Better Medicines for Children: The Effects of Best Pharmaceuticals for Children Act (BPCA) and Pediatric Research Equity Act (PREA) on Pediatric Drug Development, Labeling, and Use

By

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Abstract

In recent times, as much as 75% of pediatric prescription drug use has been "off label," or used in the absence of FDA approval. Increasingly, this off label use came to be seen as problematic, since noble goals of protecting children as vulnerable research subjects had the unintended effect of making every child an inadvertent experiment. The Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act were passed by Congress in 2002 and 2003 respectively and reauthorized in 2007 to solve this problem.

But how successful have they been? We triangulate methods, reviewing literature, analyzing public documents, and content analyzing elite interviews, to evaluate legislative success. We conclude that the Acts are achieving their intended purposes, but we make recommendations to strengthen their success.
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The Problem

Pediatric therapeutics use is "off label" from 50 to 75% of the time (Roberts et al. 2003) because many commonly used medications lack U.S. Food and Drug Administration (FDA) approval for pediatric indications. The unique problem in pediatrics is that off-label use is frequently the only kind of use possible, because so many therapeutics lack FDA approval for pediatric indications.

In recent history, children have been viewed as too vulnerable to be research subjects, and a variety of such ethical and moral concerns have joined economic and liability questions to obviate drug safety and efficacy testing in children most of the time. This is, in part, because children represent a vulnerable population. Children are vulnerable because they are not "autonomous:" they cannot give informed consent. Additionally, "minimal risk" for adults is often judged to be "significant risk" for children. For example, additional blood samples required for an adult clinical trial pose minimal risk to an adult research participant, but drawing additional blood samples from a young child or infant for research purposes, rather than as a part of care, may pose more than minimal risk, or even significant risk. Thus, enrolling children as healthy controls has usually been seen as ethically and morally unacceptable (Office for Human Research Protections, Department of Health and Human Services 2000; hereafter DHHS).

The complicated nature of conducting pediatric clinical trials, the smaller target population compared to adults (as there are fewer "eligible" children because serious conditions are rare in children), and high cost paired with the lack of incentive for pharmaceutical companies (as many physicians would continue to prescribe off-label regardless of indication), have combined to discourage studies of more than a few drugs in the pediatric population.
Despite these challenges, we must do pediatric therapeutics research. Children who are treated with medications that have not been adequately evaluated in the pediatric population are at risk of known and unknown adverse events. Children are not "small adults;" further, growing children are not even like themselves a short time in the past. Children's developmental, physiological, and even genomic profiles vary across populations and are in an almost constant state of change. Children's rates of drug metabolism and toxicity profiles change as they grow and develop. For all these reasons, extrapolating from adult data to children is not an adequate solution.

The noble goal of protecting children, as vulnerable subjects, from the risks of clinical research has the ironic unintended consequences of leaving those who care for children with an insufficient evidence base, and of making every child an inadvertent experimental subject.

Current policy results from past abuses

Recent history is noteworthy because it sheds light on the latest policy changes. We might assume that the view of children as a readily exploitable source of research subjects would have changed following exposure of the notorious twin studies in Auschwitz, where one twin was subjected to an unthinkable experiment while the other served as control, and the adoption of the Nuremburg Code, which prohibited coercive research and research without consent. In fact, highly controversial research on children continued after World War II, exemplified by the Willowbrook School hepatitis experiments during the 1950s and 1960s in which healthy mentally retarded children were intentionally inoculated with the hepatitis virus and then monitored to gauge the effects of gamma globulin treatment. These events galvanized public sentiment against pediatric research and lead to the moral position that children must be protected from being exploited as research subjects. A virtual but informal prohibition on most research

These new federal controls on pediatric human subjects research, however, arose in an environment of explosive growth in the number of drugs, devices, and biologics available to physicians. The two phenomena intersected to produce an unintended consequence, immediately recognized by pediatricians (American Academy of Pediatrics 1977): when few children have been participants in therapeutic research, then virtually every child becomes an inadvertent experimental subject.

In 1979, the FDA first issued regulations that required the presence of pediatric information on the drug label and package inserts if the pharmaceutical company marketed the drug to children. If a drug had not been tested for safety and efficacy in children, then the label had to indicate as much. Unfortunately, this rule did not stimulate pharmaceutical companies to conduct pediatric testing, they simply chose to market drugs with labels asserting that the product had not been tested for safety and efficacy in children (Wilson 1999). Samuel Maldonado MD MPH, Vice President for Pediatric Drug Development at Johnson and Johnson, argues that the 1979 rule was not the FDA's intent to stimulate pediatric drug development. On the contrary, Dr. Maldonado said: "The pediatric section of the label was introduced as a subsection of the 'Precautions' section. It was as if the FDA was telling physician 'beware of the use of this drug in children'...[not] until the labeling reforms of 2007 did things change, but since this change is so recent, most labels still have their pediatric information under 'Precautions.' ...In any case, most pharmaceutical companies didn't intent to market or promote their product to the pediatric population because it was not commercially attractive to do so" (Maldonado interview, 2008).
By the mid-1990s, the FDA, the American Academy of Pediatrics (AAP), and others were beginning to quantify the dilemma (Roberts et al. 2003). Advocates for better information on the safety and effectiveness of therapeutics used in pediatric medicine pushed pediatric human subject research onto the public agenda again. This time, the policy question became one of considering how to move beyond prohibitions toward constructing policy to assure that pediatric research minimizes harm while producing maximum therapeutic benefits.

*The 1994 Pediatric Rule.* The 1994 Pediatric Labeling Rule was another attempt by the FDA to boost the amount of pediatric information contained in the label; there was some concern that the reason pharmaceutical companies didn’t respond to the 1979 version of the rule was because they thought they would actually have to conduct the pediatric studies in order to qualify for a label. The 1994 Pediatric Labeling Rule applied to already marketed drugs and introduced the idea that adult efficacy could be extrapolated to the pediatric population if the course of the disease and expected response to therapy were sufficiently similar in the adult and pediatric populations (Code of Federal Regulations part 201, 59 Federal Register 64240 1994; hereafter CFR). While the 1994 Pediatric Rule did not make any new efficacy testing mandatory, it did require companies to review their existing data to determine if they could lead to pediatric information, and they would still be required to do testing for dosing and safety. The 1994 Pediatric Rule maintained the requirement that any manufacturer who did not submit valid information about pediatric safety and effectiveness include a disclaimer on its labels that the drug had not been tested for safety and efficacy in children.

Unfortunately, this attempt to stimulate pediatric labels failed. An analysis conducted in 1998 concluded that only 15% of supplements submitted to the Agency in response to the 1994 Pediatric Rule resulted in adequate pediatric labeling (Rodriguez,
Roberts and Murphy 2003; CFR part 201 59 Federal Register 64240 1994). Samuel Maldonado told us that the "...reason for this apparent failure was that the Pediatric Labeling Rule presupposed that the data exited in the sponsor’s databases and that it was only a matter of forcing the sponsor to submit the data to the FDA. However, the assumption that the data existed was wrong. Sponsors could not submit what they didn’t have" (Maldonado interview, 2008).

**The FDA Modernization Act.** In 1997, President Clinton signed into law the FDA Modernization Act (FDAMA). Section 111 provides for 6 months of additional marketing exclusivity, often described as patent protection, for drug manufacturers who conducted pediatric studies on their products in response to a written request issued by the FDA (FDAMA 1997). This incentive, albeit not stand-alone until it was enacted separately as the Best Pharmaceuticals for Children Act in January 2002, is known as the pediatric exclusivity provision. The exclusivity provision is voluntary and applies to new or already marketed drugs. The 6 month period of market exclusivity is linked to the active moiety that may be present in many products, thus a sponsor who is granted pediatric exclusivity for conducting pediatric studies earns the exclusivity benefit for all products with the same active moiety that have existing patent protection, in particular its adult formulations, not just the indication for a new use and/or new population. Notably, the pediatric exclusivity provision does not require the manufacturer to seek a label change in order to earn the 6 additional months of market exclusivity. The provision only requires that the pediatric studies be completed in the requested timeframe and according to FDA specifications.

To further the study of off-patent drugs, the passage of FDAMA also required the FDA—in consultation with experts in pediatric research—to develop and publish a list of drugs, including off-patent drugs, for which additional pediatric information may be beneficial. The NIH lists these drugs annually in the *Federal Register* (DHHS NIH 72
Federal Register 14588 2007) and charges the National Institute for Child Health and Human Development (NICHD) with seeking contracts to develop the pediatric data analyses.

The 1998 Pediatric Final Rule. On the heels of the failed 1994 Pediatric Rule, the FDA published a new rule, the Final Rule, in December 1998, and it took effect in April 1999 (21 CFR Parts 201, 312, 314 and 601, 63 Federal Register 66632 1998). The 1998 Pediatric Final Rule required that any new drug or biologic application or supplement contain an assessment of the drug in the pediatric population unless a deferral or waiver is granted by the FDA. For example, it routinely granted such waivers for New Drug Applications for new drugs to treat benign prostatic hypertrophy (BPH), since BPH is not a pediatric condition. The Final Rule can be applied to new applications, including a new active ingredient, new dosage form, new dosage regimen, new route of administration, and new indications (except for orphan drugs). The deferral clause was intended to allow manufacturers to submit the required pediatric studies after submission of a biologic licensing application or NDA, e.g., when a new drug for adult use already has approval but before pediatric studies are completed. The main reason for the deferral clause was to avoid preventing adults from gaining access to beneficial drugs while pharmaceutical companies completed pediatric studies.

The Final Rule attempts to balance the needs of children with the needs of adults. The Final Rule also allows the FDA to require studies on drugs that are already marketed if, first, it is used in more than 50,000 pediatric patients for a labeled indication and there is inadequate labeling that could pose significant risk, i.e. drug products have substantial use in the pediatric population, or second, it is determined that the marketed drug will provide a meaningful therapeutic benefit over exiting treatments and the absence of adequate labeling poses a significant risk (Rodriguez, Roberts, and Murphy 2003).
Controversy leads to change: conflict over the Pediatric Rule

Although children's health advocacy groups, pediatricians, and some politicians supported the FDA's ability to make pediatric testing mandatory and considered the Final Rule to be a great victory, others did not. The Association of American Physicians and Surgeons, Competitive Enterprise Institute, and Consumer Alert filed a lawsuit in 2000 that challenged the authority of the FDA to promulgate the Pediatric Final Rule; they argued that it would delay new drug approval and give the FDA lawmaking power beyond the limits set by Congress. In November 2001, the American Academy of Pediatrics (AAP), the Elizabeth Glaser Pediatric AIDS Foundation, and the Pediatric Academic Societies filed an amicus curiae brief in the lawsuit supporting the Pediatric Final Rule.

In March 2002, under pressure from the Bush administration, the FDA announced a 2 year suspension of the Pediatric Rule during which time it would study whether the rule was needed in light of the passage of BPCA. Just one month later, the Department of Health and Human Services (DHHS) reversed this decision after strong objections from the children's advocacy groups and members of Congress. They announced that they would continue to enforce the Rule and defend it in court. In October 2002, the Pediatric Rule was overturned by Judge Henry J. Kennedy of the U.S. District Court for the District of Columbia on the grounds that the FDA lacked the statutory authority to promulgate the Pediatric Rule and that the Pediatric Rule and the BPCA were incompatible (Assoc. of Am Physicians and Surgeons v. US FDA 2002).
The Best Pharmaceuticals for Children Act of 2002

As it came to be, this decision was only a temporary interruption to the process of regulating pediatric drug development. The January 2002 enactment of the Best Pharmaceuticals for Children Act (hereafter BPCA) renewed and expanded the pediatric exclusivity provision in the FDA Modernization Act of 1997 (BPCA 2002). BPCA allows FDA to grant drug sponsors 6 months of additional market exclusivity in exchange for conducting and reporting on already approved and new drug studies.

BPCA also provides mechanisms for pediatric drug studies that drug sponsors decline to conduct. The process for initiating pediatric drug studies under BPCA formally begins when FDA issues a written request to a drug sponsor to conduct pediatric drug studies for a particular drug. When a drug sponsor accepts the written request and completes the pediatric drug studies, it submits reports to the FDA describing the studies and the study results. BPCA specifies that FDA generally has 90 days to review the study reports to determine whether the pediatric drug studies met the conditions outlined in the written request. If FDA determines that the pediatric drug studies conducted by the drug sponsor were responsive to the written request, it will grant a drug pediatric exclusivity regardless of the study findings.

The FDA may issue written requests for those drugs on the list that it determines to be most in need of study. When drug manufacturers decline written requests for studies of on-patent drugs, BPCA provides for FDA to refer the study to Foundation for the National Institutes of Health (FNIH) for funding. FNIH is a nonprofit corporation independent of NIH and supports the mission of NIH by linking private sector donors and partners to NIH programs. As of December 2005, FNIH had raised $4.13 million to fund pediatric drug studies under BPCA (US Government Accountability Office, GAO-07-898T 2007; hereafter GAO).
If the drug manufacturer declines or fails to respond to the written request, the NIH can contract for, and fund, the pediatric drug studies. Drug sponsors generally decline written requests for off-patent drugs because the financial incentives are considerably limited. A drug does not need to be on the list to be eligible for the exclusivity incentive.

**The Pediatric Research Equity Act Codifies the Pediatric Rule.**

In January 2003, the Department of Health and Human Services issued a press release that contained a list of 12 commonly prescribed drugs that needed to be tested for use in children for which government supported testing would begin that year (DHHS 2003). The list, to be updated each year, was developed by the National Institute of Child Health and Human Development (hereafter NICHD) in consultation with the DHHS' FDA and experts in pediatric research. Most written requests issued by the FDA have been for drugs on this list. The press release acknowledged that most of these drugs are no longer under patent and therefore not the exclusive property of any single drug firm. For this reason, the BPCA provided for government sponsorship of these pediatric drug trials.

The press release also announced that for pediatric testing of new drugs, DHHS would take separate action. Secretary Thompson announced that the administration would seek new legislation from Congress to establish without further question the FDA's authority to require pharmaceutical manufacturers to conduct appropriate pediatric clinical trials on new drugs and biologics. He said legislative authority would be pursued because it was quicker and more decisive than legal appeals. The press release pointed out that FDA earlier asserted its right to require such tests, but the U.S. District Court for the District of Columbia ruled against the agency in October 2002 (Assoc. of Am Physicians and Surgeons v. US FDA 2002).
In March 2003, Senators Dodd (D-CT), DeWine (R-OH), and Clinton (D-NY) introduced legislation, the Pediatric Research Equity Act (PREA) that would codify the 1998 Final Pediatric Rule (21 CFR 63 Federal Register 66632 1998). All three senators had long-established interest in improving pediatric research, and something like the PREA had been talked about before the Association of American Physicians and Surgeons v US FDA decision. In July 2003, the Pediatric Research Equity Act was unanimously passed in the Senate and in November 2003, PREA passed the House on a voice vote (PREA 2003). President Bush signed PREA into law in December 2003. Under PREA, the FDA has clear Congressional authorization to require drug manufacturers to conduct pediatric studies as part of new drug development if the drug has potential for use in the pediatric population.

**BPCA and PREA reauthorized in 2007**

The 2007 reauthorization of BPCA and PREA (BPCA 2007; PREA 2007) contains several noteworthy improvements. The criteria for applying PREA to already marketed drugs are enhanced. New language allows the FDA to use a “benefit” standard as opposed to a “risk” standard to require studies. When a voluntary study is declined by a drug company, the reauthorized version of PREA provides for an expedited 30-day review of private funding before referral of declined written requests to PREA. The 2007 reauthorization also increases the authority of BPCA; it allows the FDA to issue one study request for more than one use of a drug and to capture both on- and off-label uses and to ask for preclinical studies as part of the written request. Once studies and/or assessments have been conducted under BPCA and PREA, the Secretary must make a determination whether the drug studied is safe and effective in pediatric populations or subpopulations, including whether the results are inconclusive. The label must then
include the information about whether the study results were positive, negative, or inconclusive along with a statement of the Secretary's determination.

The 2007 reauthorization contains several mandates to increase the transparency of programs and the dissemination of pediatric information. The FDA is required to make BPCA written requests public after the drug has been granted exclusivity, to track the number and type of studies completed as well as labeling changes and other data resulting from BPCA and PREA. The Secretary must also now make publicly available the actual medical, statistical, and clinical pharmacology reviews for studies completed under BPCA and PREA (not just the summaries). Drug companies that conduct studies under BPCA and PREA must provide physicians and other health care providers with new pediatric labeling information annually.

The review and oversight of BPCA and PREA have also been strengthened; new language establishes an internal FDA review committee for BPCA and PREA and asks the Institute of Medicine to review past study requests, make recommendations to the FDA for future study requests, and make recommendations for incentives to encourage the study of biologics in children. The Government Accountability Office (GAO) is also required to produce a report on the results of BPCA and PREA with recommendations for improving the programs.

Safety reporting has also been strengthened; manufacturers must submit all post-market adverse events as part of the BPCA exclusivity provision. Drugs studied under PREA are also subject to mandatory adverse event reporting and one-year review by the Pediatric Advisory Committee. The Pediatric Advisory Committee is extended through October 1, 2012.
The Current Landscape of Pediatric Research

It is apparent that initial efforts to regulate and stimulate pediatric drug development were weak, calling for voluntary action, and action on already approved or off-patent drugs. Subsequently, two laws, the Best Pharmaceuticals for Children Act (BPCA 2007) and the Pediatric Research Equity Act (PREA 2007), were enacted to incentivize, and then require, the pharmaceutical industry to conduct pediatric clinical trials and improve pediatric drug labeling. These acts evolved over the past decade and most recently were modified and reauthorized in 2007. BPCA is commonly referred to as a "carrot," that is, an incentive that rewards sponsors with a six month period of market exclusivity in the form of a patent extension for conducting pediatric studies and reporting the results in a timely fashion. PREA codified the Pediatric Final Rule and is commonly referred to as a "stick" that requires sponsors to study the safety and effectiveness of all new drugs and biologic products for their claimed indication, dose, and method of administration in all relevant pediatric subpopulations, unless a deferral or waiver is granted by the FDA. Both acts are meant to increase the safety of pediatric prescribing and improve the quality of the drug label information available to pediatric providers and families.

In less than a decade, we have moved from a position of testing very few therapeutics in pediatric populations – the leading exceptions being vaccines, where pharmaceutical companies' markets were large enough to justify surmounting research obstacles – to 842 requested studies (357 Written Requests) projected to include over 49,000 pediatric patients (FDA Pediatric Exclusivity Statistics, Breakdown 2008). The BPCA has led thus far to new labeling for pediatric indications on 148 previously approved drugs as a result of written requests from 1998-2007 (FDA Pediatric Exclusivity Statistics, Label Change 2008). In addition, PREA has motivated 64 pediatric
indications on newly approved drugs since 2002 (FDA Pediatric Exclusivity Statistics, PREA 2008).

The hard numbers suggest that BPCA and PREA have stimulated pediatric research. Although this may be true, our policy analysis of the issue uncovered several points that warrant further evaluation and policy recommendations. First, we critically analyzed the success of the legislation by way of review of the biomedical literature, public documents, and analysis of structured interviews with elite stakeholders who are especially knowledgeable about the effects of the laws. The interviews revealed that the success of the laws is more complex than the number of requested studies and subsequent label changes. For example, we considered whether the pediatric studies are conducted in the most commonly prescribed pediatric drugs, or whether the pattern of study correlates more directly to the economic value of the incentive when it is linked to the active moiety in the adult indication. Second, even if the numbers indicate the laws have been successful, we feel it is critical to consider whether the results of such studies will actually influence caregivers' prescribing practices. The studies are meaningless and their results are not helpful to the practice of medicine if caregivers do not have sufficient and user-friendly access to the study results and, more importantly, can consistently apply the results to their pediatric patients. The crux of this issue rests on whether or not physicians and other prescribers reliably use the drug label as a source of information, and if not, what can be done to ensure they have access to and actually utilize a summary of the new safety and efficacy findings that result from studies conducted under BPCA and PREA.

We uncovered another central question: Who should pay for these pediatric studies? The current incentive system is structured such that although the drug manufacturers fund the up-front cost of the studies, the taxpayers indirectly fund the incentive by paying higher costs for brand name medications while the production of
generics is halted until the expiration of the exclusivity provision. Although the cost to conduct pediatric studies can be high, and appears to be rising, where should the economic burden rest?

The elite interviews also revealed a dilemma faced by drug manufacturers and contract research organizations: how can they conduct the studies requested by the FDA successfully and ethically? The increased demand for pediatric studies highlights the need for clear ethical standards, particularly as they relate to the use of placebo, especially in the context of increasingly globalized clinical trials.

Finally, structured elite interviews and the systematic review suggest that we are still far from an ideal world in pediatric clinical research. Several research areas are insufficiently addressed by the current legislation. We conclude with policy recommendations about disseminating information, addressing unmet therapeutic needs, and improving the incentive structure.

**Methods and Hypotheses**

We used standard policy analysis methods to study the effects of the Best Pharmaceuticals for Children Act (BPCA) and Pediatric Research Equity Act (PREA) on pediatric drug development, labeling, and use. Policy analysis combines qualitative and quantitative approaches and is a triangulation of methods, including a review of biomedical literature, review of public documents, and content analysis of interviews with key elite stakeholders from carefully selected local and national organizations (Auerbach and Rockman 2002; Berry 2002; Goldstein 2002; Hochschild 2005)

We conducted a systematic review of the biomedical literature, and its results are presented in the next section. We also reviewed public documents, including public laws, the official FDA website, court testimony, and the Code of Federal Regulations.
Elite interviews
We conducted structured interviews with elites who represent the four domains of government, academe, industry, and advocacy, to triangulate perspectives on policy behavior. We identified 17 elites, using a combination of positional and reputational selection criteria, who were most likely to have critical insights into the policy process. We did this in order to impose a "process tracing" structure on the analysis. "Process tracing" is deliberately non-probabilistic in its sampling, since the objective is to trace the causal mechanisms in the emergence of a policy; with such a research purpose, anything like a "random sample" of elites risks missing those who have the most knowledge of the policy. Instead, "process tracing" depends on enough familiarity with the policy to be able to identify the specific positions from which elites might have the broadest, best-informed perspective on policy development (Tansey 2007). Our 17 requests for interviews produced 11 completed in-depth telephone interviews (see Appendix 2 for the list of respondents by position and date of interview, and Appendix 3 for the interview protocol). The 6 elites who did not permit interviews either did not respond to our request or did not feel comfortable being interviewed, or we could not arrange a convenient date for the interview. Of the 11 interviews, 3 were from academe (Duke University, Cincinnati Children's Hospital, Dartmouth), one of whom had also had industry experience, and another had had government experience. Two elites were from advocacy (American Academy of Pediatrics), 2 were from industry (Quintiles and Johnson & Johnson), 2 from government (FDA and the National Institute for Child Health and Development), and we obtained one additional interview from an elite who represented two domains: she had been an advocate for pediatric research as an officer of the Elizabeth Glaser Pediatric AIDS Foundation while the legislation was being developed, but she had become a staff member in the House of Representatives Energy and Commerce Committee by the time of the interview. As this discussion, Appendix 2,
and their subsequent comments all make clear, these elites are intimately familiar with, and in some cases helped to shape, the BPCA and PREA, and give us the best opportunity of identifying policy causes and likely effects (Auerbach and Rockman 2002; Hochschild 2005).

We designed the structured interview template to contain 6 questions, with follow-up questions, to test two original hypotheses. The first hypothesis was that BPCA and PREA in their current forms have had minimal effect on pediatric drug labeling. More specifically, we hypothesized that the number and significance of label changes under PREA has been limited, and that few drugs eligible for market exclusivity under BPCA have achieved this endpoint. The rationale for this hypothesis is that BPCA is a voluntary incentive, and, although the consequences of non-adherence to PREA (or failure to submit the assessment as requested) are such that the drug may be considered misbranded and subject to relevant enforcement action, the FDA has not yet imposed such draconian action, and we felt the mere threat may not be severe enough to motivate pharmaceutical companies to carry out the necessary testing. Pediatricians are accustomed to off-label prescribing and are likely to continue to do so for the foreseeable future, because even with the new laws, off-label use is still the most common prescription drug use in pediatric medicine.

Further, it is possible that many manufacturers completed pediatric studies in order to get six month market exclusivity provisions for adult label indications, but had no apparent intention ever of seeking a pediatric label indication for a previously approved drug. Finally, the BPCA incentive is not necessarily highly lucrative for sponsors (Li et al. 2007), because the cost of conducting the necessary trials is high, and the likely profit from marketing to the pediatric population may be low. Members of Congress (such as Senators Dodd, Clinton, and DeWine) recognized the limits of BPCA’s inducements and punishments, and tried to ameliorate those weaknesses with the passage of the PREA.
which would at least compel pediatric labeling for new drugs. Subsequent reauthorizations of both acts have reiterated the pediatric requirements for new drugs, but have not mandated pediatric studies in previously approved drugs unless the DHHS Secretary determines that a drug can confer benefit to a pediatric patient, and can therefore require pediatric studies.

The second original hypothesis was that the most recent amendment to PREA and BPCA, a mandate that drug labels include all study results along with the FDA’s determination as to whether the clinical trial results were positive, negative, or inconclusive, may further discourage sponsors from conducting the appropriate trials. Inclusion of negative information on the drug label, such as “Irbesartan, in a study at a dose of up to 4.5 mg/kg/day, once daily, did not appear to lower blood pressure effectively in pediatric patients ages 6 to 16 years,” (Bristol-Myers Squibb 2007) may cause drug manufacturers to be reluctant to perform pediatric clinical trials in already marketed drugs, as such information could negatively affect their economic success in the pediatric market, particularly when physicians practice in a climate where off-label prescribing is commonplace and will likely continue regardless of whether pediatric studies are conducted.

The interview fact sheet, protocol, and consent were approved by the Public Health-Nursing Institutional Review Board at the University of North Carolina. The interviews were transcribed and the transcriptions were systematically coded to capture counts, concepts, and illustrations.

Systematic Review

I performed a PubMed search using the keywords, “pediatric” and “exclusivity” and “legislation.” This search returned abstracts for 15 research articles. I reviewed the list to ascertain that it contained “sentinel articles.” I then performed a second PubMed
search using just the keywords, "pediatric" and "exclusivity." This search returned 9 additional research articles. I used the following inclusion criteria for abstract review: mention of pediatric exclusivity, the Best Pharmaceuticals for Children Act, pediatric drug labels, or the ethics of conducting research in children. I did not review abstracts if they were not available, if they were not written in the English language, and/or full text was not available online. These inclusion/exclusion criteria left 13 abstracts for which I then performed full article review. Two additional abstracts were identified by hand-searching the reference lists of the original articles. In summary, I identified 3 original research articles, 1 systematic review, 2 policy analyses, and 7 review articles. The table of evidence resulting from the systematic review appears as Appendix 3.

I reviewed the articles according to study design, appropriateness of use of study design, results, quality of results, and overall conclusion about quality – poor, fair, good, excellent – of evidence. Criteria for each overall conclusion category were as follows: excellent = very thorough article with no apparent bias; good = less thorough with no apparent bias; fair = limited scope and/or biased; poor = inaccurate and/or biased. As the majority of the articles identified were either review articles or policy analyses, I used special consideration for the evaluation of bias. If the author’s point of view was clear and transparent, he/she dealt fairly with the evidence, even if it opposed his/her perspective, and policy recommendations were grounded in appropriate evidence, then I graded the article as non-biased. I assessed in original research articles by evaluating for confounding, selection, and measurement bias. I constructed an evidence table to summarize the findings of the systematic review. Of note, full text of the additional abstracts identified by hand-searching of the reference lists was not available for review, but the abstracts contained relevant information and were included in the evidence table.
Legislative Success

The numbers suggest success

BPCA and PREA have stimulated many pediatric studies and label changes; as of June 2008, 842 requested studies have been requested (357 Written Requests) and are projected to include over 49,000 pediatric patients (FDA Pediatric Exclusivity Statistics, Breakdown 2008). BPCA has led to new labeling for pediatric indications on 149 previously approved drugs as a result of written requests from 1998-2008 (FDA Pediatric Exclusivity Statistics, Label Change 2008). In addition, PREA has motivated 64 pediatric indications on newly approved drugs since 2002 (FDA Pediatric Exclusivity Statistics, PREA 2008).

The success of BPCA is often quoted in the literature, “This incentive has been a driving force stimulating the conduct of pediatric studies” (Roberts et al. 2003, 906). Li and colleagues said “This program has been successful from many perspectives resulting in a substantial increase in pediatric drug research compared with the very limited amount of such research before pediatric exclusivity” (2007, 480). The success has also been represented under oath at the court hearing for the 2007 reauthorization of BPCA and PREA. The testimony of Samuel Maldonado, Vice President of Pediatric Drug Development at Johnson & Johnson, said “No regulatory effort or legislation before these has come close to stimulating the kinds of advancements in pediatric drug safety and effectiveness that we’ve seen over the past decade” (2007). In the course of conducting this policy analysis, we reached a similar conclusion: more pediatric clinical trials have been conducted since the passage of BPCA and PREA than were conducted before the laws were on the books.

The significance of the results of studies completed under BPCA and PREA is also often quoted in the literature, “In nearly half of the drugs studied, there were
unexpected results in dosing, safety, or efficacy compared with adult studies, including failure of half of the antihypertensive dose-response trials, which are pivotal for deriving dosing recommendations" (Benjamin et al. 2008, 834). Mathis and Iyasu (2007, 133) described what probably was the set of trials attracting the most media attention, that of the SSRIs:

Following the presentation of the pediatric safety reviews to the Pediatric Advisory Committee, stronger warnings were added in labeling for all five of the selective serotonin reuptake inhibitor (SSRI) antidepressants studied under the BPCA because of an increase in suicidal thinking in children and adolescents taking this class of medication. A warning was also added regarding the neonatal withdrawal syndrome, identified in infants born to mothers using SSRIs in the third trimester.

Our initial conclusion, then, and the judgment of the experts, is that our original hypothesis is not supported: numerous important dosing and safety and efficacy findings – or the lack thereof have made their way into drug labels as a result of studies conducted under BPCA and PREA.

Across the board, the elite stakeholders also shared this sentiment. All 11 respondents agreed that BPCA was generally an attractive “carrot” for sponsors. 7 had a strongly positive global impression of BPCA and 4 had a positive impression. Their opinion of the success of BPCA is best summarized by a quote from pediatric pharmacologist Daniel K. Benjamin, MD MPH: "...the only people who don’t believe the program has been a success are...the kind of people who say the world is flat" (Benjamin interview 2008).

Further, although the BPCA does not require a label change for the drug manufacturer to earn market exclusivity (the requested studies only need to be
conducted within the requested timeframe), the elites generally did not believe that pharmaceutical companies had frequently “gamed the system,” that is, conducted the requested study to earn market exclusivity without ever intending to seek a pediatric label indication. Three elites estimated that this occurred about 10% of the time, but pointed out that if a pharmaceutical company carried out the requested studies and there was not a resultant label change, it could have been a consequence of a prolonged review process at the FDA or the determination that the data were not worthy of the label. Other elites did not try to estimate a number, but used language like "in a few instances." Samuel Maldonado of Johnson and Johnson said "the FDA has also evolved on this matter. We in J&J conducted a program under BPCA and gained exclusivity but the FDA refused to include the results in the label. A new Division Director had taken the lead of the Division by the time the results of the study came out, and he disagreed with the Written Request issued by the FDA years earlier. Maldonado thought that this kind of "anomaly" spurred Congress, in its 2007 reauthorization of BPCA, to require the inclusion of pediatric studies regardless of their outcome a part of the label.

**Which drugs are actually being studied?**

Critics of the pediatric exclusivity provision question whether the pattern of study correlates with the most commonly prescribed pediatric drugs or the most commonly prescribed drugs in the adult market. Such suspicion results from the fact that the economic value of the incentive can be highly lucrative because it applies to all approved uses of the drug, not just those studied in children. Therefore, even if the studies find that the drug is not safe for use by children, the drug will still receive extended market exclusivity for the adult uses of the drug. At least one elite in industry, Dr. Maldonado, argued that a finding that the drug is not safe for children can spare significant morbidity and mortality in children. Many of the drug misadventures that occurred in the past and
lead to mortality in children, he argued, would not have happened in today’s environment in which knowledge is generate under a controlled clinical trial (Maldonado interview 2008).

Boots et al (2007) conducted a systematic search of the literature to identify drug utilization patterns in children. They found that from July 1998 to August 2006, 135 drug entities were granted pediatric exclusivity. The most frequent drug groups granted exclusivity were anti-depressants and mood stabilizers, ACE inhibitors, lipid-lowering preparations, HIV antivirals, non-steroidal anti-inflammatory, and anti-rheumatic drugs. In contrast, they found the most frequently used drugs by children are respiratory, systemic anti-infectives, and dermatologicals. They acknowledge limitations in their definition of essential drugs for children and that the method employed in the literature search may have introduced some bias toward outpatient drug consumption, thus underestimating the use anesthetic or cardiovascular drugs.

Boots et al note that the drugs granted pediatric exclusivity include 5 out of the “Top 10” prescription drugs with the highest sales figures in North America in 2005: atorvastatin (Lipitor), simvastatin (Zocor), omeprazole (Nexium), lansoprazole (Prevacid), and sertraline (Zoloft). Sales of these 5 drugs amounted to $24.1 billion US in 2005. (IMS National Sales Perspectives 2005) Somewhat on the contrary, a report from the Tufts Center for the Study of Drug Development published in the same year noted that less than one-half of the medicines awarded pediatric exclusivity are in the top 200 selling drugs (Tufts Center for the Study of Drug Development, 2005).

These apparent discrepancies could be due to bias or there could be validity in the numbers. Perhaps the reality is that a handful of blockbusters earn pediatric exclusivity and subsequent windfall profits while the majority of drugs that are awarded pediatric exclusivity are smaller market.
According to Boots et al, the majority of drugs granted pediatric exclusivity are rarely used by children, and drugs that are frequently used by children are underrepresented in the pediatric studies to obtain exclusivity. The authors conclude, "Many drug studies in children have been performed since the introduction of the FDAMA. However, children infrequently use the drugs granted pediatric exclusivity. The priorities for pediatric drug research should be set by the need of the patients, not by market considerations." (2007,849) To remedy this situation they recommend a portion of the public funds generated by postponement of generic replacements and price reductions be funneled away from the drug manufacturers and applied in an alternative manner.

Dr. Maldonado argued that the drug companies have the expertise and infrastructure to conduct pediatric trials, and that the market opportunity alone creates the incentive to do such studies, but that the BPCA can stimulate studies where market incentive alone is not enough.

As the Maldonado comment suggests, the BPCA incentive may be particularly important where market incentives are weaker, especially with generic drugs. Few of the off-patent drugs identified in the initial Pediatric Off-patent Drug Study (PODS) lists produced by the Secretary of HHS have been studied to date, despite the potential to obtain contracts to do the studies from the National Institute of Child Health and Human Development (NICHD). As with the PODS list, the BPCA provides for NIH to fund studies when drug sponsors decline written requests for off-patent drugs. By 2005, NIH had identified 40 off-patent drugs it recommended be studied for pediatric use. By 2005, FDA issued written requests for 16 of these drugs, and all but one of these written requests were declined by drug sponsors. The NIH funded pediatric drug studies for 7 of the remaining 15 written requests declined by drug sponsors through December 2005 (US GAO, GAO-07-898T 2007). Maldonado of J&J said that they declined the request
to study one drug, Ketoconazole, because they were advised that its use was no longer standard of care in the US and was not part of the WHO formulary, reducing the likelihood of its use in the rest of the world (Maldonado interview 2008). This does raise the question of determining how off-patent drugs are selected as drugs for which NIH will request studies.

The GAO report cited above describes several reasons the NIH has not pursued the study of some off-patent drugs that drug sponsors declined to study. These include concerns about incidence of the disease that the drugs were developed to treat, the feasibility of study design, drug safety, and changes in the drugs' patent status. If the NIH is unwilling to conduct such trials, it is not surprising that drug manufacturers are unwilling to conduct them. The success of "requested studies" as a strategy to induce more research seems questionable if the requests are not well justified.

The use of placebo in pediatric clinical trials

The issue of the feasibility of this approach to generating more studies was also raised by two other elite stakeholders. An academic pediatrician who also has global industry experience said that "Many of us felt that asking NICHD...to develop medicines when written requests were turned down didn't make much sense, because the vast majority of the time, the fact that written requests were turned down...were just timing issues. The companies realized there was no way to could complete a study with the year and a half remaining on exclusivity. But most of the reasons for turn-down was that there was no way to study the disease. The studies in the written requests were undoable." An elite from the pharmaceutical industry echoed his concerns, "The FDA, the regulatory bodies...are writing written requests...And many of them...absolutely cannot be performed. Or yes, they can be performed, but it will take about 5 years...Or the patient population that they are looking for us to study doesn't exist in the United..."
States or the Western world... because we have access to certain medications or a certain standard of care that precludes doing the trial... So that forces us to think about going to other areas to do it which then becomes an ethical issue... especially if it is a placebo-controlled trial. So I think the lynchpin is making sure there is sort of a thoughtful design put forward in the written request."

We examined a sample written request for the study of antidepressants in children (FDA Written Request for Antidepressants 2003). The written request is available on the FDA Pediatric Drug Development website. The FDA acknowledges that the written request is a sample and not an actual written request. Nonetheless, the written request is for several studies including pediatric efficacy, safety, and pharmacokinetics. For the efficacy studies, the FDA requests, "two randomized, double-blind, parallel group, placebo-controlled acute treatment trials, with a recommended duration of at least 6 to 8 weeks." The study population is children (ages 7 to 11) and adolescents (ages 12 to 17) with major depressive disorder.

Although this written request is an "N of 1," it illustrates the research challenges inherent in placebo-controlled study requests. It is likely that many parents and pediatricians would be uncomfortable enrolling a child or adolescent with major depression on a placebo-controlled trial, even if the placebo arm entailed increased frequency of visits or additional support and/or counseling beyond the usual standard of care.

Similar concerns have arisen in actual pediatric antihypertensive trials, and Pasquali et al. examined the pros and cons of 4 different designs in the study of pediatric antihypertensives (2002). They describe a design where patients are randomized to placebo or 1 of 3 different doses of the test medication and note that the placebo-controlled design could lead to recruitment problems because parents are often uncomfortable with the possibility that their child may be placed on placebo. Although
the 3:1 randomization scheme makes it three times more likely that the child will receive active drug, some parents may still have significant concerns about their child's participation, especially if the trial drug is available off-label (Vitiello and Jensen 1997).

The practice of placebo controlled studies in pediatrics has recently been addressed in the literature (Benjamin et al 2008). In their analysis of failed pediatric antihypertensive trials, the most common antihypertensive trial design was "type C" in which the use of a true placebo arm is avoided, while adding the power to obtain interpretable results regardless of the outcome of the trial. A type C trial employs randomization to 1 of 3 doses of the test medication. In addition, it includes a \textit{randomized withdrawal phase}. At the end of the 2 week treatment period, patients are re-randomized to continue on their assigned treatments or to be withdrawn to placebo, with close follow up and withdrawal to open-label treatment at the discretion of their physician. Benjamin et al. conclude that because the exclusivity provision is not dependent on product safety or efficacy, feasibility is of far greater importance to sponsors than optimal trial design. Eligibility for exclusivity regardless of outcome is a major advantage of type C trial design, because it is considered interpretable regardless of outcome; avoiding the use of an explicit placebo arm makes this type of trial more appealing to parents of potential subjects and institutional review boards.

\textbf{BPCA and PREA work best together}

The elite stakeholders had less enthusiasm and a less positive global impression of PREA; several of them noted that the two laws work best together, using phrases such as "inextricably linked" or "synergistic." Dr. Maldonado of Johnson & Johnson noted, "I have to say for the most part PREA is there for those companies that are reluctant to...do what's right for children...I see the value of PREA. I think PREA alone might not be as effective as BPCA. You get compliance, but you don't get people,
thinking around a room out of the box... what can we create?... that is beyond PREA and things like that happen because of BPCA. So, most of pediatric drug development so far in the last 10 years has been really the engine has been BPCA and not PREA" (Maldonado interview 2008). We believe the respondents have this opinion because PREA only requires a pediatric assessment for those conditions being studied in adults and in which significant use or benefit in pediatrics is expected.

**PREA gets the ball rolling.** Several respondents noted that one of the most effective components of PREA is that unlike BPCA, it stimulates conversation between the pharmaceutical company and the FDA early in the drug development process — a potentially critically important effect of the policy.

**How similar are children and adults?**

Under PREA, the Secretary may conclude that pediatric effectiveness can be extrapolated from adequate and well-controlled studies in adults. This begs the question of whether the disease being studied and the effects of the drug are sufficiently similar in adults and pediatric patients. One of our academic experts said that "the issue in being limited to the adult indication is the confidence with which we can say that the adult indication is indeed representative of the pediatric population. For example, let's say the adult indication is rheumatoid arthritis. Is JRA (Juvenile Rheumatoid Arthritis) the same or not? And that's what we get into, in the FDA's attempts to use extrapolation of efficacy. Is the disease sufficiently similar? And again that goes to, often our lack of understanding of disease mechanisms. The disease that looks to be typically sort of like the same thing in adults and kids may not be the same disease at all... Those are active scientific discussions. But at least the agency has the authority to ask the company 'and what is your pediatric plan?' "
It is likely that as more clinical trials are conducted in pediatrics, the scientific community will gain a better understanding of the metabolic, genomic, and developmental differences between adults and children—even between children of varying age groups. However, a determination of whether a disease and its treatment are sufficiently similar in adults and children is complex and possibly fraught with danger. This issue is one that will likely not be amenable to further legislative amendment, but highlights the need for extreme caution on the part of the research community.

**Do the study results reach practitioners?**

The ultimate determinant for the success of these laws is not only whether they stimulate the conduct of pediatric studies, but also *whether the data they generate are accessible to caregivers and ultimately, applied to pediatric patients*. Benjamin and colleagues comment, “The pediatric exclusivity program has been successful from many perspectives, including labeling, with over 100 labeling changes to date. However, the subsequent dissemination of results in the peer-reviewed medical literature has not been previously quantified. Because few pediatric studies are performed for products primarily approved and marketed for adults, it is important that the information obtained from such studies be readily available. One standard for dissemination of human experimentation results is publication in a peer-reviewed journal” (2006, 1267). Benjamin et al. enumerated the publication of main study results in peer-reviewed journals for studies conducted for pediatric exclusivity between 1998 and 2004. They found that only 113/253 (45%) of the studies were published in peer-reviewed journals. A positive labeling change such as “safety and effectiveness established” and “approved for use in children” (versus a negative labeling change such as “no meaningful clinical activity”, “black box warning”, and “increased mortality reported in the product compared to placebo”) was observed for 127/253 (50%) of studies. Efficacy studies and studies that
resulted in a positive labeling change were more likely to be published. Further, they found that there were 100 clinical trials associated with a key labeling change (defined as a study that resulted in substantive dosing changes, new safety information, or lack of efficacy in phase III testing), but only 37 were published. There were 48 trials that did not result in a labeling change (40 from completed submissions and 8 associated with products that were withdrawn from the market or the application was withdrawn), and only 19/48 (40%) were published. Thus, 3,804 children were enrolled in 29 clinical trials for 16 products resulting in no labeling change and no dissemination of results. They conclude that dissemination of the results of these studies, particularly in peer-reviewed journals, is critical to ensure pediatric public health. To address this problem, they propose that Congress consider linking part of the incentive for completion of pediatric clinical trials to publication of the results in a peer-reviewed journal, an idea that stimulated considerable disagreement among our elites, some of whom strongly support the idea, and others of whom believe attempting to force peer-reviewed publication is not feasible, not the least because of established publication bias against publishing negative findings.

The literature on dissemination of the results of studies completed under BPCA and PREA is sparse, but the Benjamin et al. report raises two important issues. First, the proportion of clinical trials completed under BPCA and PREA that are published in peer-reviewed journals is unacceptably low. Second, the ethics of enrolling children on clinical trials is undeniably linked to their publication. The lack of peer-reviewed publication of pediatric clinical trials is unfair to the research subjects and the pediatric population at large.
Will an all-inclusive label affect practice?

As noted, the 2007 reauthorization of BPCA and PREA requires that the DHHS Secretary order the labeling of the product to include information about the results of the study, including inconclusive results, and make a determination on whether the drug is safe and effective in the pediatric population. Thus, the label is a legal document that contains information about the results of the studies. This could possibly aid dissemination of information, but the several questions follow: 1.) Do pediatricians actually read the label? 2.) Is it possible that valuable information is not published in the label?

Several of the elite respondents raised this concern during the interview. Dr. Dianne Murphy, Director, Office of Pediatric Therapeutics, FDA commented "...the problem of course is that we don't usually use the label, we use our Harriet Lane or we use some other little thing that will fit in our pocket...And so I think it's a really important part of training and for the American Academy of Pediatrics to make pediatricians understand that the label is not your father's label...the label now for children is changing dynamically. . . and it's going to have more information than the adult label will ever have about negative studies, and you need to be looking at it. It's a rich resource for you, and you need to begin to think of it as part of the way you approach therapeutics" (Murphy interview 2008). Dr. Robert Ward, Director of the Pediatric Pharmacology Program and Professor of Pediatrics at the University of Utah, further commented: "And for years the Physician's Desk Reference and the drug's label was virtually useless . . .to a pediatrician. When I was a Fellow in clinical pharmacology in the 70's, we considered it a doorstop. And now it would provide a fairly accessible source of information" (Ward interview 2008).

To be sure, the label is not necessarily the only information source that prescribers and researchers need to incorporate into to their practice. This idea was
reinforced by Dr. Maldonado: 

"...There is a lot of good knowledge out there, published in peer-reviewed journals...that is very good, but it will never be worthy of a label. I know what it takes to be worth the label...And that doesn't mean that the academic knowledge is not good....It is just that...it's been planned and designed in a way that is not acceptable by the standards of the FDA. Not to say that the standards of the FDA are higher than academia. They are different....So there is a good knowledge out there that probably won't ever be worthy of label, and if we focus on label, we are really missing the boat..."

When considered in combination with the Benjamin et al. findings (2006), it is clear that some meaningful data that are published in the peer-reviewed journals are never published in the label and vice versa. This lack of consistency puts both prescribers and pediatric patients at risk. The comprehensive list of label changes posted on the FDA website is an attempt to address this problem, but again, its success is dependent upon whether prescribers are aware of the listing and incorporate regular review into their practice.

We conclude that the label contains essential information, but it may not contain all of the information. Respondents repeatedly noted that the pre-specified goals of the writers of these laws were to stimulate labels, but if there was no resultant label, the data could be just as useful. Therefore, physicians must consider using the label as a source of prescribing information. Alternatively, and more likely to reach the masses, peer-reviewed publication of study results should be incorporated in the exclusivity incentive, but in this case, both authors and journals must accustom themselves to seeing the value of publishing negative results.
Negative information in the label is practice changing

If prescribers used the label as a source of prescribing information, the elite stakeholders uniformly agreed that the inclusion of negative results in the label would make a difference to prescribers. They felt it was a positive effect of the legislation, would be useful to prescribers, and had the potential to improve pediatric practice.

The FDA's Dr. Murphy noted “that a negative study doesn't necessarily mean the product would never work.” She further explained, “we actually now have labels which have information on the failed studies...and you can understand that it doesn't mean that this product would never work. It just means that the way it was studied it didn't work. And some of [the labels] say why they think it failed. The other reason it's really important to have this negative information in the label is that you're never going to get the next study. So you need to know that when it was studied at that dose in this way, it didn't work...and in some of these, not only did it not work at that dose, but we had serious adverse effects” (Murphy interview 2008).

One of the academic experts echoed her concern, “...negative results, if they're true negative, you act on them. But if they're negative because the study design isn't right or we don't understand the disease or we're missing a subpopulation that really benefits, I'm very much worried about that. But that's a general statement for adults and kids.” These sentiments highlight the need for careful interpretation of the data with caution toward under- and over-interpretation of the results.

Inconclusive label information may help researchers more than prescribers

When asked whether the inclusion of inconclusive results in the label would make a difference to prescribers, the elites gave a mixed response. This did not surprise me because even the inclusion of negative results, which one might instinctively consider to be more “usable” than inconclusive results, elicited noteworthy caveats. As
described above, several elites mentioned that negative results are not necessarily “definitive” and the scientific community must consider this when treating children and designing subsequent studies. Thus, inconclusive results carry even more uncertainty for prescribers, although they do maintain the spirit of full-disclosure. At the very least, the prescriber will know that a drug has been studied in a particular pediatric population.

Even among elite stakeholders, several of whom practiced pediatrics for decades, the dilemma of how to use inconclusive results was apparent. In general, they felt that inconclusive results may be more difficult to incorporate into practice, but that the data generated were important to our overall understanding of pediatric patients and their diseases. Dr. Richard Gorman, Chair of the AAP Section on Clinical Pharmacology and Therapeutics, commented on the true intent of the FDA when deciding to publish inconclusive results in the label, “The group that that was really aimed at was young researchers to keep them from going down the same blind alley… and subjecting other children to the same research that would probably fail again” (Gorman interview 2008).

These quotes are a further sampling of the layers of complexity that comprise the issue of publishing inconclusive results in the label. An elite from industry noted, “...I think the net effect would be it's [the drug] going to be used as long as there are no bad safety signals.” Mr. Mark Delmonte, Assistant Director, Department of Federal Affairs at the American Academy of Pediatrics, noted “…If there has been a drug studied, good, bad or neutral...we should know that that drug has been studied…in the environment of off-label prescribing...more data are better than less.” Finally, Dr. Donald Mattison, Senior Advisor to the Directors of the NICHD and the Center for Research for Mothers and Children (CRMC) and Chief of the Obstetric and Pediatric Pharmacology Branch in the CRMC, commented, “I think from a scientific perspective, making the inconclusive information publicly available whether it's in the label or the FDA medical reviews and on
the FDA website, is important, because it lays out areas where clinical trial design or understanding mode of action need to be improved...I think it's important from a scientific perspective. I'm not sure that it will influence prescriber behavior.”

**Transparency is essential**

Perhaps it is the concept of transparency that lies at the core of this debate. Publishing the results of all studies in the label may only have a modest effect on prescribing practice, but *it prevents sponsors from conducting studies without ever publishing the results*. The establishment of transparency may be one of the biggest successes of BPCA and PREA—to prevent what happened in adult medicine where studies were done, but the results of negative studies (and even positive or inconclusive studies) were never made available to the public.

This concept was also described by Dr. Benjamin: “the agency has the ability to put positive and negative results into the label...which is unique in the pediatric studies...that's actually not true for an adult study. If you do an adult study and it fails, unless there is some crucial public health concern, the agency actually doesn't put that into the label and if the company does not publish it...the results they buried, which of course draws into question the ethics of doing clinical trials and not disseminating the data” (Benjamin interview, 2008).

We conclude that the inclusion of inconclusive results in the label will likely have minimal effect on prescriber behavior, but it is an extremely insightful way to maximize transparency and ensure there is at least one mechanism for sharing the results of pediatric studies with the public, especially in light of the fact that many studies are not published in peer-reviewed journals.
The Cost of Pediatric Research

Although the exclusivity provision has experienced much praise, it has also received a fair amount of criticism. Cost is one of the most frequent issues raised by critics. They argue that the current incentive structure results in windfall profits for pharmaceutical companies and disproportionately rewards them to conduct studies for blockbuster drugs with minimal financial incentive for smaller market drugs (Public Citizen 2001). The incentive has potential for such significant profitability in large part because the 6 month period of market exclusivity is linked to the active moiety, thus a sponsor who is granted pediatric exclusivity for conducting pediatric studies earns that exclusivity benefit for all indications that include the active moiety, including adult indications.

Li et al. examined this question by quantifying the economic return to industry for completing pediatric exclusivity trials (2007). They analyzed a cohort of 9 studies that were conducted for pediatric exclusivity. They estimated the cost of performing each study and converted the cost into estimates of after-tax cash outflows. Three-year market sales were also obtained and converted into estimates of after-tax cash inflows based on 6 months of additional market protection. They calculated net economic return (cash inflows minus outflows) and the net return-to-costs ratio (net economic return divided by cash outflows).

The distribution of net economic return for 6 months of exclusivity varied substantially among products. The net economic return ranged from −$8.9 million to $507.9 million and net return-to-cost ratio ranged from −0.68 to 73.63. Li et al. concluded the economic return for pediatric exclusivity is variable; pediatric exclusivity can generate lucrative returns or produce more modest returns on investment.
As complexity increases, costs rise

Estimates of the cost to conduct a pediatric study are highly variable. The National Institute of Child Health and Development estimated that a safety and efficacy study may cost between $1 million and $7.5 million, while the cost of a pharmacokinetic study can cost from $250,000 to $750,000 per age group (US GAO, GAO-01-705T 2001). The Pharmaceutical Research and Manufacturers of America estimated higher study costs, ranging from $5 million to more than $35 million. In a study based on a survey of drug companies, the cost of pediatric studies was estimated to average $3.87 million per written request (Milne 2001).

As our pediatric knowledge base has expanded, the complexity of pediatric studies has also grown. The proportion of efficacy and safety studies, which are the most resource-intensive and expensive type of study has increased from 25% to 40%, the mean number of patients required for studies in response to an FDA written request increased 178% between 2000 and 2006, and the time required to complete a study and submit a final report has nearly doubled since 2000. In 2007, the Tufts Center for the Study of Drug Development reported that the average cost to respond to a written request grew from 3.93 million in 2000 to 30.82 million in 2006, an 8-fold increase (2007).

From the perspective of a contract research organization, an elite stakeholder commented, “if the written requests are so difficult that the companies have to put a lot of money on the table upfront to basically fail...to then go back to the FDA and say we can’t do the study. We have tried. We’ve done our due diligence. We cannot get this population. Now that’s not an absolute. You can have lots of discussion with the reviewers...which is what they encourage but...sometimes...they don’t stay on it...because it's marketed...and they're looking for new indications and trying to do this
500-patient, Phase III, safety and efficacy pediatric trial that requires 7 countries and the cost is double... it's just not attractive."

These comments underscore the need for thoughtful written requests and guidance from the FDA. One of the academic pediatric pharmacologists elaborated: "...the FDA [should] publish this guide that insists on how to do studies.... I'll give the example because I did pediatric hypertension for twenty-five years. ... We want you to take your hypertensive kids... off medication for 2 weeks and then start them on a double-blind, placebo-controlled trial. Not going to happen. And any parent who would sign for it is crazy. And any IRB that approved it is wrong. But because the FDA said the study that you did in adults has to be repeated in children the, the sponsors are forced to do that. So what is it they do? They go to India. They go to China. They go to... a private practitioner in St. Stephanie and the swamp hospitals."

To date, the FDA has not published a comprehensive guide for the conduct of pediatric clinical trials, but recently Benjamin et al. in collaboration with the FDA, published an analysis of end points and dose range in failed pediatric antihypertensive trials (2008). They describe, "We found poor dose selection, lack of acknowledgement of differences between adult and pediatric populations, and lack of pediatric formulations to be associated with failures. More importantly, our ability to combine data across trials allowed us to evaluate and potentially improve trial design" (834). This sort of publication is crucial for the success of future trials and should become standard practice.

**Who should pay?**

The cost to conduct pediatric clinical trials in response to a written request from the FDA is clearly rising. Many children's advocates and researchers argue that no matter the cost, the information learned from the studies is an invaluable benefit for
children. In the long term, it is probable that some of the cost of conducting the studies will be offset by health care cost savings; as appropriate labeling of drugs used in the pediatric population is increased, health outcomes will improve.

The US General Accountability Office reported on the cost to the public of providing the brand named drugs with an additional 6 months of market exclusivity, as this delays consumer access to lower-cost generic drugs. Delaying access to lower cost generic drugs increases health care spending overall and may be particularly burdensome for those without prescription drug coverage that must pay for the drugs out-of-pocket (US GAO 2001). The FDA estimates that the delay in availability of generic drugs could increase national drug spending by about one half of one percent or on average about $695 million per year over a 20-year period (FDA Pediatric Exclusivity Provision Status Report to Congress 2001). The one half of one percent estimate is based on a report from The Health Care Financing Administration that indicates prescription drug spending reached just over $100 billion in 1999 and projected this figure would rise to about $185 billion by 2005 (Office of the Actuary, Health Care Financing Administration).

Albeit the most recent, these figures are likely an underestimate of the actual cost to the public because the complexity, and subsequently, the cost to conduct pediatric clinical trials has risen so dramatically (Tufts Center for the Study of Drug Development 2007). A government accountability office report is mandated as part of the most current version of BPCA. This report is due no later than January 1, 2011 and must include, among other requirements, a description of the number and importance of drugs and biological products for children that are being tested and the importance of the labeling changes made as a result of the testing. It must also include the number and importance of drugs and biological products for children that are not being tested and possible reasons for lack of testing. There is currently no required reporting of an
estimate of cost to the public versus cost savings for improved pediatric health outcomes as a result of improved drug labeling.

**Should the incentive structure be modified?**

BPCA and PREA have a 5 year sunset clause that results in their continual re-evaluation and scrutiny. With the passage of each version—from the pediatric exclusivity provision of FDAMA in 1997, to the first BPCA in 2002, followed by the reauthorization in 2007—the pediatric exclusivity provision has been tweaked. We asked all of the elite stakeholders if they felt other “carrots” could be more effective. Generally, they were satisfied with the BPCA in its current form, particularly with the length of the market exclusivity. Cross-drug patent extension was one suggestion for improvement. Benjamin, of Duke University, suggested, “The only thing I could see really being as effective or more effective is if the agency were able to give patent extension for trials conducted in other arenas to block-bluster drugs. For example, if a company was able to successfully develop a malaria vaccine . . . then they got an extra 6 months' patent extension for an SSRI or an antacid or a lipid lowering agent, a multibillion-dollar drug . . . that might incentivize large companies to put resources into HIV vaccines or malaria vaccines or a message to supply safe water . . .” (Benjamin interview, 2008). Several elites mentioned a gradation system for the incentive based on earning potential or usefulness in pediatric population. Overall, the interviews with the key elite stakeholders did not leave us with the impression that BPCA and PREA were in need of a major overhaul.

Of note, three stakeholders mentioned that the sunset clause was a drain on resources or functioned as a barrier to progress. Dr. Maldonado, Vice President of Pediatric Drug Development at Johnson & Johnson, feels it prevents drug manufacturers from fully committing to a pediatric drug development infrastructure. He furthered, "After
10 years, I'm still somewhat dismayed to see that industry has not created a very strong infrastructure for pediatric drug development...I talked to my management [about this]...and they pointed to a policy that keeps changing every 5 years. They said, 'You have a sunset clause...This whole issue of BPCA may disappear...or it may be modified.' So they're very reluctant to create an infrastructure...for a moving target.”

Although ongoing evaluation of the BPCA and PREA programs is vital, removal of the sunset clause may cause drug manufacturers to finally acknowledge that pediatric drug development is here to stay and they ought to fund and create the appropriate infrastructure within their organizations.

The most pressing pediatric therapeutic needs

The majority of the elite stakeholders, although they represented different domains, had practiced clinical pediatrics. They had strong feelings regarding the gaps in pediatric therapeutics. They identified the following areas of need: the study of generics, neonates, pediatric formulations, old antibiotics, acute diseases, and information transfer (how we translate what we know into practice). Others mentioned the need for more well-trained pediatric investigators and clinical pharmacologists, a better understanding of subtypes of disease (e.g., bipolar disorder vs. hyperactivity) so that clinical trial design can become more sophisticated (e.g., genotype testing), and improved collaboration between medicine and pharmacy.

The elite interviews also revealed financial tension. An academic expert noted that “We've got to figure out how to deal with a for-profit world and a not-for-profit population... I think we need to deal with fact that the profit motive is driving chronic disease therapy. So acute treatment, which is what most kids have, acute diseases are lagging. [That's] because you make money on people who take a lot of medicine for a
long period of time." This comment likely explains part of the underlying reason why few systemic antibiotics are studied in children.

**It is unethical not to study children.** Several respondents mentioned the ethics of conducting pediatric research. Mr. Delmonte of the AAP, best summarized their sentiment, "Our basic premise about this is not radical. It's pretty basic. Kids are people and deserve what adults have. The problem is: kids are not little adults. You can't just extrapolate the data. Kids are hard to study. The populations are smaller. You're going to have to think creatively, and it will be expensive, and that's too bad. 1977 was the first time the American Academy of Pediatrics spoke on this, and said a groundbreaking thing, which was, 'It is not unethical to study drugs in kids. It's unethical not to.'" (Delmonte interview, 2008). Despite the fact that pediatric research is complicated, expensive, and requires a commitment to ethical practice, the elite stakeholders passionately agreed that pediatric research must be conducted.

**Policy Recommendations**

Our policy analysis included a systematic review of the biomedical literature, review of public documents, and content analysis of interviews with key elite stakeholders. This triangulation of methods created a very rich dataset yielding insight into the history, strengths, and weaknesses of BPCA and PREA. We believe the following policy recommendations could further enhance the success of these laws.

**Removal of the sunset clause.** So long as the legislation can "sunset," as Maldonado noted, industry sees it as a "moving target" – and, by extension, will be unlikely to devote the resources to development of permanent infrastructure for pediatric development. The simplest and yet potentially most important policy change we recommend is to remove the sunset clause. BPCA and PREA permanence – subject
only to the regular reauthorization affecting most policy – would both motivate manufacturers, and keep their feet to the fire. We should note that two elites disagreed with removing the sunset clause, since they believe the period of incentives should end, and pharmaceutical companies should simply adjust to maintaining the infrastructure necessary to do pediatric research.

**Limited liability protection in lieu of unlimited incentive.** Once pediatric clinical trials infrastructure has been firmly established, government could offer limited liability protection – understood by both plaintiffs and defendants to be in effect (to prevent Vioxx-like scenarios of no end to the number of lawsuits), perhaps organized similarly to the liability protections created for vaccine development. Government can continue to offer the patent exclusivity incentive, but it should remain limited to an extension of six months’ duration. Further, to maintain some balance between industry benefit and public good, profits above $500 million earned during the extension period will be subject to a special surcharge tax, the revenues from which will be devoted to pediatric studies of off patent drugs. Further incentives are unwarranted if the requested studies are feasible, infrastructure is adequate, and the manufacturer is offered limited liability protection for accepting the risks associated with studying a vulnerable population. We recognize that attempting to cap what might otherwise be viewed as the workings of the market is controversial, but the patent extension itself alters market dynamics, and does so for the purpose of achieving a clear public goal. Our present recommendation is in the spirit of continued attempts to balance market value with the health care needs of children.

**Published study guidelines.** As of yet, the FDA has not published a comprehensive guide to the conduct of pediatric clinical trials. Others, such as Pasquali et al. and Benjamin et al., have analyzed study designs and endpoints to increase the
success of future pediatric clinical trials. The FDA also publishes a generic Guidance to Industry document for pediatric studies (Department of Health and Human Services 2000). Although such publications are helpful, they are not comprehensive. The Pediatric Advisory Committee at the FDA should be charged with overseeing the development of a comprehensive resource to guide drug manufacturers in the conduct of pediatric clinical trials, including thoroughly developed manuals of methods, ethics, assays, and all such questions unique to pediatric trials, as well as other communication venues, such as a forum for discussion and exchange. Congress can provide necessary appropriations, perhaps in the next reauthorization of the bills, to allow the FDA to award grants, task order contracts, or other funding mechanisms to enable academic researchers at the Academic Medical Centers (AMCs) to begin the process by conducting evidence reviews on which such guidelines can be built. We also recommend the development of a "Pediatric CONSORT" for the reporting of pediatric trial data. Information to aid researchers in conducting and reporting trials is not enough, however. Pediatric research needs to be disseminated in such a way that it can influence practice.

**Dissemination of information.** We require genuinely usable mechanisms for dissemination of pediatric study results. Some stakeholders advocate for requiring drug manufacturers to publish the results of studies conducted under BPCA and PREA in a peer-reviewed journal to be eligible for the incentive (Benjamin et al. 2006), going so far as to say that Congress should consider mandating peer-reviewed publication. As at least one of our elites noted, it is not clear that scientific journals can be forced to publish articles, but the need for dissemination is clear, and the FDA's "Summaries of Medical and Pharmacological Reviews of Pediatric Studies" (see http://www.fda.gov/cder/pediatric/Summaryreview.htm) is not likely to become widely
used by the practice community. Dissemination is so important that the Pediatric Advisory Committee at the FDA should be charged with the responsibility of overseeing a program to develop the necessary evidence reports and guidelines (see below) to assure that the results of studies conducted under BPCA and PREA can be more readily translated into practice. As we have noted, it is unlikely that community providers regularly visit the FDA website. The FDA and the Pediatric Advisory Committee, however, can work with the AAP, the AAFP and state pediatric and family medicine societies to provide regular – perhaps quarterly – updates of label changes, new indications, and other safety and effectiveness news. AMCs are an important resource to the FDA and the practice societies, who should take advantage of AMC expertise to accomplish these goals. If we cannot compel peer-reviewed publication, we can nonetheless require that studies be designed and conducted with sufficient rigor that results would be "publishable," even if we cannot mandate "publication," and it is also true that we have two precedents for encouraging the dissemination of results. First, the Evidence Reports created by the federally funded Evidence-based Practice Centers are almost always accompanied by reviews published in peer-reviewed journals, as a way of disseminating findings more quickly into practice. Second, the NIH has begun requiring that research supported by federal funds be published in such a way that relevant communities have open access to the publications. Both precedents fit our case, since the goals of the legislation are to create and disseminate evidence, and we can argue that patent exclusivity incentives are, in fact, public support of research. We recognize that this recommendation may even call for the creation of a new journal – perhaps an internet-based peer-reviewed journal like the PLoS (Public Library of Science) journals (see www.plos.org). We also note that this recommendation comports with but is distinct from the recommendation about disclosure of study information in the label, because we are calling for additional peer-review, and because some study results are not "label-
worthy," but nonetheless should enter the public evidence base in the interest of complete transparency.

In conclusion, some off-label drug is likely always to be necessary in the practice of pediatrics – some drugs are likely never to get the kind of clinical trial studies that label indications require, and yet their use will continue to be a part of common practice. This does not mean, however, that children do no deserve the same standard of care as do adults. The authors and supporters of BPCA and PREA have done a great service to children's health.
References


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Berry, Jeffrey. 2002. Validity and reliability issues in elite interviewing. PS: Political Science and Politics. 35:679-682.


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Appendix 1: In-depth Interview Protocol

Better Medicines for Children: The Potential Policy Effects of the BPCA and PREA on Pediatric Drug Development, Labeling, and Use:

A Study by Carrie Lee, MD,
The University of North Carolina at Chapel Hill

Information Sheet

IRB Study # Consent Form Version Date: January 23, 2008

Principal Investigator: Carrie Lee, MD
UNC-Chapel Hill Department: Public Health Leadership Program

Faculty Advisor: Sue Tolleson-Rinehart PhD
UNC-Chapel Hill Department: UNC Center for Education and Research on Therapeutics and Departments of Public Health Leadership, Pediatrics, and Political Science

Advisor Phone #: (919) 843-9477
Advisor e-mail: suetrr@unc.edu

Study Contact telephone number: (919) 630-5304

Study Contact email: clee@unch.unc.edu

[Introductory script, embedding fact sheet and consent information]:

Hello, my name is Carrie Lee. Thank you so much for talking with me today. I am a doctor doing my Medical Oncology fellowship and working in the Preventive Medicine program at The University of North Carolina. I am doing this research to complete my Master of Public Health degree at UNC.

I have asked to talk to you today because you are an expert on pediatric pharmaceutical questions. I am interested in your general views and, more specifically, your views on the potential for policies to change pediatric drug labels and prescribing practices.

My faculty advisor is Dr. Sue Tolleson-Rinehart, who is a faculty member of the UNC Schools of Public Health and Medicine. We have gotten IRB approval to conduct these interviews, and if you can bear with me for just a moment, I need to talk for just a moment about the study information I sent you in my e-mail message of [insert date].

As you recall, I told you that the interview has several open-ended questions, and that it will take about 20 minutes to an hour, depending on your time today, what you want to tell me. I do want to record this interview on a digital voice recorder to make absolutely sure that I have the most accurate record of your comments, but I won’t do this without your permission. I will be transcribing the recording, and I will destroy the recording as soon as my Master’s Paper has been accepted by the Graduate School. I will be happy to give you a copy of the transcript at your request. I will be keeping the transcription
until we publish the findings, but I will remove any identifying information from it unless you give me permission to identify you. As I mentioned in my e-mail message, you can withdraw your permission and you can stop the interview at any time.

In my e-mail message, I mentioned that I would be protecting the digital recording of your interview on my password-protected computer, and Dr. Tolleson-Rinehart will also have a copy on her password-protected computer. Our computers have all the security requirements of the university and the School of Medicine. Do you have any questions about the recording?

Your participation in this study is completely voluntary. Your choice of whether or not to participate will not influence your future relations with the University of North Carolina at Chapel Hill. If you decide to participate, you are free to withdraw your consent and to stop your participation at any time without penalty. At any point in the interview, you may refuse to answer any particular question or stop participation altogether.

Dr. Tolleson-Rinehart and I intend to publish the results of this project, and will be glad to make findings available to you.

You are welcome to ask us anything about this research now or later. If you have questions later, please don't hesitate to contact me by phone or e-mail at the addresses I sent you in my e-mail message to you. I will be glad to send that contact information again.

[If Respondent asks for contact information now: Dr. Lee: (919) 843-6281 or clee@UNCH.UNC.EDU. Dr. Tolleson-Rinehart: 919.843.9477 or suetr@ UNC.EDU.]

**Risks and Benefits:** I don't know of any risk to you from completing this interview. I don't know of any personal benefit you may get from participating, but I do believe that you will be helping the larger health care community by enabling us to understand how policies designed to increase pediatric prescribing safety can be most effective.

Before we continue, would you please agree to any or all of the statements I'm about to read?

☐ I AGREE to having this interview recorded with a digital voice recorder.

☐ I GIVE PERMISSION for the following information to be included in publications resulting from this study:

☐ my name   ☐ my title   ☐ direct quotes from this interview

_________________________  ___________________________
Name of Participant          Date
Thank you for your help with my project! Now we are ready to begin.

Pediatric Pharmaceutical Policy Questions:

First, let me tell you my framework for the research. As you know, the Best Pharmaceuticals for Children Act, or BPCA, came out of the FDA's Pediatric Rule. BPCA, as we know, gave legislative authority to the Pediatric Rule's intention of getting more manufacturers to provide pediatric data on safety and effectiveness. Of course, BPCA dealt with drugs that were already approved, and it was voluntary. The Pediatric Research Equity Act, or PREA, then came into being to require, rather than request, pediatric studies as a part of most new drug applications. My research is on the likely effects on pediatric therapeutics resulting from both BPCA and PREA.

1. As you know, BPCA incentivizes the completion of pediatric studies by granting sponsors a 6-month patent extension on adult label indications, in exchange for conducting pediatric studies. Do you think this incentive is generally an attractive "carrot" for sponsors? Why? Why not? Would other "carrots" be more effective? Would a "stick" be effective for drugs that have already been approved?

2. Next, I want to read you a little summary of some thinking about BPCA. Some people argue that manufacturers might complete pediatric studies under BPCA in order to get a six month patent extension for adult label indications without ever intending to seek a pediatric label indication. Some think that getting the pediatric data is worth it, even without a new pediatric label. Others think that this is contrary to the spirit of the BPCA.

   a. What is your judgment about how all this has played out?

   b. Do you think getting the extension without seeking the label change has happened frequently?

   c. Do you think BPCA has actually motivated more new indications?

   d. Was this what the authors of BPCA expected, do you think – that they'd get more pediatric data, no matter what? Or do you think the supporters were hoping this would stimulate more pediatric labels?

3. PREA, on the other hand, might be called all "stick," and no carrot, since it simply requires pediatric safety and efficacy data, with very few exceptions. And the consequences of not complying with PREA could be significant. If PREA's goal is to make sure that new drugs have pediatric indications, is PREA the right way to go about
this, or not? [if necessary, then probe with "Do you think having a drug labeled as 'misbranded' is enough of a potential consequence to get manufacturers to comply?]

4. The 2007 amendments to BPCA and PREA both require that pediatric studies, no matter their conclusions, be included in the label. I want to ask you a couple of questions about these new requirements.

   a. First, the amendments require including even inconclusive pediatric results in the label. What is the effect of publishing inconclusive results? For example, do you think this will make a difference to prescribers?

   b. Second, the amendments require publishing negative pediatric information on the label. Once again, what do you think the effect will be of publishing negative results? And will this have any effect on manufacturers' approach to completing their NDAs?

5. What about doing the pediatric trials in the first place? I would like to have your views on pediatric drug development research generally. [If necessary, probe with "Well, I'd like to know anything you might want to say about cost, logistics, or ethics."

6. We are almost done! All things considered, where do you think pediatric therapeutics is today? What are our most pressing pediatric therapeutic needs? [If necessary, probe with "Those needs might be whatever you think is most important...?"

   a. Do policies like BPCA and PREA get us to the goals you believe are most important? Take [the first thing somebody mentions, whatever it is]: how do you see BPCA and PREA helping with that?

   b. If you could recommend more, or different, pediatric therapeutic policy, what you want to see?

That's it! We are finished! Thank you so very much for your time and thoughts! Do you have any additional questions or comments? Would you like a copy of this interview once it is transcribed? Thank you again!
Appendix 2
List of Interviews

Dr. Daniel Benjamin
Associate Professor of Pediatrics
Duke University
Date: February 21, 2008

Mr. Mark Delmonte
Assistant Director, Department of Federal Affairs
American Academy of Pediatrics
Date: March 3, 2008

Dr. Richard Gorman
Chair, Section on Clinical Pharmacology and Therapeutics
American Academy of Pediatrics
Date: February 28, 2008

Ms. Jeanne Ireland
Director, Public Policy at the Elizabeth Frazier Pediatric AIDS Foundation
Position at the time of interview: Chief Public Health Policy Advisor, House Energy and Commerce Committee
Date: March 26, 2008

Dr. Samuel Maldonado
Vice President of Pediatric Drug Development
Johnson & Johnson
Date: March 6, 2008

Dr. Donald Mattison
Senior Advisor to the Directors of the NICHD and the Center for Research for Mothers and Children (CRMC)
Chief of the Obstetric and Pediatric Pharmacology Branch, CRMC
Date: March 11, 2008

Dr. Dianne Murphy,
Director, Office of Pediatric Therapeutics, FDA
Date: March 11, 2008

Dr. Stephen Spielberg
Professor Pediatrics, Pharmacology, and Toxicology
Dartmouth Medical School
Date: February 28, 2008

Dr. Philip Walson
Professor of Pediatrics & Pharmacology
The University of Cincinnati
Director of the Clinical Pharmacology Division and Clinical Trials Office
Cincinnati Children's Hospital Medical Center
Date: February 22, 2008
Dr. Robert Ward
Professor of Pediatrics
Director, Pediatric Pharmacology Program
The University of Utah
Date: March 11, 2008

Elite Stakeholder
Contract Research Organization
Date: March 6, 2008
## Citation
- Mathis LL, Yavu G, Safidy
- Li J, Eisenstein EL, Gistowday
- Boots I, Sulaiman RN, Klein R, Hol
- The Red Pharmacists for
- Grine A, Yorsh J, Reith D, Nanto
- Rodriguez WJ, Roberts R, Murphy
- Roberts R, Rodriguez W, Murphy
- Passaniti SK, Sanders EP, Li J, S
- Mine CP
- Henderson S, Shapin A, Cusken R
- Benjamin DK Jr, Smith PB, Jough
- Benjamin DK Jr, Smith PB, Mushv
- Tauer CA, Tufts Center for the Study of Drug
- Tufts Center for the Study of Drug

## Research Design
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- review

## Quality
- A - very thorough
- B - less thorough
- C - fair
- D - poor

## Conclusion
- Safety reviews of
- Economic return
- US incentives
- Reflects on which drugs ARE studied, and which drugs OUGHT to be studied
- Should the covariance pay for studies? Shouldn't the patients pay? See p. 44
- Blockbuster drugs appear to be overcompensated
- Not all drugs
- The exclusivity
- Exclusivity has
- The exclusivity
- The exclusivity
- Written to inform
- Some of the
- Does 4-week efficacy study that oeth exclusivity really tell enough?
- Written to inform
- Pay careful attention to study design & endpoints.
- The pediatric
- Dissemination of information base-reviewed publication of pediatric trials is essential
- NEED clear and uniform ethical guidelines for the study of children.
- The cost of
- The avg. cost is

## Definition of Grades:
- A/Excellent - very thorough, apparently unbiased
- B/Good - less thorough, apparently unbiased
- C/Fair - limited scope and/or biased
- D/Poor - Inaccurate, and/or biased

## Criterions for evaluating policy analyses:
1. Is the author's point of view transparent? Does the author make her standpoint clear?
2. Does the author deal fairly with the evidence? Even when the evidence opposes the author's perspective?
3. Does the recommendation seem both plausible and grounded in appropriate evidence?

## Appendix 3: Evidence Table

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