

Assessing the Effects of Federal Pediatric Drug Safety Policies

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EXECUTIVE SUMMARY

This analysis provides an overview of federal pediatric drug safety policy. It also assesses the economic effectiveness of one aspect of this policy, known as “pediatric exclusivity.”

The safety and efficacy of pharmaceuticals for children is a fundamental aspect of overall pediatric health policy. Moreover, the growing focus on patient safety and medical error reduction, as well as evidence of growing insurer resistance to coverage of off-label prescribing (which is the most common means by which physicians prescribe drugs to children), have combined to make pediatric drug safety a matter of mounting policy importance. Indeed, two-thirds of all drugs prescribed for children have not been tested and labeled for pediatric use.

Current federal policy provides a “carrot and stick” approach to pediatric drug safety. The Best Pharmaceuticals for Children Act (BPCA) encourages drug companies to voluntarily test drugs for pediatric safety in response to an FDA request, by granting a six-month period of market exclusivity. The Pediatric Research

Equity Act of 2003 (PREA) empowers the FDA to require pediatric drug studies under certain conditions. Both laws contain “sunset” provisions and are set to expire in October 2007.

BPCA has helped contribute to expanded drug testing, which in turn has led to labeling improvements. Better labeling might reasonably be expected to lead to more appropriate prescribing in accordance with clinical guidelines, which in turn would promote greater patient compliance. As compliance improves, health care costs are affected. Asthma, for example, is a pediatric condition in which noncompliance with clinical guidelines greatly contributes to significant and unnecessary pediatric hospitalization rates. To predict potential savings resulting from better compliance through improved labeling, this analysis: calculated the cost of hospitalizations resulting from adverse drug reactions, obtained aggregate estimates of direct medical costs other than hospitalizations, and considered indirect costs arising from childhood asthma. Based on 2002 data trended forward to 2005 dollars, we estimate

that increased compliance would result in a \$96 million reduction in hospitalization costs, a \$107 million reduction in non-hospital costs, a \$16 million reduction in the loss of caregiver productivity and \$5.29 million in savings related to adverse drug reactions (ADR). In total, we estimate that for asthma alone, the potential cost savings associated with improved pediatric labeling could reach some \$225 million annually.

Our analysis suggests the beneficial effects of a robust pediatric testing policy that relies in part on reasonable incentives, as well as on additional safeguards aimed at ensuring that necessary testing in fact happens. This analysis underscores the patient and societal benefits of testing. As a result, we recommend strengthening BPCA to include a provision that would ensure that where a testing request is declined, manufacturers furnish clear and convincing evidence of net financial losses associated with testing in relation to the incentives promised.

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INTRODUCTION

This policy analysis examines the effectiveness of pediatric exclusivity, one of the policy approaches the federal government uses to promote drug safety for children. Federal policy in this area is highly complex, and provisions

related to pediatric drug safety, including pediatric exclusivity, are set to expire in 2007. Following a policy overview, this analysis summarizes the impact of pediatric exclusivity and reports on the results of our effort to shed light

on the economic value of pediatric exclusivity. The analysis concludes with a discussion of options for further promoting a safe environment for drug use in children.

BACKGROUND

Pediatric drug testing as a health care and public health policy imperative

The safety and efficacy of pharmaceuticals for children is of fundamental importance to sound, national pediatric health policy. In the modern health care system, pharmaceuticals play a prominent role in health care, and the appropriate use of prescription drug therapies can dramatically affect the course, quality, and outcome of patient treatment. Furthermore, drug safety protections are essential to lowering the risk of adverse outcomes.

Yet drug safety protections for children are significantly less than optimal. The United States Government Accountability Office (GAO) recently reported that approximately two-thirds of all drugs prescribed for children have not been tested and labeled for pediatric use (GAO 2007), and this figure is supported by earlier research (Budetti 2003, 950-951). Food and Drug Administration (FDA) data suggest that only 20% to 30% of drugs granted marketing approval have an approved pediatric indica-

tion (Meadows 2003, 12-17). One hospital-based study conducted from January through June 2004 found that 31% of drugs used were prescribed off-label in relation to either indication or age. The majority of indication-related off-label uses involved gastrointestinal and respiratory disorders, while off-label uses related to age mainly involved asthma medications and anti-convulsants (Eiland et al. 2006, 1062-1065). A more comprehensive study of pediatric off-label use in hospitals found that almost 80% of children receive off-label medications (Shah et al. 2007, 282-290). Indeed, off-label use in children is so pervasive that the practice is considered a "cornerstone of pediatric medical therapeutics" (Budetti 2003, 950-951).

The need for a comprehensive approach to ensuring pediatric drug testing and labeling has taken on added importance in recent years, as third party payer cost containment efforts have come to focus increasingly on off-label pre-

scribing, which represents the principal means by which drugs are used in children given the absence of a robust testing policy. Indeed, the potential for cost containment reforms to implicate the primary means by which drugs are prescribed for children is not speculative. While the extent of insurer coverage practices where off-label use is concerned is not known, one state already has enacted Medicaid reforms that, until subsequently modified, would have denied coverage for virtually all off-label drug use by limiting coverage to pharmaceuticals shown to be safe and effective for a specific indication (Schneider 2004).

In sum, the absence of a sufficient pediatric drug testing policy threatens not only to reduce quality and safety but also to "leave children behind" (Iyasu et al. 2007, 497-508) where advances in prescription drug therapy are concerned, to the extent that insurers begin to deny coverage for off-label therapies.

The early policy framework for pediatric drug safety

Government possesses the inherent power to protect patients from poor quality or unsafe health conditions, including the use of inadequately tested drugs in children (Gostin 2003). Although federal law gives the government the authority to require drug testing in children, these regulatory powers have been exercised but only to a limited degree and not in the case

of prescribed drugs already on the market. Increasingly, the federal government has adopted an incentivization approach to promoting pediatric drug safety.

Prior to 1962, federal drug regulatory policy required consideration only of the safety of a drug proposed for market entry. Legislation

enacted in 1962 added the dimension of "efficacy" to FDA review, but the legislation neither required nor encouraged pediatric studies as a specific aim.

Regulations promulgated in 1979 by the FDA sought to improve standards by requiring that pediatric labeling claims be supported by ad-

¹ Funding for this analysis comes from the Elizabeth Glaser Pediatric AIDS Foundation and the American Academy of Pediatrics.

equate pediatric test data, but these requirements did little to alter the status quo, as the agency continued to permit the approval of adult drugs untested in children, so long as labeling (known as “orphaning clauses”) disclosed the lack of pediatric testing. Boilerplate language such as “Safety and efficacy in pediatric patients have not been established” became the norm. Indeed, the 1979 rule appeared to impede rather than spur pediatric drug research, since prescription drug manufacturers concluded that disclosure was a more efficient approach than testing (Breslow 2003, 133). As a result, pediatric testing remained dormant.

However, the rise of HIV/AIDS as a pediatric disease sparked a new sense of urgency regarding the need for a national pediatric drug testing policy (Lynch 2007, 79 and Milne 1999). In 1990, the FDA announced a new policy of incorporating a “Pediatric Page” into its review process for all new molecular entities submitted for approval. This change in policy required manufacturers to provide detailed information regarding pediatric use, so that the agency could assess the adequacy of a prescription drug label in a child health context. Manufacturers were also required to disclose any need, plans, or agreements with the FDA that were related to further studies in children. In prac-

tice, this regulatory scheme tended to simply summarize the state of pediatric studies as part of the FDA drug review process (Lynch 2007, FN 78).

The FDA sought to refine its pediatric policy in 1994 by specifying conditions under which manufacturers could use adult studies, in addition to other specific and relevant data, in order to support pediatric labeling; however, the new policy did not actually require any new testing. Drug manufacturers could continue to opt for simple disclosure through a disclaimer approach if the necessary information was absent.

A decade of legislative reform

The 1997 enactment of the U.S. Food and Drug Administration Modernization Act represented a major advance in national policy related to promoting the safety and quality of pharmaceuticals for children. Included in the legislation was a provision – that has come to be known as “pediatric exclusivity” – whose purpose was to encourage pediatric clinical drug trials by providing an incentive to pharmaceutical companies. The pediatric exclusivity law was reauthorized in 2002 as the Best Pharmaceuticals for Children Act (BPCA). This reauthorization was followed in 2003 by the enactment of the Pediatric Research Equity Act (PREA), which

complimented the BPCA by requiring companies to study certain drugs for use in children. The BPCA provides a “carrot” for more extensive pediatric drug testing through the use of financial incentives, along with the vesting of total discretion in pharmaceutical companies to determine when incentives are sufficiently beneficial to justify testing. In the case of on-patent drugs, the BPCA carrot consists of an additional period of protection from market competition (for example, the market entry of a generic competitor) when a manufacturer of an on-patent drug conducts certain pediatric studies in response to an FDA request.

The PREA provides a “stick.” The statute expressly empowers the FDA to require pediatric drug studies where the pediatric indication is the same as the adult indication and the agency has determined that certain criteria are met to require pediatric testing. Because PREA emphasizes a more regulatory approach, it applies regardless of whether a drug or biologic product is on-patent or off-patent.

Both laws contain “sunset” provisions and unless they are reauthorized, will expire in October 2007.

The Best Pharmaceuticals for Children Act

Pediatric exclusivity offers a simple and straight-forward incentive: in exchange for conducting pediatric trials specifically requested by the FDA, drug manufacturers of on-patent drugs – or those applying for approval of new drugs that will receive patent protection if approved – can obtain a six-month extension of market exclusivity for all of their products with the same active ingredient as the drug under study. During this six-month extension period, the FDA cannot grant marketing approval applications for a generic

version of the drug where the application for marketing approval relies on the safety and efficacy data from the originator’s marketing application. Thus pediatric exclusivity has the effect of delaying generic competition.

The process, as detailed in the BPCA itself, is as follows: In cases in which the Secretary determines that “information relating to the use of a new drug in the pediatric population may produce health benefits for that population,” the FDA then makes a written

request to a manufacturer asking that it conduct specific pediatric studies within a certain timeframe, the age groups to be tested, and the study design and goals. These studies are then completed and submitted as part of a new drug application or supplement thereto for the new pediatric indication of an already-marketed drug. The Secretary then has 90 days to review the application and determine whether the submission meets the study requirements and, if so, exclusivity is granted; thus, the six-month extension is not

² Drug Amendments of 1962, Pub. L. No. 87-781, 76 Stat. 780 (codified in scattered sections of 21 USC).

³ Labeling and Prescription Drug Advertising; Content and Format for Labeling for Human Prescription Drugs, 44 Fed. Reg. 37, 434 (June 26, 1979) (codified as amended in 21 C.F.R. pt. 201 and 202).

contingent upon an actual labeling change, but instead, on provision by a company of data in response to the agency's request. If a new indication or other labeling change is warranted, the FDA and the drug company then negotiate these changes. But because the program is voluntary, a company that receives an FDA request to conduct a pediatric trial can choose whether or not to participate. There appears to be no evidence regarding the reasons underlying a decline; presumably factors such as the cost of the study in relation to the economic benefit to the firm, or the company's own judgment regarding the need for further study would affect a manufacturer's determination (Li et al. 2007).

The pediatric exclusivity provision was set to expire in 2002 but was reauthorized that year as the Best Pharmaceuticals for Children Act. Reauthorization followed in the wake of evidence regarding the law's success in spurring pediatric testing and labeling changes (Li et al. 2007 and Lynch 2007, 94), as well as evidence regarding a need for further reforms. Specifically, an FDA report to Congress in 2001 found that the exclusivity provision resulted in new studies and "has been highly effective in generating pediatric studies on many drugs and in providing useful new information in product labeling" (FDA 2001, i). The FDA also noted that the incentive "naturally tended to produce pediatric studies on those products where the exclusivity has the greatest value," and noted that the incentive was not adequate for old antibiotics and other drugs lacking patent protections or for certain younger age groups, especially neonates (FDA 2001, iii).

The 2002 law reauthorized the pediatric exclusivity provision for five years and added several significant improvements, including mechanisms to conduct both studies of on-

patent drugs for which a manufacturer declined a written request and for older off-patent drugs, a shorter timeline for determining labeling changes, and a provision to disseminate important study and labeling information to the public; but did not fundamentally alter the actual 1997 legislation regarding pediatric exclusivity.

To address the gap in pediatric drug trials involving off-patent drugs, the 2002 amendments created a "Program for Pediatric Studies" which established a protocol for testing off-patent drugs. Under this protocol, the FDA and the National Institutes of Health (NIH) are required to develop an annual list of off-patent/off-exclusivity drugs that the agencies believe need to be studied in order to assess safety and efficacy in children. The FDA selects an off-patent drug from the list and sends a request for pediatric studies to all manufacturers that have registered versions of the drug. If none respond to this request within 30 days, the FDA is then authorized to publish a request for proposals and to contract with organizations such as universities, teaching hospitals, contract research organizations, laboratories, etc. to conduct the relevant trials. As of December 2005, the FDA had sent sixteen requests for pediatric studies of off-patent drugs to manufacturers under this provision. Fifteen were declined by the manufacturer(s). Of the fifteen declined studies, the NIH has funded seven, spending an estimated \$52.5 million. One of the reasons the NIH has not pursued more studies of off-patent drugs is a lack of funding. The NIH does not receive a specific appropriation for pediatric drug trials, rather it utilizes 'lump sum appropriations' received by other institutes (GAO 2007).

For on-patent drugs, if a manufacturer declines to perform a pediatric study, the 2002

BPCA amendments allow the FDA to refer the drug to a quasi-governmental "Foundation for the National Institutes of Health" (also called the Foundation for Pediatric Research), a private, non-governmental foundation to facilitate the pediatric trials. This Foundation is designated under the law to address concerns that, in the event public funding is unavailable to conduct the test, independent funding can be secured for this purpose. The Foundation is empowered to collect funds through gifts, donations, and grants, and to then award grants for pediatric drug research of on-patent drugs to outside groups. If the Foundation itself is unable to secure sufficient funds to conduct the study, the FDA can then include the drug on the list of drugs for the Program for Pediatric Studies described above. As of December 2005, the FNIH collected \$4.13 million for pediatric drug studies. This amount was insufficient to conduct a full clinical study but is being used to supplement the cost of a clinical trial on baclofen, an on-patent drug whose manufacturer declined a written request (GAO 2007).

Additional changes made by the 2002 reforms are aimed at achieving greater specificity regarding when the FDA can make a request for pediatric trials, establishing a process for resolving disputes over labeling changes, and assuring public disclosure of the results of all studies conducted under this law through publication on FDA's website. All of these provisions taken together provide the "carrot" to induce more pediatric research.

⁴ Specific Requirements on Content and Format of Labeling for Human Prescription Drugs; Revision of "Pediatric Use" Subsection in the Labeling, 59 Fed. Reg. 64, 240 (Dec. 13, 1994) (codified as amended in 21 C.F.R. pt. 201).

⁵ Food and Drug Administration Modernization Act of 1997, P.L. 105-115 (105th Cong., 1st Sess.) (codified as amended in scattered sections of 21 U.S.C.)

⁶ Food and Drug Administration Modernization Act of 1997, P.L. 105-115 (105th Cong., 1st Sess.) amending the Federal Food, Drug, and Cosmetic Act § 505A, 21 U.S.C. § 355a (b-c) (West Supp. 2006).

⁷ Best Pharmaceuticals for Children Act, Pub. L. No. 107-109, 115 Stat. 1408 (2002).

⁸ Pediatric Research Equity Act, Pub. L. No. 108-155, 117 Stat. 1936 (2003) (codified as amended in scattered sections of 21 U.S.C.).

⁹ 21 U.S.C. § 355a (b), (c) (West Supp. 2006). The BPCA provides for additional market exclusivity for drugs protected by patents as well as for other forms of market exclusivity held by the drug manufacturer (i.e., exclusivity for drugs with new chemical entities, drugs designed to treat rare diseases, and for new uses of approved drugs). This report uses the term "on-patent" to describe drugs that have patent protection or another form of market exclusivity. This report uses the term "off-patent" for those drugs whose patent protection or other forms of market exclusivity have expired.

¹⁰ 21 U.S.C. §355c (b) (1). (West Supp. 2006).

Pediatric Research Equity Act

The Pediatric Research Equity Act of 2003 (PREA)²³ had as its purpose the codification of a federal regulation promulgated in 1998 by the FDA (known as the “Pediatric Rule”) but subsequently overturned in court as exceeding FDA authority.²⁴ The 2003 legislation expressly authorizes the agency to do what a court refused to permit in the case of pediatric drug testing: require pediatric testing of certain already-marketed drugs and biological products – regardless of their patent status – and to institute a presumption in favor of express pediatric testing and labeling for new drugs.

With respect to new drugs and biologics, the PREA requires that a manufacturer submit, with any New Drug Application (NDA), adequate data to assess the safety and efficacy of the drug for the claimed indications in all relevant pediatric subpopulations, even if the drug company has not claimed any specific pediatric uses.²⁵ In addition, in the case of new drugs and biologics, the law requires the submission of data to support dosing and administration information for any pediatric population in which the manufacturer claims the drug has been found to be safe and effective.²⁶ These new drug requirements can be waived by the Secretary if a pharmaceutical company can demonstrate that (1) necessary studies are impossible or highly impracticable;²⁷ (2) the evidence strongly suggests the drug would be ineffective or unsafe in all pediatric groups;²⁸ or (3) the drug is not thought to represent a meaningful therapeutic benefit over existing therapies for children.²⁹

Apart from a waiver, PREA also permits the FDA to grant a deferral to drug manufacturers which allows the applicant to submit the pediatric assessment after the submission of an NDA.³⁰ A deferral acknowledges that a pediatric assessment is required, but it delays the submission of the pediatric study data until a specified date after approval of the drug. The FDA may grant a deferral if it finds one or more of the following: (1) the drug is ready for approval for use in adults before the pediatric studies are complete; or (2) pediatric studies should be delayed until additional safety or efficacy data have been collected; or (3) there is another appropriate reason for deferral.³¹ To obtain a deferral, the drug manufacturer must submit the reasons a deferral is warranted, a description of the planned studies, and evidence that the studies will be conducted on time.³²

In practice, drug manufacturers appear to submit with their NDA a request for a deferral of the pediatric assessment for any of the reasons stated above. It is possible that at this point the FDA will grant a deferral and that the deferral is indefinite (i.e., the study does not take place). Consistent with this assumption, an FDA draft guidance on compliance with PREA points out that the failure to submit a pediatric assessment will not be the basis for withdrawing approval of a new drug³³ (FDA 2005, 14).

For drugs that are already approved and thus outside the NDA process, the PREA also gives the FDA authority to require pediatric data if the drug is currently being used for a substantial

number of pediatric patients for its labeled indications, or if there is reason to believe that the drug could represent a meaningful therapeutic benefit over existing therapies.³⁴ Both of these scenarios require a finding by the HHS Secretary that the absence of adequate labeling could pose significant risks to pediatric patients.³⁵ Even considering its broad exceptions, the legislation provides a “stick” in the government’s policy arsenal related to pediatric health safety.

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¹¹ 21 U.S.C. § 355a (b), (c). (West Supp. 2006).

¹² But, the FDA could still approve generics during this six-month window if the applicant submitted its own research and did not rely on any data from the originator’s submission. (Milne 1999, 269)

¹³ 21 U.S.C. § 355a (b), (c). (West Supp. 2006).

¹⁴ Li et al illustrate the variability of the financial benefits enjoyed by pharmaceutical companies that choose to conduct pediatric clinical trials. See also Government Accountability Office, Report to Congressional Committees, Pediatric Drug Research: Studies Conducted Under the Best Pharmaceuticals for Children Act. March 2007, at p.39.

¹⁵ Best Pharmaceuticals for Children Act, Pub. L. No. 107-109, 115 Stat. 1408 (2002) (codified as amended in scattered sections of USC, however the exclusivity language remains at 21 U.S.C. § 355a (b), (c) (West Supp. 2006).

¹⁶ 42 U.S.C. § 284(m).

¹⁷ 42 U.S.C. § 284(m) (a).

¹⁸ 42 U.S.C. § 284(m) (b).

¹⁹ Public Health Services Act, 42 U.S.C. § 290b (West Supp. 2006).

²⁰ *Id.* at § 290b (c) (1).

²¹ FDA is authorized to make written requests under the following circumstances: (1) based on the availability of information concerning the safe and effective use of the drug in the pediatric population; (2) whether new pediatric studies concerning the drug will produce health benefits for children; and (3) whether the reformulation of the drug for pediatric use is necessary. BPCA, 42 U.S.C. § 284m (West Supp. 2006).

data to support dosing and administration information for any pediatric population in which the manufacturer claims the drug has been found to be safe and effective. These new drug requirements can be waived by the Secretary if a pharmaceutical company can demonstrate that (1) necessary studies are impossible or highly impracticable; (2) the evidence strongly suggests the drug would be ineffective or unsafe in all pediatric groups; or (3) the drug is not thought to represent a meaningful therapeutic benefit over existing therapies for children.

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have been collected; or (3) there is another appropriate reason for deferral. To obtain a deferral, the drug manufacturer must submit the reasons a deferral is warranted, a description of the planned studies, and evidence that the studies will be conducted on time.

In practice, drug manufacturers appear to submit with their NDA a request for a deferral of the pediatric assessment for any of the reasons stated above. It is possible that at this point, the FDA will grant a deferral and that the deferral could be for an indefinite time period, although no systematic study has ever been made of the extent to which deferrals do in fact become permanent. Consistent with this assumption, an FDA draft guidance on compliance with PREA points out that the failure to submit a pediatric assessment will not be the basis for withdrawing approval of a new drug (FDA 2005, 14).

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cations, or if there is reason to believe that the drug could represent a meaningful therapeutic benefit over existing therapies. Both of these scenarios require a finding by the HHS Secretary that the absence of adequate labeling could pose significant risks to pediatric patients. Even considering its broad exceptions, the legislation provides a “stick” in the government’s policy arsenal related to pediatric health safety. To date, however, this provision has not been used.

While there are little public data regarding the FDA’s use of PREA to require pediatric drug studies, following the promulgation of the Pediatric Rule that ultimately was struck down, the FDA instituted a series of actions. Out of a total of 517 new drug applications submitted to the FDA during the 1999-2002 time period, the agency issued 264 waivers and 206 deferrals. Ultimately, 129 applications resulted in completed pediatric studies, 67 of which were not associated with pediatric exclusivity. In other words, the Pediatric Rule generated additional pediatric studies (FDA 2003 and Politis 2005, 271, 288). Moreover, the government’s use of PREA has resulted in 55 label changes.

**Table 1: Pediatric Rule Update
April 1999 - December 2002 (FDA 2005)**

	Total # of Applications	Waivers	Full Waivers	Partial Waivers	Applications with Deferred Studies	Applications with Completed Studies	Applications with Completed Studies not Associated with Pediatric Exclusivity
Apr 1999 – Mar 2002	404	195	130	65	172	94	52
Apr – Dec 2002	113	69	34	35	34	35	15
Total	517	264	164	100	206	129	67

²² 42 U.S.C. § 284m (West Supp. 2006).

²³ 42 U.S.C. § 290b (West Supp. 2006).

The Current Policy Landscape

The pediatric exclusivity reauthorization debate is unfolding in a shifting policy landscape. Part of this landscape, as noted, is a possible growing resistance to off-label prescribing among insurers. Another aspect of this changing policy landscape is the Medicare Modernization Act of 2003, which has resulted in an enormous expansion of direct federal involvement in financing prescription drugs and biologicals for Medicare beneficiaries, thereby raising federal budgetary implications for reauthorization. In addition, the continued growth of federal and state prescription drug expenditures under Medicaid and the State Children's Health Insurance Programs (CHIP) underscores the financial aspects of exclusivity. Thus, while the evidence suggests value in reauthorizing the BPCA, significant concerns have been raised over the cost to both the federal government and consumers regarding the length of time (currently 6 months) of the market exclusivity extension.

Thus, it becomes increasingly important to understand the nature of the contribution made by pediatric exclusivity, particularly since PREA itself grants the FDA considerable regulatory power to require testing. Although evidence suggests that patent exclusivity can create a strong incentive to conduct requested safety studies (Li et al. 2007), the extent to which policy makers can rely on incentives alone as a means of ensuring appropriate testing remains unclear. Evidence suggests that in certain instances, a six-month extension of the patent exclusivity can be highly profitable for certain drugs while in other instances, the incentive does not yield any economic benefit for the drug. One study that presented a detailed comparison of the cost of pediatric trials in relation to the economic return of exclusivity reported a median cost per written request of \$12.34 million and a median economic benefit of \$134 million (Li et al. 2007).

In sum, although the direct federal cost associated with pediatric drug testing may have increased, countervailing considerations, if anything, point toward greater investment in expanded safety testing in children. Thus, it is essential to understand the value of the federal financial investment that a pediatric exclusivity policy represents. This financial investment comes in the form of higher outlays under federal health care programs when lower cost competitors experience delayed entry into the market. And of course this investment does not reflect the broader governmental and social costs incurred by private payers, particularly those administering employer-sponsored health plans that are themselves heavily tax subsidized.

RESEARCH METHODOLOGY

The purpose of this analysis was twofold: first, to examine the available evidence regarding the impact and efficacy of pediatric exclusivity in the years following the enactment of pediatric

exclusivity in 1997 and its 2002 legislative reauthorization; second, to determine whether it is possible to develop preliminary estimates of cost savings that might be achieved from a

pediatric exclusivity incentive, thereby balancing the cost of governmental investment.

Review of the literature

Using standard literature review techniques, researchers sought evidence of pediatric clinical drug trials from both formally published studies, as well as data published by the FDA on its website regarding the 132 drugs that have been granted exclusivity extensions under the pediatric exclusivity provision. In addition to reviewing evidence from the FDA website, we

analyzed the peer-reviewed literature on the overall health impact of pediatric clinical trials. A literature search was performed using PubMed, Medline and Cochrane databases. Various combinations of the following keywords were used: pediatric clinical trials, pediatric pharmaceutical interventions, pediatric drug therapy, public health, health benefits, health

impact, as well as the individual drug names that have been tested under the pediatric exclusivity provision. We excluded studies that presented the results of individual clinical trials of drugs that were not tested under the pediatric exclusivity provision.

²⁴ Pediatric Research Equity Act, Pub. L. No. 108-155, 117 Stat. 1936 (2003) (codified as amended in scattered sections of 21 U.S.C.).

²⁵ See *Ass'n Am. Physicians & Surgeons, Inc. v. FDA*, 226 F. Supp.2d 204, 212 (D.D.C. 2002).

²⁶ FDCA § 505B, 21 U.S.C. §355c(a)(2)(A)(i) (West Supp. 2006). These data do not need to come from pediatric trials exclusively, but can be extrapolated from adult studies when possible.

²⁷ FDCA § 505B, 21 U.S.C. §355c(a)(2)(A)(ii) (West Supp. 2006).

²⁸ 21 U.S.C. §355c(a)(4)(A).

²⁹ *Id.*

³⁰ *Id.*

³¹ 21 U.S.C. §355c(a)(3).

³² *Id.*

³³ *Id.*

Estimates of potential cost savings

In our analysis we have attempted to compute the potential savings that may accrue from improved pediatric labeling resulting from pediatric drug trials undertaken in response to the pediatric exclusivity incentive. Our main interest in assessing potential cost savings for consumers, insurers, patients and others that can be attributed to improved pediatric testing and labeling grows out of the survey of the literature described above, although previous research and analysis has been scant at best. A 2001 report from the FDA (FDA 2001) concluded that improved pediatric labeling would lead to savings of \$228 million annually as a result of reduction in hospital costs associated with five major diagnoses: asthma, HIV/AIDS, cancer, pneumonia, and kidney infection. This estimate however, was based on somewhat arbitrary assumptions (see below). While all such analyses, including our own require such assumptions, we opted to base our own conclusions on research findings reported in the general literature.

Relying on a relatively broad body of literature on adherence and non-compliance with medications, our analysis is founded on an assump-

tion that improved drug labeling will improve compliance by children, and our approach has been to map the relationship between improved compliance and reduced costs associated with hospital and medical care and other financial burdens of illness in children. For this cost estimate, we rely on published studies and thus limit the number of conditions to be examined; however, unlike the previous FDA study, we are able to use assumptions based on previous analyses, rather than invoke more arbitrary rules of thumb (in its 2001 study, the FDA arrived at its estimate using the assumption that 25% of the excess incidence of hospitalizations for children versus adults could be eliminated due to improved labeling).

Another analysis that has some relevance to the policy question posed was performed by Sokol et al (Sokol et al. 2005). Using data from a large insurance plan, the authors estimated the relationship between medication adherence and outcomes for four major medical conditions: diabetes, hypertension, hypercholesterolemia, and CHF. They found that an increase in compliance from a "medium" compliance range to a "high" range resulted in declines in

the risk of hospitalization ranging from 48% to 12%. However, when the authors considered the impact of compliance on direct net medical costs (outpatient and inpatient costs, minus drug costs), the findings were mixed: the increase compliance resulted in cost reductions for diabetes and hypertension (30% and 8% respectively), no significant change for hypercholesterolemia, and a 12% increase in costs associated with CHF. Even though one out of every five subjects in the Sokol sample were aged 0-18, it was not possible to extrapolate the effects for any specific age group from published tables. Based on our extensive search of the literature, no study similar to that performed by Sokol - linking compliance directly with medical costs specific to children - has been published to date. However, it was possible to extrapolate for the pediatric population using a combination of results to address this limitation, as explained below.

³⁴ The FDA's Draft Guidance (FDA 2005) clarifies that failure to submit a pediatric assessment could instigate an FDA injunction or seizure proceeding if the drug is found to be misbranded for lack of pediatric data. Since the guidance has not been issued as a rule and is still in draft, this outcome is unlikely.

³⁵ 21 U.S.C. §355c(b)(1).

³⁶ *Id.*

³⁷ http://www.fda.gov/cder/pediatric/Prea_label_post-mar_2_mtg.htm

³⁸ Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Pub. L. No. 108-173, 117 Stat. 2066 (codified as amended in scattered sections of 42 U.S.C.).

³⁹ The Congressional Budget Office has recently estimated the impact of the modified extension of pediatric exclusivity contained in the Senate's reform measure at \$150 million over 10 years due to the delay of market entry by generic competitors.

⁴⁰ <http://www.fda.gov>

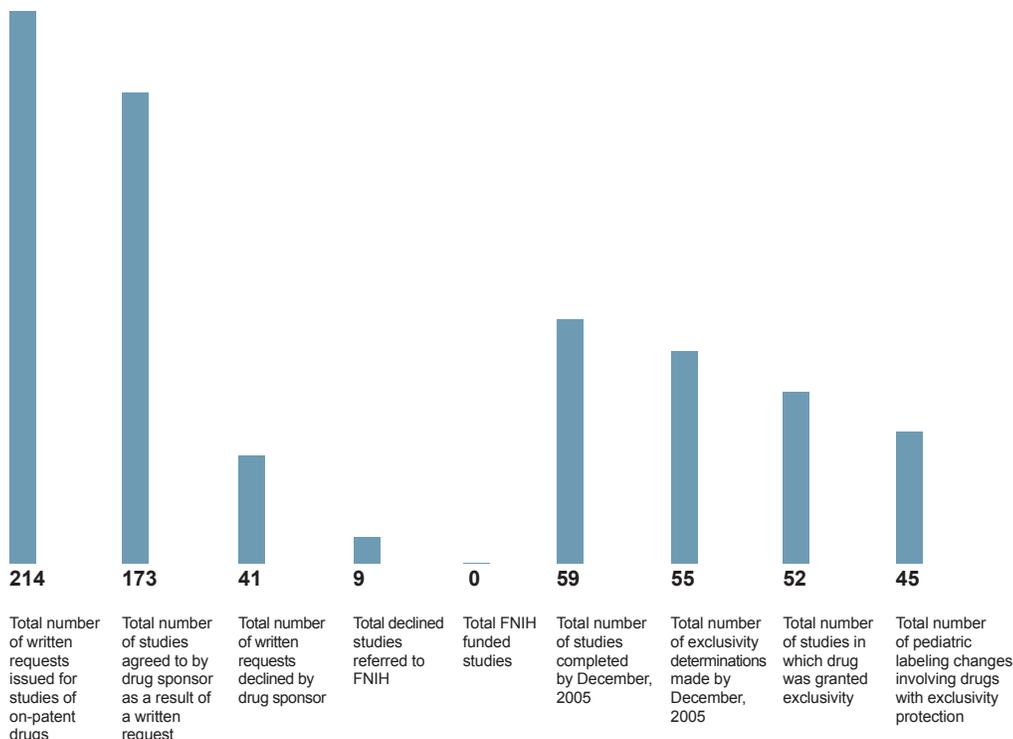
⁴¹ Compliance was measured using the medical possession ratio (MPR = prescription days filled/number days in prescription period).

FINDINGS

1. A decade of pediatric drug safety testing shows the importance of an active pediatric drug safety policy

The Government Accountability Office (GAO) recently studied the impact of the BPCA on pediatric trials and labeling changes. The report illustrates the relationship between legislative policy and improvements in pediatric drug testing. It also highlights the difficulty in conducting pediatric trials if the drug sponsor declines to do so. Table 2 summarizes this information.

Table 2: Drug Safety Testing Under BPCA (2002-2005)



Highlights of findings from the literature:

- Under the BPCA, when drug sponsor declines a written request for pediatric study, the FDA may refer the drug to the FNIH for further study. Since the BPCA's inception, however, only 9 of the 41 declined studies (22%) have been referred. According to NIH estimates, the cost of these pediatric trials exceeds \$43 million. Cost and a lack of funding meant that as of December 2005, none of the referred drugs had undergone study.
- The drugs, for which written study requests were issued address a variety of conditions. The severity of these conditions varies greatly, from simple conditions such as headaches to more severe conditions such as leukemia, chronic pain management, weight loss, diabetes, rheumatoid arthritis and the treatment of HIV.

- Of the 52 drugs granted pediatric exclusivity, 45 (87 percent) were later subject to one or more labeling changes. Of these 45, one-third had alterations to the age limits for use;³⁹ two-thirds had changes to adverse event information; recommended dosages were modified in forty percent; and almost 30 percent had amendments to safety and efficacy indicators.
- In nearly one quarter, labeling changes included a determination that the drug had not been proven safe or efficacious for pediatric use (thereby requiring further pediatric studies); seventeen percent were not recommended for pediatric use and seven percent had changes to contraindication information. One drug was completely withdrawn from the market and 2 showed results that were not significantly different from placebos.
- Of the 52 drugs granted pediatric exclusivity, 19 percent involved one label change, 25 percent involved 2 label changes, 33 percent involved 3 label changes and 10 percent involved 4 label changes. None involved more than four label changes.

The literature on pediatric drug testing confirms the importance of an improved pediatric testing policy. Adams et al (Adams et al. 2001, 706) found that use of cromolyn significantly decreased the risk for hospitalization and emergency department visits for children with asthma. Whalley et al (Whalley et al. 2002, 1133) found that use of pimecrolimus to treat pediatric atopic dermatitis was associated with a significant increase in the quality life of caregivers. Gillman et al (Gillman et al. 2002, 687) found that the use of cetirizine to treat pediatric seasonal allergic rhinitis was associated with a significant increase in the health-related quality of life (physical, psychological, and social functioning and well-being) of the patient.

No studies were found that addressed the health impact of pediatric clinical trials in general since enactment of the pediatric safety law. However, we did find two relevant articles on the

specific impact of pediatric cancer clinical trials. Both Pratt (Pratt 1996, 169-172) and Caldwell et al (Caldwell et al. 2004, 808) address the significant advances made in childhood cancer survival rates and attribute this success to the large number and highly coordinated nature of pediatric cancer clinical trials. Cancer is one of the leading causes of death in children, second only to accidents for children over one year of age (Pratt 1996, 169). The reasons for testing cancer drugs specifically in children include: 1) cancers may present, progress and respond to treatment differently in children than in adults; and 2) toxicity levels and tolerance of treatment agents may also differ (Pratt 1996, 170).

Because of the compelling nature of cancer, almost all pediatric cancer patients in the U.S. are treated by physicians or institutions participating in the Children's Cancer Group or Pediatric Oncology Group, each of which conducts

national and international pediatric clinical trials (Pratt 1996, 170). This allows for substantial coordination and information sharing regarding the results of clinical trials and the resulting revisions to treatment protocols. The positive health impact of the large number and coordinated nature of pediatric cancer clinical trials in the US is undisputed: survival rates for some pediatric cancers, both in the US and internationally, have increased dramatically over the last 40 years. For example, the survival rate of acute lymphoblastic leukemia increased from 5% in 1960 to over 70% in 1996 (Pratt 1996, 169). The experience of pediatric cancer clinical trials in the US confirms the long-term health benefits of pediatric clinical trials. In light of this success, study authors report that "pediatric cancer trials offer a paradigm for pediatric clinical research" (Caldwell et al. 2004, 808).

2. Adherence to more appropriate drug regimens – a possible outcome of greater testing – would be associated with both improved health outcomes and lower pediatric health care costs

Few would disagree that increased pediatric testing and the resulting improvements in labeling should improve the quality of pediatric health care. Improved labeling may be expected to reduce inappropriate drug utilization, by identifying those circumstances in which the use of a particular drug is contraindicated in children or requires a previously unanticipated dose adjustment. Improved labeling should

also increase appropriate utilization of a particular drug therapy in situations in which testing prompts labeling changes that identify safe and efficacious use of drugs previously underutilized in pediatric populations.

Taken together these changes should contribute to improved standards of care, provided of course that they are adequately promulgated to

prescribers, and that prescribers modify their prescribing patterns accordingly. Significantly, we were unable to identify any literature that directly reported changes in prescriber behavior arising from labeling changes, and we found a similar lack of substantive, peer-reviewed literature on the effects of pediatric testing on health care costs associated with inappropriate drug use.

⁴² Age limit means either the approved ages were extended or they were shortened (i.e. was 12-18 years now 3-18 years or was 3-18 years now 12-18 years old).

Thus in order to model the impact of improved labeling on health care costs, we elected to use the impact of changes in patient compliance as a proxy for the effects of both reductions in inappropriate use of medication in children and increases in appropriate use. In this way we were able to estimate the associated health care cost savings arising from better health outcomes. In addition, given that inappropriate drug use often results in adverse drug reactions, we were also able to calculate the costs of hospitalizations resulting from adverse drug reactions, a cost that may be expected to be reduced to a significant extent with improved drug labeling.

While it is acknowledged that the assumptions made at each step introduce an additional level

of uncertainty in these estimates, the analysis is inherently conservative in that it assumes that more appropriate labeling will have an effect similar to a modest improvement in compliance. Moreover the analysis is limited to assessing the impact only in the treatment of asthma. While the most common chronic illness affecting children (6.2 million or 9% of children according to a recent GAO report), asthma is only one of several conditions for which inappropriate prescribing may be expected to contribute to unnecessary hospitalizations (GAO 2007). Asthma is the leading cause of hospitalization for children between 1 and 17 years old, according to a recent report from the Agency for Healthcare Research and Quality (AHRQ) (AHRQ 2005). In 2002 alone, AHRQ reported 128,000 asthma-related hospitalizations among

children, with a mean charge of \$10,400 for an asthma-related hospitalization. Noncompliance with clinical guidelines for asthma therapy results in a significant increase in the risk of an asthma-related hospitalization among affected children (Bauman et al. 2002). Therefore, an increase in compliance with clinical guidelines should substantially reduce the number of hospital admissions for asthmatic children, thereby generating significant cost savings.

The methodology below was employed to estimate the savings that would result from an increase in compliance with clinical guidelines:

Hospital costs associated with a pediatric compliance group =

$$P1 * P2 * P3 * N * C$$

Where P1 = % in the compliance group (low, medium or high)

P2 = % risk of hospitalization in that compliance group

P3 = % risk of hospitalization for the population⁴³

N = number of asthmatic children in the population (ages 1-17)

C = average hospital charge for asthmatic children (ages 1-17)⁴¹

The next step was to calculate changes in costs resulting from a shift of the low compliance group to medium compliance, and from a shift of medium compliance group to high compliance.

In addition, we relied on past studies to obtain aggregate estimates of direct medical costs

other than hospitalizations, as well as indirect costs due to childhood asthma (Weiss et al. 2001, 5). For non-hospital costs we assumed that non-compliance would result in similar effects as in hospital costs. Thus, we acknowledge the relatively imprecise nature of the estimates for the non-hospital component; for this

our estimates should be taken only as a reflection of relative order of magnitude.

⁴³ P3 needs to be included because the estimates for P1 and P2 from Bauman et al (Bauman et al. 2002) pertain to children likely to be hospitalized (conditional probability).

⁴⁴ We used data on all hospitalization costs for the U.S. population and children, and the age distribution hospitalized patients to extrapolate the average cost of a pediatric asthma-related hospitalization. In 2002 there were 128,000 pediatric asthma-related hospitalization and 404,483 total asthma-related hospitalizations.

⁴⁵ Further detail on methods and values are available from a technical appendix upon request.

⁴⁶ To adjust for inflation, we trended forward estimate reported in Weiss et al (Weiss et al. 2001, 5) for 1994 and 1998 using the medical component of CPI.

⁴⁷ Level of caregiver compliance was ranked on the following scale: high (no admission of noncompliance), medium (1 instance of noncompliance admitted), and low (>1 instance of noncompliance admitted).

⁴⁸ Calculation : Annual cost of ADR-caused pediatric hospitalizations for kids 1-17 years old

Hospital costs

The most recent year for which relevant hospitalization cost data were available was 2002. Dollar amounts for hospital and other medical care were trended forward to 2005 using the medical component of the consumer price index (CPI). The value of lost productivity was trended forward using the overall CPI. Results are given below.

Our analysis indicates that increasing compliance with prescribed medications would have

Value of Caregiver Lost Productivity

A previous study reported that pediatric asthma results in about 11.8 million missed school days. It was further estimated that, on average, this resulted in loss of caregiver productivity valued at \$108 per day (2005 dollars) (Weiss et al. 2000, 495). Assuming that increased compliance (in the same manner as described in our Methodology section) would have the same impact on the incidence of school days lost as on the incidence of hospitalizations, we calculated that an additional \$16 million dollars could be saved.

Asthma, All Sources

Given that asthma accounts for 1.82% of all hospital costs for children (AHRQ 2003), from the above we further calculated that about \$5.29 million in ADR-related savings in hospital costs may be attributable to asthma alone. Adding this to the previous components of cost savings associated with improved compliance and reduction in ADRs (hospital care, other

resulted in an 11% decline in asthma-related hospital costs for children (ages 0-17). In dollar terms this reduction amounts to \$96 million in 2005 dollars. Of this, about \$32 million would result from increasing compliance of low compliers, while \$62 million would be associated with increasing 'medium' or partial compliance to full compliance.

Cost Savings from Reductions in Adverse Drug Reactions (ADRs)

ADRs resulting from inappropriate use of medication are another potential source of morbidity and result in higher health care costs that should be reduced with improved drug labeling. It has been estimated that 2% of all pediatric hospital admissions are prompted by adverse drug reactions (i.e. asthma and others but excluding cancer-related ADRs and NICU admissions) (Mitchell et al. 1988, 24). Using national data, this implies that eliminating ADRs for children ages 1-17 could have potentially resulted in overall savings of \$290 million. (Note that

Other Medical Costs

Using a similar approach we estimate that increasing compliance would result in total asthma-related healthcare cost savings of 11% of the total cost of non-hospital asthma-related healthcare (excluding drug costs) for children in 2002, or about \$107 million (in 2005 dollars).

costs for newborns and children under one year of age are excluded since they are greatly susceptible to outlier costs.) Since hospitalization from ADRs cannot be fully corrected through better labeling (some ADR-related hospitalizations arise from other causes), this figure represents the strongest possible effect, since the literature does not allow for adjustment of ADR-related hospitalizations to reflect other causes.

duce all of the behavioral changes by consumers and providers needed to achieve all of the above cost savings, we note that our estimates should be taken as a lower bound, since they are based on rather conservative assumptions, (e.g. lowest compliance would not be raised to full compliance, productivity losses due only to lost school days); therefore, our estimates

= # pediatric hospitalizations (1-17yo) x % caused by ADRs x avg cost per hospitalizations
= \$ 256,650,000 in 2002 dollars = \$ 290,438,655.46 in 2005 dollars

Note however that this assumes full effect in reducing ADRs due to appropriate labeling. Values for the formula above were obtained information as follows: In 2002, there were 1.711 million hospital discharges for children 1-17 (AHRQ 2005, 12); In 2003, the average total charge for all pediatric hospitalizations was \$7,500. (AHRQ 2003, 35)

⁴⁹ It is acknowledged that there may be some overlap in ADR-related savings in hospital costs and those attributable to improved compliance as calculated in the previous section. However since the magnitude of ADR-related savings is small compared to the potential savings achievable through improved compliance, and the estimates of savings due to fewer ADRs are conservative, the impact of this potential "double counting" is likely to be small.

⁵⁰ Using similar methodology we calculated the hospitalization cost savings that would result from increasing compliance with medical regimens for additional conditions for which incidence and cost of hospitalization for the pediatric population were available from the literature. This yielded cost savings resulting from increased compliance \$53,649,046., \$45,016,973., \$48,756,239.36 (in 2005 dollars) for hospitalizations associated with pediatric pneumonia, pediatric affective or mood disorder, and pediatric epilepsy/convulsions respectively. Note However, that corresponding information for pediatric noncompliance could not be found for these conditions as had been the case for pediatric asthma; this required us to make an ad hoc assumption that the increased compliance for these medical conditions would result in the same percent hospitalization cost savings as the 11% hospitalization cost savings that was reported for pediatric asthma.

should be taken as a lower bound, suggesting the full level of savings is attainable through simple policy intervention. Moreover the cost

reductions we find for only one major medical condition, asthma (albeit from several sources) approximate the total savings in hospital costs

the FDA found for five medical conditions, suggesting a greater benefit from labeling than previously thought.

Social Benefits and Social Costs

Averted costs (savings) due to better compliance or reduced ADRs represent the potential benefits of pediatric labeling. Preliminary estimates suggest a total cost (in additional drug purchases) to the Federal government of \$150 million from 2008 to 2017 due to delayed generic entry under marketing exclusivity provi-

sions, with an additional \$26 million incurred by states over a similar period (CBO 2007). While comparing these costs with our estimates of benefits above (\$220 due to pediatric asthma compliance, and \$290 million due to reduced ADRs for most conditions, annually) is to some extent an “apple and oranges” comparison, the

orders of magnitude suggest that efforts to improve pediatric labeling may be cost effective from a societal perspective, even with market exclusivity arrangements such as those under the BPCA.

Table 3: Potential Annual Savings Due to Improved Pediatric Labeling (Asthma, Ages 1-17)⁴⁸

Source of Potential Savings:	Potential Annual Savings in millions (2005 Dollars)	Data Sources ⁴⁹
All Sources:	\$224.3	
Improved Compliance:		
Hospitalization Costs	\$96	Bauman et al, 2002; AHRQ Fact Book, 2003 and 2005; American Lung Association Fact Sheet, 2006
Other Medical Costs	\$107	Piecoro et al, 2001
Averted Caretaker productivity loss	\$16	Bauman et al, 2002; Weiss et al, 2000
Averted ADR:	\$5.3	Mitchell et al, 1988; AHRQ Fact Book, 2003 and 2005

CONCLUSION AND POLICY IMPLICATIONS

Although the direct federal cost associated with pediatric drug testing may have increased, countervailing considerations, if anything, point toward the need for expanded safety testing. Not only does broader testing respond to the growing demand for evidence-based care, but it also contributes to the growing focus on patient safety. To the extent that better testing ultimately leads to more cost-effective treatments

and therapies – through the substitution of less costly drug regimens for higher-cost and avoidable medical and institutional care – promoting a culture of safety ultimately is considered cost effective as well.

Perhaps the single most important factor that militates in the direction of greater emphasis on pediatric testing is the growing focus on patient

safety and medical error reduction as equally fundamental aspects of a national health quality policy. Achieving such basic reforms may entail societal investment in the research and studies that shed light on safe practices for the population as a whole, as well as sub-populations such as children, who are deemed particularly vulnerable to error and adverse events.

⁵¹ We wish to note an important caveat: the methods from the CBO Cost Estimate (CBO 2007) were not provided. Therefore these estimates remain to be verified.

⁵² A summary of these calculations is given in the body of the report.

⁵³ These references are the sources of the variables that were used to calculate the potential cost savings due to improved pediatric labeling. For complete references, please see attached bibliography.

⁵⁴ A recent New Yorker article focused on mental illness in children illustrates the degree of risk that can arise when children with serious mental health conditions are treated through inadequately tested prescription drug regimens combining multiple drugs over a prolonged time period. (Groopman 2007, 28-34).

In sum, improving pediatric drug safety policy is a compelling goal that justifies strong governmental investment. How this investment is made – through greater direct government investment in testing, greater regulation of testing by the pharmaceutical industry, incentivization of industry testing, or a combination of the three approaches – is a far broader question and one that transcends this specific analysis. This analysis does suggest that if adherence to appropriate drug regimens is viewed as a possible, downstream outcome of better testing, then incentives can be associated with important results in terms of both health outcomes and health care costs. Thus, incentivization, along with other policy interventions, can be viewed as one of an arsenal of policy levers whose aim is to improve the safety and quality of pediatric care.

Several observations are also worth noting. First, in view of what would appear to be a generous incentive, BPCA should be modified to create a more robust standard for testing. In our view, this more robust approach is warranted despite the existence of the government's direct regulatory authority over testing under PREA,

since the government tends to use its authority only to a limited degree. As a result, lawmakers might consider strengthening BPCA's incentivization approach by requiring manufacturers who elect not to undertake a requested test to submit clear and convincing evidence that pediatric testing would result in a direct and net loss to the manufacturer in comparison to the long term value of the incentive. Since pediatric exclusivity effectively means that government is paying companies – through higher drug pricing – to study the effects of drugs in children, the payment should result in a presumption of testing in our opinion in the absence of strong evidence that such an incentive in fact does not exist in particular cases. In some cases, incentives may be lucrative, while in others, they may be modest. But the fact that some cases of exclusivity are less profitable should not diminish the net value of the incentive. The key issue is the safety of drug use in children.

Second, this study does not compare government expenditures through incentives to the cost of alternative government approaches to pediatric drug testing through regulation and direct investment in testing. It may well be that

from a purely economic vantage point, it would be less expensive and more reliable for the government to simply underwrite the cost of pediatric drug testing and to move toward a policy in which tests that are believed to be necessary by the government's chief scientific body simply are performed. Indeed, in our opinion there is much to be learned about the government's use of its regulatory authority under PREA. Under what circumstances has the government used its PREA powers and with what results? What has been the health outcomes record in the case of pediatric use of drugs for which studies were recommended but indefinitely deferred? These questions all compel further research in the quest for an effective pediatric drug safety policy.

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