) (“FDA Opp.”) (App. Exh. 7). If Congress truly believed that the Rule constituted the “permanent, comprehensive solution” that FDA claims it is, however, it would not have reauthorized and expanded voluntary pediatric testing legislation containing provisions that address the very same gaps that the agency identified to justify the Pediatric Rule, but in a very different manner.<sup>6</sup> We address those conflicting provisions below.

### **1. No Endorsement of the Pediatric Rule**

One obvious threshold indication that the Rule and the BPCA fundamentally conflict with each other is that Congress has repeatedly refused to endorse the mandatory approach to pediatric testing taken in the Rule. When Congress first considered the issue of pediatric testing, there was at least some consideration of adopting a mandatory approach to increase pediatric labeling before it settled upon a voluntary incentive scheme. Senator Christopher Dodd, one of the co-sponsors of FDAMA’s pediatric exclusivity provisions, stated that in drafting those provisions:

Senator DeWine and I, in 1997, as part of the Food and Drug Administration modernization bill, crafted this legislation as a way to see if we could not induce – there was a debate on whether we should mandate it and say you have to do it whether you like it or not, which is one approach, or should we say we will give you a chance to prove to us you can do it by providing 6 months of exclusivity in the marketplace. There was a debate about that.

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<sup>6</sup> Even if FDA did perceive FDAMA to be a “temporary, partial” solution to the alleged problem, the remedy is not agency regulation but congressional action. See *Am. Mining Cong. v. United States Army Corps of Eng’rs*, 951 F. Supp. 267, 278 (D.D.C. 1997) (invalidating agency rule intended “to close a longstanding alleged loophole in [congressional] Act” and explaining that “appropriate remedy for what the agencies now perceive to be an imperfect statute ... is Congressional action”), *aff’d*, 145 F.3d 1399 (D.C. Cir. 1998).

147 Cong. Rec. S10826 (daily ed. Oct. 18, 2001) (emphasis added) (App. Exh. 8). The fact that Congress opted to increase pediatric labeling through a voluntary, rather than mandatory, approach belies FDA's attempt to harmonize the Rule with FDAMA's incentive provisions, now reauthorized in the BPCA. As the Supreme Court observed in its analogous decision rejecting FDA's assertion of jurisdiction over tobacco:

Indeed, this is not a case of simple inaction by Congress that purportedly represents its acquiescence in an agency's position. To the contrary, Congress has enacted several statutes addressing the particular subject of tobacco and health, creating a distinct regulatory scheme for cigarettes and smokeless tobacco.

Brown & Williamson, 529 U.S. at 155. The existence of Congress's "distinct regulatory scheme" for increasing pediatric labeling demonstrates the illegitimacy of FDA's attempt to impose its own scheme in the Rule.

When the time came for Congress to reauthorize its pediatric testing incentives in FDAMA, FDA explicitly asked Congress to authorize, post hoc, the mandatory testing and formulation provisions in the Pediatric Rule. FDAMA Report at 21 (App. Exh. 6). Certain senators did, in fact, unsuccessfully attempt to give FDA such authority in the Senate version of the bill. For example, "Senator Kennedy offered and then withdrew an amendment to require pediatric testing of new drugs for their approved uses in adults." S. Rep. No. 107-79, at 7 (2001) (App. Exh. 9). Similarly, Senator Clinton offered and then withdrew an amendment "to require manufacturers to include in an application for study of a new drug their intent for pediatric studies of the drug." *Id.* In the end, Congress refused to give FDA the requested authorization, instead reenacting and expanding its chosen voluntary means of accomplishing its goal. See generally BPCA (App. Exh. 5). Congress's refusal to do so coupled with its own enactment of provisions intended to solve the same problem confirm FDA's lack of statutory authority to issue the Rule. See Brown & Williamson, 529 U.S. at 144 (refusing to give FDA jurisdiction over tobacco where, *inter alia*, "Congress considered and rejected bills that would have granted the FDA such jurisdiction").

Congress's latest actions with respect to the Pediatric Rule again demonstrate Congress's view that the Pediatric Rule lacks statutory authority. If Congress truly believed that the Pediatric Rule were a statutorily permissible approach at the time it enacted the BPCA, as FDA's advanced notice of proposed rulemaking appears to assume it did, there would be no need for further legislative action legitimizing the Rule. Yet within the past ten weeks, a member from each House has proposed precisely such action – Senator Clinton and Representative Waxman have each introduced bills in their respective Houses

that, if enacted into law, would, in fact, authorize FDA to require pediatric testing. See S. 2394, 107th Cong. (Apr. 29, 2002) (App. Exh. 10); H.R. 4730, 107th Cong. (May 14, 2002) (App. Exh. 11). This step by sympathetic members of Congress further confirms that the existing federal drug laws leave no room for operation of the Pediatric Rule,

2. **Reauthorization of Voluntary Pediatric Testing Incentives for Products with Marketing Exclusivity**

Another fundamental indication that Congress did not believe that the Pediatric Rule constituted the “permanent, comprehensive solution” that FDA billed it as is the very fact that Congress found it necessary to reauthorize in the BPCA the voluntary pediatric testing incentives set forth in FDAMA through the end of fiscal year 2007. Pursuant to those incentives, a manufacturer receives an additional six months of marketing exclusivity on a new drug or marketed drug with exclusivity if (a) FDA determines that pediatric testing of the drug “may produce health benefits in that population,” (b) FDA makes a written request to the manufacturer to conduct such testing, (c) the manufacturer agrees to test the drug within an appropriate timeframe and submits reports of the tests to FDA, and (d) FDA accepts the testing reports. 21 U.S.C. § 355a(a), (c) (2000); BPCA § 2, 115 Stat. at 1408.

No reauthorization would have been necessary if FDA simply could have ordered manufacturers to test and reformulate their products for children – incentives are unnecessary to encourage conduct that is already legally required. It would be wholly anomalous, for example, for Congress to pass a law authorizing substantial sums of money to be paid out to motorists who are shown by traffic cameras to be complying with the speed limits in order to encourage such compliance. That is precisely the type of bizarre scenario created by FDA’s ongoing attempt to square the Rule and the BPCA.

3. **Manufacturers’ Right To Refuse To Conduct Pediatric Testing in Exchange for Exclusivity on New or Marketed Drugs; Alternative Means by Which FDA May Elicit Such Studies**

Yet another clash between the Rule and the BPCA is that the BPCA allows manufacturers of both new and marketed drugs to decline to test their products on pediatric populations in exchange for exclusivity and instead establishes alternative means of conducting those studies. The BPCA’s approach, set forth below, stands in sharp contrast to FDA’s approach in the Pediatric Rule, under which FDA asserts the authority to refuse to approve new drugs and to declare drugs to be misbranded if the manufacturer refuses to conduct pediatric testing.

**a) New Drugs**

The BPCA allows manufacturers of new drugs to decline to conduct pediatric testing on their products without risking denial of their New Drug Applications (“NDAs”). Unlike the Pediatric Rule, under which FDA asserts the authority to refuse to approve NDAs if manufacturers decline to conduct pediatric studies, the BPCA instead contemplates that such products will be approved. If FDA determines that “there is a continuing need” for pediatric use information for a new drug that the manufacturer did not test on children, the BPCA authorizes the agency to request such testing a second time “after the date of approval of the drug” pursuant to 21 U.S.C. § 355a(c), the pediatric exclusivity provision relating to marketed drugs. BPCA, § 4, 115 Stat. at 1412 (emphasis added). As set forth in more detail below, the manufacturer again may decline to conduct such testing, in which case FDA may seek to have the testing conducted by a third party through either a privately funded foundation or a publicly funded contracting process. See infra pp. 13-14.

**b) Marketed Drugs with Exclusivity**

For marketed drugs with remaining exclusivity for which FDA has requested manufacturers to conduct pediatric testing, the BPCA, unlike the Pediatric Rule, allows manufacturers to decline to conduct such testing without risking that their products will be deemed misbranded and pulled off the market. Where FDA determines, however, that “there is a continuing need for information relating to the use of the drug in the pediatric population,” the BPCA establishes two alternative means for conducting such testing. BPCA § 4, 115 Stat. at 1412. In the first instance, FDA may “refer the drug to the Foundation for the National Institutes of Health” (“Foundation”), a private, nonprofit foundation authorized to “collect funds for pediatric pharmacologic research and studies” on drugs. See id.; id. § 13, 115 Stat. at 1417; 42 U.S.C. § 290b. The Foundation will then “issue a proposal to award a grant to conduct the requested studies,” and the grant recipient must provide FDA and the National Institutes of Health with “a report describing the results of the research and studies” and “all data generated in connection with the research and studies.” BPCA § 4, 115 Stat. at 1412; id. § 13, 115 Stat. at 1418.

Alternatively, if the Foundation certifies to FDA that it does not have sufficient private funds to pay for the pediatric testing, the BPCA establishes a public fund of \$200 million for fiscal year 2002 and “such sums as are necessary for each of the five succeeding fiscal years” that FDA may use to pay a third party to conduct such testing. Id. § 3, 115 Stat. at 1411; id. § 4, 115 Stat. at 1412. FDA must “publish a request for contract proposals to conduct the pediatric studies,” to which qualified third parties may submit bids. Id. § 3, 115 Stat. at 1409-10. Once a study is completed, a report of the study must be submitted,

including “all data generated in connection with the study,” to FDA and the National Institutes of Health, and the report will be considered in the public domain. *Id.* § 3, 115 Stat. at 1410. Why the very substantial appropriation to encourage conduct to occur voluntarily if FDA through the Pediatric Rule may already require it? And how diligently will FDA pursue the Foundation alternative if it contemplates use of the unlawful Pediatric Rule?

**4. Establishment of Means by Which FDA May Elicit Pediatric Studies on Marketed Drugs Lacking Exclusivity Where Manufacturer Elects Not To Conduct Such Studies**

One of the “gaps” in FDAMA identified by FDA that supposedly necessitated issuance of the Pediatric Rule was that FDAMA provided no incentive to encourage testing on drugs that lack exclusivity. FDAMA Report at 21 (App. Exh. 6); FDA Opp. at 9-12 (App. Exh. 7). Even though the Pediatric Rule allows FDA to require pediatric testing of these drugs under certain circumstances, Congress nonetheless included a provision in the BPCA that addresses this precise issue through very different means.

Unlike the Pediatric Rule, the BPCA allows manufacturers of products lacking patent or other marketing exclusivity to refuse FDA’s request to study these products on children, and instead establishes an alternative mechanism for conducting such testing. Specifically, FDA may “issue a written request . . . for pediatric studies” of approved drugs “to all holders of an approved application” where (1) “there is no patent protection or market exclusivity protection” or there is an approved or approvable ANDA for the drug and (2) “additional studies are needed to assess the safety and effectiveness of the use of the drug in the pediatric population.” BPCA § 3, 115 Stat. at 1408-09. If FDA receives no response from the manufacturer within thirty days, FDA may contract with a third party to perform the testing pursuant to the same process, and paid for with the same public funding, discussed in the previous section. *Id.* § 3, 115 Stat. at 1409-10. If FDA all along had the authority to require such testing, Congress would not have allowed manufacturers to refuse to conduct such testing and provided funding for third parties to conduct it instead.

**5. Voluntary Development of Pediatric Formulations**

FDA’s means of increasing pediatric formulations in the Pediatric Rule constitutes a particularly striking example of the direct conflict between those provisions and Congress’s chosen approach in the BPCA. While the Pediatric Rule purports to require manufacturers to develop pediatric formulations (21 C.F.R. §§ 201.23(a), 314.55(c)), the BPCA only authorizes FDA to “send a nonbinding letter of recommendation” seeking a change in formulation where “a pediatric study completed under public contract indicates that a formulation

change is necessary and [FDA] agrees.” BPCA, § 3, 115 Stat. at 1411 (emphasis added). The BPCA provision would be entirely superfluous if Congress believed FDA had the power all along to require manufacturers to reformulate their products for pediatric use.

#### **6. Procedure for Effectuating Labeling Changes**

The BPCA’s elaborate procedure for effectuating labeling changes based on additional information discovered as a result of pediatric testing conducted pursuant to the Act also conflicts with the approach taken in the Pediatric Rule. Unlike the Pediatric Rule, the BPCA does not allow FDA simply to declare a drug to be misbranded because the product has not been established to be safe and effective in pediatric populations when this fact is accurately reflected in the product’s label pursuant to FDA’s regulations. Cf. 21 C.F.R. § 201.57(f)(9)(vi). Rather, FDA may only exercise its misbranding authority in this instance where (a) additional pediatric use information is known, but not included on a product’s label, and (b) FDA has complied with the multiple procedural requirements set forth in the BPCA – including a requirement that it first submit the request to an oversight body – for seeking a labeling change.

Specifically, FDA first must attempt to reach agreement with the holder(s) of an approved or approvable application for the drug concerning proposed labeling changes. BPCA § 3, 115 Stat. at 1410; id. § 5, 115 Stat. at 1413. If they are unable to agree, FDA “shall refer the request to the Pediatric Advisory Subcommittee of the Anti-Infective Drugs Advisory Committee,” which will review the drug’s pediatric use information and recommend labeling changes within ninety days of receiving the referral. Id. § 3, 115 Stat. at 1410-11; id. § 5, 115 Stat. at 1413. Within thirty days of receiving such a recommendation, FDA will review the Subcommittee’s recommendations and, if appropriate, request that the holder(s) of an approved or approvable application for the drug make labeling changes. Id. § 3, 115 Stat. at 1411; id. § 5, 115 Stat. at 1414. If a holder does not agree within thirty days to make the requested change, FDA may then deem the drug to be misbranded. Id. § 3, 115 Stat. at 1411; id. § 5, 115 Stat. at 1414.

#### **7. Prompt Approval of ANDA Drugs with Appropriate Labeling Disclaimers Where Pioneer Drug Subject to Pediatric Exclusivity**

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The BPCA also is inconsistent with the Pediatric Rule in that it forbids FDA from exercising its approval or misbranding authority to keep generic drugs off the market whose labels do not contain pediatric use information because the pediatric indication is protected by patent or other exclusivity. Rather, the Act requires FDA to approve such drugs and allows the agency to require labeling

statements (a) advising why the product is not labeled for such pediatric use and (b) listing “any appropriate pediatric contraindications, warnings, or precautions that [FDA] considers necessary.” BPCA § 11, 115 Stat. at 1416. This provision of the Act reflects Congress’s determinations that despite the lack of pediatric use information:

- such products are safe and effective “for use under the conditions prescribed, recommended, or suggested in the proposed labeling” (21 U.S.C. § 355(d));
- the products’ labeling is not “false or misleading in any particular” (*id.* §§ 352(a), 355(d)); and
- the products bear “adequate directions for use” (*id.* § 352(f)).

Otherwise, the product could not be approved and/or would be misbranded. *Id.* §§ 352(a), (f), 355(d). In other words, contrary to FDA’s theory underlying the Pediatric Rule, Congress has decided in this instance to allow products with known pediatric uses to be marketed without pediatric labeling – and has expressly forbidden FDA from declaring them to be misbranded – so long as the labeling includes appropriate disclaimers and other disclosures.

### **Responses to FDA’s Specific Questions**

In addition to the above comments, we offer the following brief responses to FDA’s specific questions in its advanced notice of proposed rulemaking:

- 1. “What changes to the pediatric rule, if any, would be necessary to integrate the BPCA and the pediatric rule more effectively?”**

As explained above, there is no way to “integrate” the BPCA and the Pediatric Rule – the BPCA, coupled with other FDCA provisions, leave no room for the Rule. The key areas of operation of the Pediatric Rule are to require manufacturers to (1) conduct pediatric testing and (2) to develop pediatric formulations. *See* 21 C.F.R. §§ 201.23(a), 314.55(a), 601.27(a). The BPCA expressly addresses both of these areas. With respect to testing, the BPCA provides that FDA may only request that manufacturers conduct pediatric testing and, in the case of approved drugs lacking marketing exclusivity, provides that FDA “shall publish a request for contract proposals to conduct ... pediatric studies” if the manufacturer fails to respond within 30 days to a request that it conduct such studies. BPCA, § 3, 115 Stat. at 1408-09, 1412 (emphasis added). With respect to formulations, the BPCA provides that FDA “shall send a nonbinding letter” that merely recommends a change in formulation “[i]f a

pediatric study completed under public contract indicates that a formulation change is necessary and the Secretary agrees.” Id. § 3, 115 Stat. at 1411 (emphasis added). FDA cannot simply choose at its whim between sending a nonbinding letter recommending a change in formulation and requiring that such a formulation be developed. To do so would defy well-settled principles of statutory interpretation. See, e.g., UAW v. Dole, 919 F.2d 753, 756 (D.C. Cir. 1990) (acknowledging “the usual presumption that ‘may’ confers discretion, while ‘shall’ imposes an obligation to act” and stating that “[c]onsidering the frequency with which it uses the two words, Congress can be expected to distinguish between ‘may’ and ‘shall’”).

Moreover, if Congress truly believed that FDA’s mandatory pediatric testing and formulation regulations were legitimate, why would it have:

- provided marketing incentives to induce manufacturers to conduct those same tests voluntarily,
- created alternative means by which those tests could be conducted if manufacturers decided not to do so,
- authorized \$200 million for 2002 alone to fund that testing, and
- confined FDA to sending “nonbinding” letters that merely “recommend” that manufacturers reformulate their products for children in certain cases

There would have been no need for any of these provisions if all along there already were a legal duty for manufacturers to test and reformulate their products for children. As previously mentioned, Congress’s enactment of these provisions in the face of a statutorily legitimate Pediatric Rule would be akin to enacting a law appropriating large sums of money to be paid out to motorists who are shown by traffic cameras to be complying with the speed limits in order to encourage such compliance. See supra p. 12.

We reiterate that where Congress has chosen a particular approach to address an issue, an administrative agency is bound to implement Congress’s preferred method and cannot employ a different approach to achieve the desired result. See supra pp. 8-9; see also UAW-Labor Employment & Training Corp., 2002 WL 21720, at \*7-\*8 (finding “clear conflict” between an executive order and a statute where the executive order “sets a different standard of conduct”) (App. Exh. 13). In light of this established principle, the Pediatric Rule cannot coexist with the BPCA and the FDCA.

2. “How would the criteria used by NIH and FDA under section **3 of the BPCA** to request studies of already approved drugs relate to the standards **promulgated** in the pediatric rule and described in 21 **CFR 201.23, 314.55**, and 601.27 for requiring **pediatric labeling for certain drugs and biological products? Which criteria are more appropriate for determining when studies are conducted?**”

FDA’s question misses the point. FDA is not a coequal entity with Congress but rather is limited to implementing congressional intent. Therefore, FDA is not at liberty to choose between conflicting criteria but rather must employ those already established by Congress as the most “appropriate.”

3. “What provisions, if any, of the BPCA could apply to **biological products regulated under section 351 of the PHSA?**”

We express no opinion on this question. To the extent, however, that FDA has posed this question to attempt to justify the Pediatric Rule as filling a gap in the BPCA, FDA’s inquiry is inappropriate. See suprap. 10n.6.

4. “How does the provision in section 3 of the BPCA providing for a recommendation for a formulation change relate to the pediatric rule provision stating that in certain cases a sponsor may be required to develop a pediatric formulation? Should **pediatric formulations be required in certain cases?**”

As previously discussed, the BPCA only provides that FDA may request the development of pediatric formulations, whereas the Pediatric Rule purports to authorize FDA to require that those formulations be developed. See suprap. 14-15.

Where Congress has provided that FDA seek the development of pediatric formulations in a particular manner, FDA cannot simply ignore that directive and demand that those formulations be developed. See suprap. 8-9. Whether pediatric formulations “should ... be required in certain cases” is not for FDA to decide – Congress has already answered that question in the negative.

#### Conclusion

There is a reason why Congress settled upon voluntary, instead of mandatory, measures for encouraging pediatric testing and the development of pediatric formulations. By ensuring that drugs for adult use will not be kept off the market until pediatric testing is completed, while at the same time

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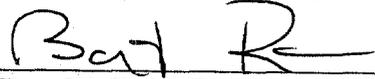
safeguarding against premature and precipitous drug testing on children, Congress has struck the right balance in the BPCA, in a much more effective manner than the Pediatric Rule, between

- consumer drug access,
- adequate pediatric labeling information,
- safe and ethical pediatric drug studies, and
- minimal mandatory governmental interference into drug manufacturers' private decisions concerning the timing and manner of pediatric testing of their products.

FDA should allow the BPCA to do the job that Congress intended it to do instead of trying to salvage the far more draconian and improper extra-statutory measures embodied in the Pediatric Rule in its advanced notice of proposed rulemaking. *AAPS*, *CEI*, and *Consumer Alert* request that FDA acknowledge the limitations on its authority that are starkly highlighted by the BPCA, immediately revoke the Rule and direct its energies toward implementing Congress's voluntary approach.

Respectfully submitted,

Sam Kazman (D.C. Bar ID No. 946376)  
COMPETITIVE ENTERPRISE INSTITUTE  
1001 Connecticut Avenue NW  
Suite 1250  
Washington, DC 20036  
202.331.1010 x. 218  
202.331.0640 (facsimile)

  
Bert W. Rein (D.C. Bar ID No. 67215)  
Andrew S. Krulwich (D.C. Bar ID No. 85852)  
WILEY REIN & FIELDING LLP  
1776 K Street NW  
Washington, DC 20006  
202.719.7000  
202.719.7049 (facsimile)

Attorneys for

Association of American  
Physicians and Surgeons, Inc.  
Competitive Enterprise Institute  
Consumer Alert

Dated: July 8, 2002

## APPENDIX

### TO COMMENTS TO THE FOOD AND DRUG ADMINISTRATION'S ADVANCED NOTICE OF PROPOSED RULEMAKING

DOCKET NO. 02N-0152

**Submitted By:**  
**Association of American Physicians and Surgeons, Inc.**  
**Competitive Enterprise Institute**  
**Consumer Alert**

Sam Kazman (D.C. Bar ID No. 946376)  
COMPETITIVE ENTERPRISE INSTITUTE  
1001 Connecticut Avenue NW  
Suite 1250  
Washington, DC 20036  
202.331.1010 x. 218  
202.331.0640 (facsimile)

Bert W. Rein (D.C. Bar ID No. 67215)  
Andrew S. Krulwich (D.C. Bar ID No. 85852)  
WILEY REIN & FIELDING LLP  
1776 K Street NW  
Washington, DC 20006  
202.719.7000  
202.719.7049 (facsimile)

Attorneys for

Association of American  
Physicians and Surgeons, Inc.  
Competitive Enterprise Institute  
Consumer Alert

Dated: July 8, 2002

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