Peter Lurie, MD, MPH
Deputy Director, Public Citizen's Health Research Group
Testimony before the Health Subcommittee
Committee on Energy and Commerce
U.S. House of Representatives
on Programs Affecting Safety and Innovation in Pediatric Therapies
May 22, 2007

Thank you for the opportunity to address the Subcommittee on the critical issue of the safety and effectiveness of pediatric therapies. My comments today will address two principal areas: a. how to ensure that the most important studies of pediatric drugs and biologics are indeed conducted; and b. issues surrounding the approval of medical devices, including for children.

A. Pediatric Studies

Much of the testimony you heard this morning will have extolled the successes of the current system for encouraging pediatric studies of drugs and biologics. To simplify somewhat, the system consists of a carrot and a stick. The carrot is the Best Pharmaceuticals for Children Act (BPCA) of 2002,[1] which grants six additional months of marketing exclusivity to companies that conduct pediatric studies consistent with a Written Request issued by the Food and Drug Administration (FDA). The stick is a codification of an FDA regulation known as the Pediatric Rule,[2] which was successfully challenged in the courts; that ruling was later appealed. With the fate of the Pediatric

[1] BPCA was actually a successor to the exclusivity provisions in the Food and Drug Modernization Act of 1997.
[2] 63 Fed Reg 66632, December 2, 1998.

Rule unclear, Congress in 2003 passed the largely similar Pediatric Research Equity Act (PREA) which contains the essential elements of the Pediatric Rule: the ability of the FDA to require pediatric studies whenever a sponsor seeks approval for a new ingredient, indication, dosage form, dosing regimen or route of administration.

The successes of the present system are clear enough. They include, as of May 2005, 299 Written Requests under the BPCA, many of which would never have taken place without the Act, 110 patent extensions and 90 labeling changes.[3] (The number of drugs relabeled has since risen to 128.[4]) Yet, the question is not simply whether the system has had successes. That much is undeniable. Rather, the issues are, first, whether the system could have been more successful and, second, whether these successes (or even greater successes) could have been obtained through alternate methods. Let us take these issues in turn.

There remain numerous gaps in current pediatric testing

While many studies have been undertaken, significant gaps remain. The biggest deficiency is with drugs that are off patent, an observation that should surprise no-one. Tellingly, the data on off-patent drugs in the Government Accountability Office's (GAO's) report[5] on the BPCA have been relegated to an appendix.[6] But the results are

[3] Mathis D. Pediatric drug development: BPCA and PREA. Presentation before the Drug Information Association. Division of Pediatric Drug Development, U.S. Food and Drug Administration, June 28, 2005. Available at: http://www.fda.gov/cder/present/DIA2005/mathis.pdf.
[4] http://www.fda.gov/cder/pediatric/labelchange.htm.
[5] Government Accountability Office. Pediatric drug research: studies conducted under Best Pharmaceuticals for Children Act. GAO-07-557, March 2007.
[6] The PREA has little impact upon off-patent drugs.

disconcerting. Following the process outlined under the BPCA, the National Institutes of Health (NIH) had by 2005 identified 40 off-patent drugs for which pediatric studies would have been useful. Yet the FDA issued Written Requests for only 16 of these and the drugs' sponsors declined to conduct all but one of them. While the NIH had funded studies of seven of the remaining 15, that still left the great majority (83%) of the NIH's list unstudied. In part, this is because the NIH has received no appropriations specifically for these pediatric studies.

Even with respect to on-patent drugs, significant deficiencies remain. According to the GAO, between 2002 and 2005 sponsors declined 41 of 214 (19%) Written Requests from the FDA, presumably because they did not think it was in their financial interest to conduct the requested studies. This is an underestimate of the extent to which companies are not complying with the FDA's priorities in that many of the Written Requests are generated at the urging of the sponsor; presumably these are not being declined. The BPCA does provide a mechanism for the study of drugs for which Written Requests have been declined: the FDA can refer such studies to the Foundation for the National Institutes of Health (FNIH). This mechanism has been an abject failure. Of the 41 declined Written Requests, the FDA referred only nine to the FNIH, which in turn had funded none.

The third area of deficiency relates to the kinds of diseases being studied. Since the majority of sales for most drugs will be derived from adult sales, fundamental economic principles predict that companies would undertake pediatric studies (and thus expect

exclusivity under the BPCA) in relation not to their pediatric sales, but to their adult sales. Using two different data sources, the GAO determined that only four or five of the 10 most commonly prescribed pediatric drugs had been studied under the BPCA.[5] The FDA acknowledged in its report to Congress in 2001 that the BPCA was inadequate for old antibiotics and other off-patent drugs, certain drugs with low sales and for the younger pediatric age groups.[7]

A group of researchers in the Netherlands, where a European law similar to the BPCA comes into effect this year, has studied the U.S. experience.[8] They found that the diseases for which drugs were most frequently granted pediatric exclusivity treated depression and mood disorders, hypertension, elevated cholesterol, HIV and pain, common conditions in adults. The top three drug categories granted pediatric exclusivity precisely matched (in category and sequence) the top three prescribing categories for adults, while none of the top three prescribing categories for children appeared in the top three for the granting of pediatric exclusivity. In general, the researchers concluded, "The distribution of the different drugs closely matched the distribution of these drugs over the adult market, and not the drug utilization by children."

The fact that the primary motivation for studying pediatric patients is, in many instances, sales in adults raises significant ethical questions. Because the primary beneficiaries of such studies are often pharmaceutical companies rather than the study participants or the

[7] Department of Health and Human Services, U.S. Food and Drug Administration. The pediatric exclusivity provision: report to Congress. January 2001. Available at: http://www.fda.gov/cder/pediatric/reportcong01.pdf.
[8] Boots I, Sukhai RN, Klein RH, et al. Stimulation programs for pediatric drug research – do children really benefit? European Journal of Pediatrics, January 17, 2007.

pediatric population from which the participants are drawn, Institutional Review Boards should compensate for this dynamic by lowering the amount of acceptable risk for these pediatric patients. Moreover, patients and their surrogates have a right to be fully apprised of the financial arrangements that underly the research.[9]

With significant deficiencies in the study of both off- and on-patent drugs, and a profile of studies that leaves many important pediatric conditions neglected, it is clear that, whatever its successes, the current system is far from perfect.

The successes of the current program can be retained without such massive handouts to industry

The second major question is whether the successes of today's system could be realized through other means. Specifically, are the current patent extensions too generous or, more fundamentally, are they needed at all? Here we turn to the PREA, the exemplar of the stick approach to this issue.

Although only enacted in December 2003, the PREA has already produced 55 changes in drug labels. Like the labeling changes under the BPCA, these changes have ranged from new indications to proof of ineffectiveness in certain subgroups to better descriptions of the drug's adverse event profile in the pediatric population. All of these benefits were obtained without the patent extensions that are at the core of the BPCA.

[9] For a fuller discussion of these issues, see Lurie P. Statement before the National Academy of Sciences' Committee on Clinical Research Involving Children, July 9, 2003. Available at: http://www.citizen.org/publications/print_release.cfm?ID=7261.

Recently published research[10] indicates that the exclusivity provisions under the BPCA are absurdly generous, at least for some drugs. The authors studied nine drugs from a variety of disease categories to determine whether the value of patent extensions exceeded the costs of conducting the supporting pediatric trials. For the current six-month patent extension, the net economic returns on individual drugs were as high as $508 million, with a median of $134 million. Only one drug did not produce a net financial gain, a loss of $8.9 million on $28.3 million in annual sales. One drug product, with $3.8 billion in annual sales, produced economic benefits to the sponsor 74 times as high as its expenses (median for all drugs: 12.4 times). Even with the patent extension reduced to three months, only one company had expenditures that would have exceeded the value of the added exclusivity (median for all drugs: 5.7 times greater returns than costs). The version of PDUFA recently passed in the Senate[11] reduces the patent extension to three months for drugs with sales exceeding $1 billion in any year prior to the time the sponsor agrees to the Written Request. This is a move in the right direction, but still seems too generous.

The costs of this generosity are substantial. The FDA estimated in 2001 that the undiscounted value of the six-month patent extensions would be $13.9 billion over the following 20 years.[7] Much of this will come out of the pockets of consumers, but increasingly the government will be footing the bill for its own generosity, in the form of its contribution to funding Medicare Part D.

[10] Li JS, Eisenstein EL, Grabowski HG, et al. Economic return of clinical trials performed under the pediatric exclusivity program. Journal of the American Medical Association 2007;297:480-8.
[11] http://thomas.loc.gov. Search on S. 1082.

Unless there is a strong reason to believe that pediatric usage will be minimal, conducting pediatric studies should be seen as the responsibility of all companies seeking to market or continue marketing a drug, not an undertaking for which companies should be rewarded, let alone as generously as they currently are. The FDA should have the authority to compel such studies, by expanding the provisions of the PREA, no matter what the stage in the drug's lifespan, without having to resort to patent extensions. This authority would extent to old and new drugs, to on-patent and off-patent drugs.

The pediatric testing process is not transparent

In addition to ending the excesses of the patent extension provisions, Congress should pay attention to the lack of transparency in the process. The FDA does not announce which products are being studied pursuant to Written Requests and generic companies have been forced to destroy drug lots after they learned at the last minute that a patent extension would be granted.[5] In addition, there can be a significant delay between initial submission of the pediatric trial results and any label change that may result. For drugs granted pediatric exclusivity between 2002 and 2005 that resulted in a label change, that change took place eight months or more after the data were originally submitted to the FDA in 40% of cases and over a year later in 16% of cases.[5] Inadequacies in the data submitted by the sponsors and the FDA's lack of authority to dictate label changes help explain these delays.

Although many products have been relabeled as a result of pediatric trials under the PREA and the BPCA, many physicians do not read these FDA-approved labels on a regular basis. The published medical literature is not a satisfactory substitute as only 45% of BPCA studies completed between 1998 and 2004 were published.[12] Studies were more likely to be published if they addressed questions of efficacy or if the labeling changes were favorable to the product. Congress should require a clinical trials registry that would publicize the existence and design of all pediatric studies that have commenced and the detailed results of those that have been completed.

B. Medical Devices

The issues with respect to pediatric medical devices are generally similar to those raised for pediatric drugs (lack of studies, devices too large for children, improper extrapolation from adult studies, etc.). Yet medical device regulation raises a number of specific issues, all of which apply equally to adult and pediatric devices.

The medical device approval standard is too low

The first problem is that the approval standard for devices that treat diseases is lower than that for drugs. Thus, to receive permission to be marketed, a drug must demonstrate "substantial evidence of effectiveness for the claimed indications,"[13] whereas a device

[12] Benjamin DK, Smith PB, Murphy D, et al. Peer-reviewed publication of clinical trials completed for pediatric exclusivity. Journal of the American Medical Asssociation 2006;296:1266-73.
[13] 21 CFR 314.50(d)(5)(v).

need only demonstrate a "reasonable assurance that the device is safe and effective."[14] Thus data that could never support the approval of a drug can result in the approval of a device used to treat the same condition, potentially diverting patients from effective drugs to devices. This is not a merely theoretical concern. The vagus nerve stimulator was approved in 2005 by the Center for Devices and Radiological Health (CDRH) for treatment-resistant depression even though the only randomized, controlled trial of the device did not demonstrate efficacy. According to a report from the Senate Finance Committee,[15] officials in the Center for Drug Evaluation and Research advised CDRH that if it had received similar data for an antidepressant drug, it would not have sanctioned even the filing of a New Drug Application (NDA). Yet the device was approved.

Most devices do not undergo full premarket review

A second major issue is the abuse of the 510(k) process for Class III medical devices. The Medical Device Amendments of 1976 allow two pathways to approval for such devices: a Premarket Application (PMA), analogous to the NDA for drugs, and the 510(k) process, in which new devices are approved based on their "substantial equivalence" to an existing (predicate) device. Intended at the time of the enactment of the amendments to be the exception, rather than the rule, the 510(k) process is now the

[14] 21 CFR 860.7(4)(c)(1).
[15] Committee on Finance, United States Senate. Review of the FDA's approval process for the vagus nerve stimulation therapy system for treatment-resistant depression. February 2006. Available at: http://finance.senate.gov/press/Gpress/02_2006%20report.pdf.

route to approval for 99% of new Class III devices,[16] resulting in a less rigorous approval process, including no ability to require advisory committee meetings. Moreover, a device can be declared "substantially equivalent" to the predicate device even if it does not have the same technological characteristics as the predicate device as long as it "does not raise new questions of safety and effectiveness and demonstrates that the device is at least as safe and effective as the legally marketed device."[17]

The dangers of this loophole, derived directly from the statute, are graphically illustrated by another device for the treatment of depression, Repetitive Transcranial Magnetic Stimulation (rTMS). The FDA allowed this new device to be reviewed under the 510(k) process with electroconvulsive therapy (ECT) as the predicate device, even though ECT uses electrical currents and rTMS applies a magnetic field. Remarkably, the company then compared rTMS to a placebo, even though ECT was the predicate device. Ironically this study, which is the only randomized, controlled trial of rTMS, did not prove that the device was more effective than a placebo. At this time, it appears unlikely that rTMS will be approved.

Devices known to be defective continue to be marketed even after the defect is corrected

Third, at times when the FDA has identified or been apprised of a defect in an already marketed device, it has allowed the sponsor to correct the defect but to continue to deplete its inventory of the device it acknowledged to be defective. The best known

[16] Riegel v. Medtronic, Inc., 451 F.3d 104, 111-12 & n.7 (2d Cir. 2006).
[17] http://www.fda.gov/cdrh/devadvice/314.html.

example of this involved the Guidant pacemakers,[18,19] but we have brought another such case to light.[20] In this instance, a patient had his St. Jude pacemaker removed due to a short-circuit that depleted the battery. However, when his new pacemaker was implanted, he received one from a group of pacemakers that still could carry the defect, even though the company was already selling a new pacemaker with the defect corrected. Fortunately, his new pacemaker has not failed.

The medical device testing process is not transparent

Fourth, as with pediatric drug and biologic studies, there are a number of respects in which procedures regarding devices are less than transparent. According to a report from the National Academy of Sciences (NAS), "The most obvious deficits in FDA's performance [with respect to the safety of medical devices in children] are the agency's lack of effective procedures for monitoring the status of required postmarket studies and the lack of public information regarding such studies."[21] The report went on to recommend expanded FDA authority to order postmarketing studies as well as a public registry that would track all postmarketing studies on medical devices. These elements are included in H.R. 1494, the Pediatric Medical Device Safety and Improvement Act, which goes beyond the NAS recommendations to also require the posting of study results but, unfortunately, allows non-disclosure of results if the sponsor provides "an

[18] Meier B. Maker of heart device kept flaw from doctors. New York Times, May 24, 2005, p. A1.
[19] Meier B. Heart device sold despite flaw, data shows. New York Times, June 2, 2005.
[20] http://www.citizen.org/publications/release.cfm?ID=7401.
[21] Field MJ, Tilson H, eds. Safe Medical Devices for Children. Committee on Postmarket Surveillance of Pediatric Medical Devices, Institute of Medicine, 2005.

explanation as to why the results and key findings do not warrant public availability."[22] This loophole is not justifiable.

I would be happy to address any questions members of the committee may have.

[22] http://thomas.loc.gov. Search on H.R. 1494.

Summary of Major Points

A. Pediatric Studies

1. There remain numerous gaps in current pediatric testing

    Off-patent drugs

    Certain on-patent drugs

    Certain conditions

2. The successes of the current program can be retained without such massive handouts to industry

3. The pediatric testing process is not transparent

B. Medical Devices

1. The medical device approval standard is too low

2. Most devices do not undergo full premarket review

3. Devices known to be defective continue to be marketed even after the defect is corrected

4. The medical device testing process is not transparent