Clinical Trial Perspective

CLINICAL INVESTIGATION

Pediatric exclusivity and other contemporary regulatory changes: impact on pediatric drug study, labeling and safety

Clin. Invest. (2013) 3(3), 227–239

Historically, most drugs have been used 'off-label' in children due to a lack of specific information on dosing, safety and efficacy. This practice risks adverse events, leading to serious public health consequences. Regulatory changes have attempted to address such issues by mandating and incentivizing the study of drugs in children. By all accounts, these regulatory changes have been enormously successful in stimulating >400 pediatric clinical trials enrolling >170,000 children over the last 5 years. These trials and others conducted over the preceding 15 years have resulted in >400 pediatric-specific labeling changes. While these labeling changes have improved pediatric drug safety, critics voice continuing concerns about the 'financial windfall' for industry, relative lack of study of off-patent agents and continued neglect of several important pediatric subpopulations (e.g., neonates).

Keywords: Best Pharmaceuticals for Children Act • pediatric clinical trials • pediatric drug safety • pediatric exclusivity • pediatric labeling

Kevin D Hill*, P Brian Smith, Michael Cohen-Wolkowiez, Daniel K Benjamin Jr & Jennifer S Li

Department of Pediatrics & the Duke Clinical Research Institute, Duke University Medical Center, Durham, NC 27705, USA
*Author for correspondence:
Tel.: +1 919 668 8305
Fax: +1 919 681 9457
E-mail: kevin.hill@duke.edu

Historically, children are underrepresented in drug trials; consequently, most drugs are used 'off-label' in this population [1–3] by extrapolating dosages from clinical trial data in adults. This practice is inappropriate because children have unique differences due to development: these differences affect both pharmacokinetics and disease pathophysiology when compared with adults. Recognizing these differences and the importance of conducting trials in children, the US Congress has enacted, over the last 15 years, several regulatory initiatives aimed at stimulating pediatric drug development and research. These initiatives have included a pathway for National Institutes of Health (NIH)-sponsored pediatric drug research, as well as incentives and mandates for industry – the so-called 'carrot and stick' approach [4–6,101–103]. Pediatric research has been successfully fostered by these programs as evidenced by 405 labeling changes since their inception. However, some limitations encountered thus far include the cost of the programs stemming from prolonged patent protections, few studies of off-patent therapeutics and continued neglect of certain pediatric subpopulations [6,104,105]. The purpose of this article is to review the history of pediatric drug prescribing, the impact of recent regulatory changes, and the successes and failures of these efforts.

Off-label pediatric prescribing

Off-label drug use occurs when a drug is used in a different way than is described in the US FDA-approved drug label. This typically means that the drug is used in an unstudied or understudied patient population or for an unstudied or understudied indication. Off-label drug use is common in children. In a review of 2000 drugs in

FUTURE SCIENCE part of fsg

the 1973 Physician's Desk Reference, 79% of drug monographs lacked sufficient information or labeling regarding pediatric use, while a similar review in 1991 found no change, with 81% of drugs lacking pediatric information [2,3]. A review of 350,000 pediatric hospital discharges at 36 tertiary care children's hospitals found that 79% of pediatric in-patients received an off-label drug [1].

In children, off-label drug use can lead to efficacy failures or undesired toxicities. Despite numerous notable historical examples [7,8], safety concerns remain common. In a contemporary analysis evaluating previously off-label pediatric drugs studied under the auspices of pediatric exclusivity, serious safety concerns were identified in 33 out of 137 (24%) products. These included 12 products with neuropsychiatric adverse events, including suicidal ideation (ribavarin and interferon α), aggressive behavior (tolterodine) and stroke, vision loss and death (sumatriptan). There were also safety events related to growth (betamethasone, mometasone), musculoskeletal events (ciprofloxacin, levofloxacin), inadequate antibiotic CNS penetration (linezolid, ertapenem), and increased mortality (propofol) [9]. These examples illustrate that, although off-label drug use is a common practice in pediatrics, there is clearly a risk of inadequate efficacy or potentially serious adverse events. Furthermore, off-label use of multiple agents risks unanticipated drug–drug interactions that can affect dosing, safety, or efficacy.

Regulatory history & the process of pediatric drug study

Despite recognition of the dangers of off-label drug prescribing in children, for many years drug testing was not required in children, and manufacturers could claim efficacy based on adult data **(Figure 1)** [6]. In 1979, the FDA made its first attempt to limit these claims and required that drugs marketed to children include pediatric information on the label [6,10]. This policy did little to increase the study of drugs in children as most pharmaceutical companies chose instead to include a disclaimer stating that safety and efficacy had not been established in children [6].

The FDA responded by issuing the 'Pediatric Rule,' which allowed the labeling of drugs for pediatric use based on extrapolation of efficacy from adults and additional pharmacokinetic, pharmacodynamic and safety studies to pediatric populations. Although controlled pediatric efficacy studies were encouraged under this rule, they were not required by law, and consequently this voluntary program did not result in an increase in the number of pediatric studies [10]. Of the 430 drugs for which labeling supplements were submitted, only 23% supplied sufficient pediatric information for labeling, and most of these submissions targeted narrow age ranges (e.g., studies limited to adolescents) [11].

In 1997, responding to the continued lack of pediatric data, Congress passed the FDA Modernization Act including section 505A, known as the pediatric exclusivity provision [106]. The exclusivity provision granted an additional 6 months of marketing exclusivity (the 'carrot') for conducting pediatric studies in response to an FDA written request. The pediatric exclusivity provision fundamentally changed the pediatric clinical trials landscape. Now the financial incentive for industry was potentially large, and the regulations ensured that the risks of failure were low as long as sponsors adhered to the FDA's stipulations.

The pediatric exclusivity provision was broadly popular among the pediatric community as it resulted in an increase in pediatric drug studies [5,107,108]. The major limitation, however, was that there was no incentive for pharmaceutical companies to study off-patent drugs. Therefore, drugs commonly used in children still lacked critical dosing, safety and efficacy information. The 2002 Best Pharmaceuticals for Children Act (BPCA) addressed this problem by establishing the 'Program for Pediatric Studies' [102]. Under this program, the National Institute of Child Health and Human Development (NICHD) and the FDA were tasked with developing a priority list of off-patent drugs **(Table 1)** [12]. The FDA could then issue a written request for study of a drug on the priority list. If the request was declined by the drug sponsors (only one such request has ever been accepted), then the FDA could publish requests for study to third parties, including academic institutions. Other important amendments under the BPCA included:

- Clear language indicating that the FDA can request studies in differing pediatric subpopulations (including neonates);
- A requirement for review of safety events for 1 year after granting of exclusivity [13].

The 2002 BPCA required review and reauthorization in 2007. At that time, Congress further refined the process for the study of off-patent drugs by requiring that the priority list focus on therapeutic areas of need rather than specific drugs. The 2007 reauthorization also established a process whereby the NIH (in addition to the FDA) could initiate the study of an off-patent drug, provided that the drug was needed in one of the priority therapeutic areas [101]. Finally, in the summer of 2012, Congress permanently reauthorized BPCA with further refinements to the process. Some of the more important changes are summarized in **Box 1** [109].

While the pediatric exclusivity provision initiated a voluntary testing program for on-patent and subsequently off-patent agents, critics had long argued that drug study should also be a requirement for all new

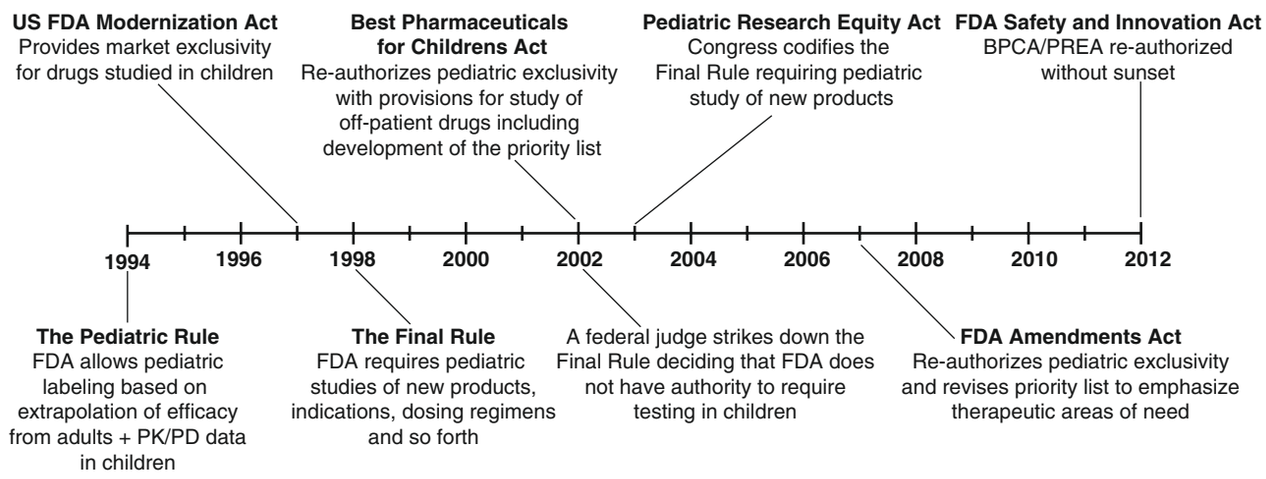

Figure 1. Timeline of recent regulatory changes.
BPCA: Best Pharmaceuticals for Children Act; PD: Pharmacodynamic; PK: Pharmacokinetics; PREA: Pediatric Research Equity Act.

pediatric drug applications as it already is for adults [6]. To regulate pediatric study for new drug applications, Congress passed the Pediatric Research Equity Act (PREA) in 2003. This act required that, for all applications submitted to the FDA for new drugs (including new indications or dosage forms), sponsors must include data that:

- Assess safety and effectiveness of the product in pediatric subpopulations;
- Support dosing and administration of the product for each relevant pediatric age group [13,103]. New drug applications can also qualify for pediatric exclusivity but only if the FDA issues a written request and the sponsors effectively meet the requirements [4,102].

Together, BPCA and PREA have established mechanisms for study of three broad classifications of pediatric therapeutic agents:

- Drugs that are still on patent;
- Drugs that are off patent;
- Drugs not yet approved for marketing (Figure 2).

Measuring the success of regulatory changes

In a 2001 status report to Congress, the FDA noted that the pediatric exclusivity provision "had done more to generate clinical studies and useful prescribing information for the pediatric population than any other regulatory or legislative process to date" (Box 2) [108]. This assessment was based largely on the number of pediatric-specific labeling changes, and by this metric, there has been continued progress. Between 1 June 1998 and 25 October 2011, the FDA approved 425 pediatric-specific labeling changes as a result of studies conducted under BPCA or required by PREA [4]. Labeling changes have added significantly to our knowledge of safety and dosing of many drugs in children. In an analysis of the first 108 products with labeling changes in response to a written request, Rodriguez *et al.* [14] found that:

- Twenty three contained new or revised pediatric information such as new dosing, dosing changes, or pharmacokinetic information;
- Thirty four included new or enhanced safety information;
- Nineteen included information on lack of efficacy;
- Seventy seven extended age limits for the product.

Overall, >50% of products studied had substantive differences in dosing, safety or efficacy. Approximately 20% of the labeling changes highlighted age-related changes in drug absorption or elimination. For example, clearance of the commonly used attention deficit hyperactivity disorder medication Concerta® (methylphenidate HCl) in children ages 6–12 years was approximately 50% lower in comparison with adolescents or adults, while the opposite relationship was seen for clearance of the antihypertensive Lotensin® (benazapril HCl), where clearance in the 6–12-year-old age

Table 1. Priority list of needs in pediatric therapeutics.

Therapeutic Areas	Drugs
Infectious disease	
Methicillin-resistant *Staphylococcus aureus* infections	Clindamycin, trimethoprim sulfamethoxazole
Infections	Benzathine penicillin G, acyclovir, doxycycline
Tinea capitis	Griseofulvin
Antituberculous drugs	No specific drug
Antiparasitic drugs	Albendazole†
Influenza	Oseltamivir
Cardiovascular disease	
Hypertension	Hydrochlorothiazide, lisinopril†, β blockers, amlodipine†
Hypotension	Sodium nitroprusside, dopamine
Dyslipidemia†	Statins†
Respiratory disease	
Asthma	Therapeutics in young children, drug-delivery systems, albuterol
Pulmonary hypertension†	No specific drug
Intensive care	
Anesthesia/sedation	Ketamine, inhaled anesthetics†/isofluorane, lorazepam
Biodefense research	
Nerve agent exposure	Drug delivery systems, midazolam†
Cyanide toxicity	Hydroxycobalamine†
Organophosphate poisoning	Praladoxime
Pediatric cancer	
Neuroblastoma	13-*cis*-retinoic acid
Leukemias and solid tumors	Methotrexate, vincristine, daunomycin, actinomycin-D, 6-mercaptopurine†
Psychiatric disorder	
ADHD	Methylphenidate
Bipolar disease	Lithium
Psychosis/aggression†	Atypical antipsychotics
Neurological disease	
Cerebral palsy	Lorazepam
Seizures†	Fosphenytoin
Neonatal research	
Neonatal BPD/lung development	Betamethasone, azithromycin (intravenous)
Pain	Morphine
Neonatal abstinence syndrome	Methadone
Infections in neonates	Metronidazole†
Necrotizing enterocolitis	Ampicillin, meropenem
Adolescent research	
OTC drug use	No specific drug
Adolescent pharmacology	No specific drug

†Drug and indications newly added to the Best Pharmaceuticals for Children Act list from the 2010 prioritization process or other sources identified by the NICHD as a priority.
ADHD: Attention deficit hyperactivity disorder; BPD: Bronchopulmonary dysplasia; OTC: Over the counter.
Adapted from [111].

Table 1. Priority list of needs in pediatric therapeutics (Cont.).

Therapeutic Areas	Drugs
Hematologic disease	
Sickle cell anemia	Hydroxyurea
Thrombosis and thromboprophylaxis	No specific drug
Endocrine disease and diseases with limited alternative therapies	
Fragile X	MGluR5 antagonists
Type I diabetes	No specific drug
Dermatologic disease	
Atopic dermatitis	Hydrocortisone valerate
Severe inflammatory skin disease†	Methotrexate†
Gastrointestinal disease	
Gastroesophageal reflux	Prokinetic drugs, H2 blockers
Cyclic vomiting and weight gain†	Cyproheptadine†
Cholestatic disease†	Ursodeoxycholic acid†
Renal disease	
Chronic kidney failure	Devices used in dialysis
Anemia of chronic disease	Agents to stimulate erythropoiesis†
Rheumatologic disease	
Connective tissue diseases	Hydroxychloroquin
Special considerations	
Therapeutics in children with intellectual and physical disabilities†	No specific drug or indication†
Pediatric formulations†	Multiple drugs and indications†
Pediatric devices†	General issues†

†Drug and indications newly added to the Best Pharmaceuticals for Children Act list from the 2010 prioritization process or other sources identified by the NICHD as a priority.
ADHD: Attention deficit hyperactivity disorder; BPD: Bronchopulmonary dysplasia; OTC: Over the counter.
Adapted from [111].

group was approximately 50% higher in comparison with adults [14].

Another important assessment of the success of BPCA and PREA is the number of pediatric clinical trials conducted in children. Over a 6-year period before passage of the pediatric exclusivity provision (1991–1996), drug sponsors promised to complete 71 postmarketing studies, but only 11 were actually completed [108]. In the first 2 years after passage of pediatric exclusivity (1998–2000), sponsors completed 58 pediatric studies that resulted in 25 grants of pediatric exclusivity [108]. This trend has continued, and over the 5 years since renewal of the pediatric exclusivity program, >400 studies have been conducted in children under the auspices of PREA and BPCA, enrolling >170,000 study subjects [110].

Increasing trial experience and monetary investment has resulted in important intellectual gains. Trials in children are particularly challenging because of specific concerns related to ethics, dosing, outcome measures, low blood volume and difficulty analyzing small samples, assessment of long-term effects on growth/development, and the inability to use 'healthy' volunteers for early-phase studies. Consequently, more than half of all trials conducted under BPCA have been considered failed trials [111]. However, increasing trial experience has improved our understanding of the specific differences between pediatric and adult trials, and these intellectual gains will enhance future trials and improve child health.

As an example, an analysis of anti-hypertensive trials completed for pediatric exclusivity highlighted pediatric-specific factors that contributed to the inability of several dose-ranging trials to demonstrate an effective dose–response relationship [15]. In this analysis, failed trials often used a narrow dose range, failed to use weight-based dosing, or did not use liquid-based formulations. These findings and others have resulted in substantial changes to the FDA's written request, including a requirement that an age-specific formulation be developed along with age-specific enrollment criteria.

Box 1. Summary of pediatric drug provisions included in the 2012 US FDA Safety and Innovation Act.
Permanently reauthorizes pediatric drug laws
■ PREA and BPCA reauthorized without sunset
Requires earlier and better pediatric study planning
■ Drug companies must submit pediatric study plans at the end of Phase II trials in adults
■ The FDA and drug companies must meet to discuss pediatric studies
■ The FDA must publish, within 1 year, a proposed rule detailing the pediatric study planning process
Adds new enforcement tools
■ The FDA must issue public non-compliance letters to companies that do not fulfill PREA requirements
■ Allows companies to request an extension for good cause if PREA studies are delayed
Increases focus on neonatal drug studies
■ Requires all written requests to include studies in neonates or to outline reasons for not doing so
■ Requires that a neonatologist sit on the FDA's internal Pediatric Review Committee
■ Requires the FDA to hire a neonatologist to assist the agency in neonatal application of BPCA and PREA
Increases transparency
■ Requires the FDA to release data reviews of BPCA studies submitted between 2002 and 2007 that have never been made publicly available
Improves accountability
■ Requires PeRC review of deferral extension requests
■ Requires the FDA to publish a publicly available report on BPCA and PREA every 5 years
Other improvements
■ Extends the mandatory reporting of adverse events period from 1 year to 18 months
■ Renews the authorization of appropriations for the NIH BPCA program for 5 years at US$25 million per year
■ Requires the FDA to hold a public meeting on accelerating development of therapies for pediatric rare diseases and develop a strategic plan

BPCA: Best Pharmaceuticals for Children Act; PeRC: Pediatric Review Committee; PREA: Pediatric Research Equity Act.
Adapted from [109].

There have been important clinical trial infrastructure improvements as well. The 2002 BPCA required the NIH to establish a program for pediatric drug testing and development. The NICHD was charged with implementing this plan and therefore developed the Obstetric and Pediatric Pharmacology Branch (OPPB), which was established in 2004. The annual budget of the OPPB has ranged from US$29–37 million with $25 million annually from BPCA grants and contracts [16]. The OPPB has provided a central organizing branch at NIH dedicated to the study of pediatric and obstetric therapeutics and also to the training of individuals with a focus in pediatric/obstetric clinical pharmacology. The OPPB is also required to develop the 'priority list' of off-patent therapeutic agents that require study [16]. The BPCA also required the FDA to establish the Office of Pediatric Therapeutics within the FDA. The Office of Pediatric Therapeutics's primary mission is to ensure access for children to innovative, safe and effective medical products.

The creation of these defined branches within the NIH and FDA that are dedicated to the study of pediatric therapeutics has been enormously important to centralizing and coordinating pediatric trials. Centralized oversight has allowed the development of a strategic focus and has helped map out common goals and objectives to ensure that relevant stakeholders are involved at all levels of coordination, planning and implementation of pediatric study. A good example is the development of the priority list (Table 1). This list of off-patent drugs is revised every 3 years under the guidance of the OPPB and involves input from pediatricians and subspecialist providers, pharmacologists and basic scientists, as well as industry and advocacy representatives. The process to develop the priority list is continually refined and currently focuses on distinct areas of therapeutic need, with priority areas of study identified every year. To facilitate study of therapeutics on the priority list, the NICHD has supported over 60 research networks or consortia [112]. Two examples related to BPCA include:

- The Pediatric Pharmacology Research Unit Network, which existed from 1994–2010 and was designed to

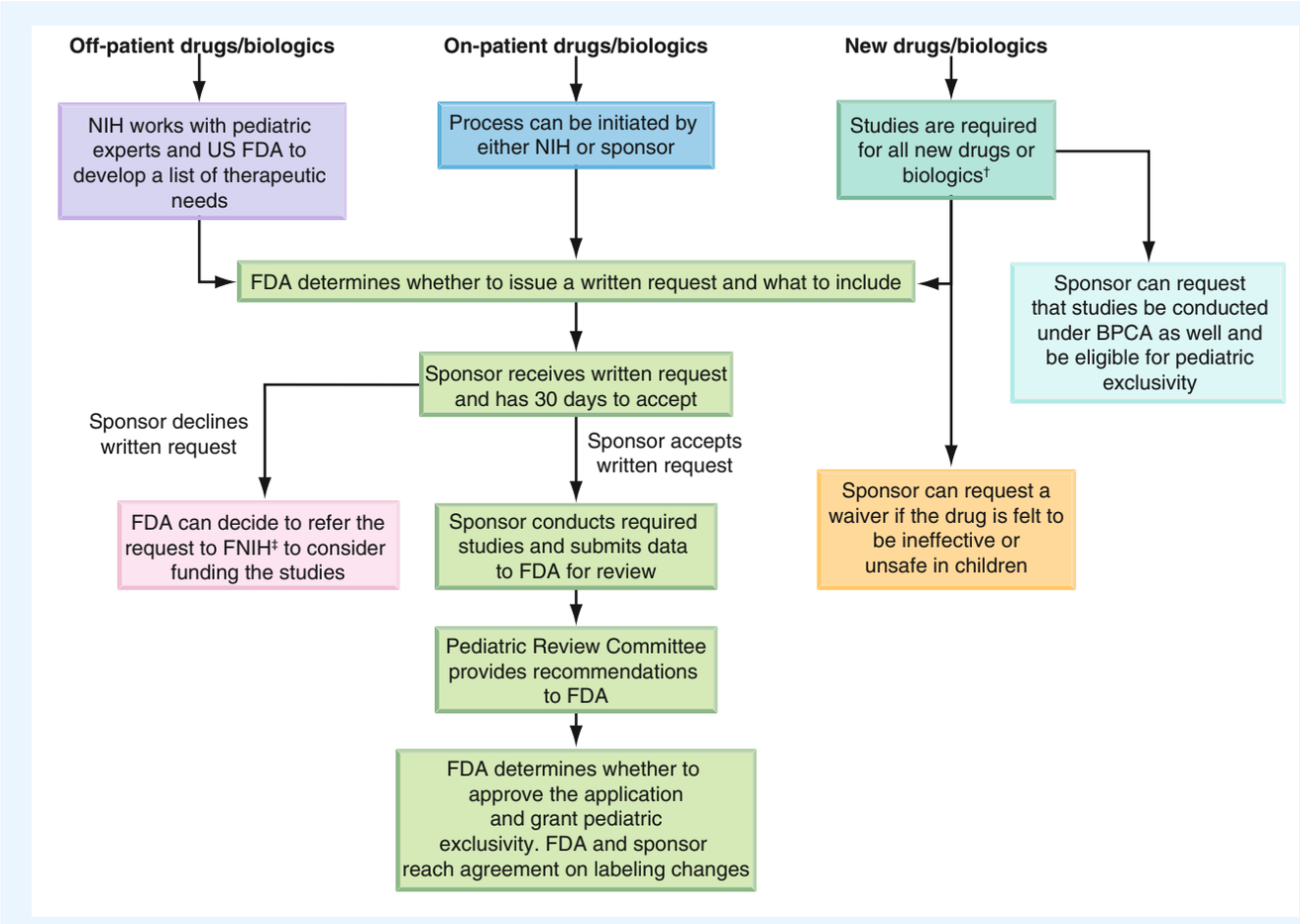

Figure 2. Process for study of drugs or biologics under Best Pharmaceuticals for Children Act and Pediatric Research Equity Act.
†New drugs/biologics have: new active ingredients; new indications; new dosage forms; new dosing regimens; or new reoutes of administration.
‡FNIH is an independent, nonprofit corporation. The majority of funds that the FNIH receives are from the private sector. The FNIH has partially funded two prior studies, but has not funded any studies since 2007. More recently, a study of most 'on-patent' agents has been picked up by the Pediatric Trials Network.
BPCA: Best Pharmaceuticals for Children Act; FNIH: Foundation for the National Institutes of Health.

facilitate collaboration among the NIH, academia, and industry and to develop a comprehensive program in pediatric clinical/developmental pharmacology. The Pediatric Pharmacology Research Unit conducted over 250 studies and contributed to labeling changes for 23 different therapeutic agents [113];

- The Pediatric Trials Network (PTN), which was initiated in 2010 by the NICHD as the primary avenue for study of off-patent agents after a written request has been declined. Although still in its infancy, the PTN currently has 30 molecules under active study and includes a network of 60 participating sites across the USA. The PTN has initiated study of 16 off-patent agents currently listed on the BPCA priority list [114].

In addition to infrastructure improvements in the USA, BPCA and PREA regulations have contributed to an increased global emphasis on pediatric drug study. In 2006, the European Parliament followed the US example, passing legislation requiring pediatric-specific study of drugs. In response, the European Medicines Agency has developed 'pediatric investigation plans' [115]. Likewise, in 2007, the WHO initiated its 'Make Medicines Child Size' program [116]. Globally, pediatric-based practitioners have been inspired by the increased commitment to pediatric drug study. An example is the Standards for Research in Child Health Initiative – a global initiative supported by the FDA, the European Medicines Agency and the WHO, that aims to "improve the quality of design, conduct, and reporting of pediatric clinical research by

Box 2. Results of studies conducted under Best Pharmaceuticals for Children Act and Pediatric Research Equity Act.

Mandated (new drug/biologics applications)
■ 134 products studied since BPCA reauthorized in 2007†
■ 335 studies conducted since BPCA reauthorized in 2007‡
■ 211 pediatric-specific labeling changes§
Incentivized (primarily on-patent drugs/biologics)
■ 57 products studied since BPCA reauthorized in 2007†
■ 152 studies conducted since BPCA reauthorized in 2007‡
■ 253 pediatric-specific labeling changes§
Prioritized (primarily off-patent drugs/biologics)
■ 17 off-patent products referred to NIH for study¶
■ 5 studies with results submitted to NIH for review¶
■ 0 labeling changes¶

The US FDA has been required to track products studied and studies conducted since BPCA was reauthorized in September 2007. A total of 30 products, 82 studies and 59 labeling changes were conducted under both Pediatric Research Equity Act and BPCA and were thus mandated and incentivized.

†Data taken from [119].

‡Data taken from [120].

§Data taken from [121].

¶A 2012 Institute of Medicine Report [4].

BPCA: Best Pharmaceuticals for Children Act.

promoting the use of modern research standards" [17]. There have also been global infrastructure gains. In an analysis of published trials completed under the pediatric exclusivity provision between 1998 and 2007, trials were conducted in over 50 different countries, including more than a third with sites in developing nations [18]. While there certainly are ethical and quality concerns related to the globalization of pediatric research, it is likely that such a global investment in pediatric trial infrastructure will improve the ability to conduct future trials.

Critiques

■ Cost

While few would debate the importance of investing in pediatric trials, the public cost of pediatric exclusivity has been criticized. Six months of patent extension can result in tremendous economic gain for pharmaceutical companies when the patent extension is for a 'blockbuster drug' (defined as a drug with annual sales exceeding $1 billion). For example, a public watchdog group estimated that the added revenue for 6 months of patent extension for Prilosec® would exceed $1.4 billion [105]. This cost is passed on to the general public as these drugs will not be available in generic form until the patent extension expires. In a cost analysis of 14 drugs granted pediatric exclusivity in three blockbuster drug classes – ACE inhibitors, statins, and serotonin selective reuptake inhibitors – extrapolated cost to the US Medicaid program was estimated at $340 million for the 6 months of patent extension [19].

It should be noted that there is an upfront cost for study sponsors with no guarantee of a positive profit margin. In an analysis of drugs across nine different pediatric subspecialty areas, the median cost per written request for studies performed under the pediatric exclusivity program was $12.3 million (range: $5.1–43.8 million). When accounting for economic returns resulting from patent extension (8/9 drugs studied received patent extensions), the median net benefit was $134.3 million (range: -$8.9–507.9 million), and the net benefit/cost ratio ranged widely from -0.68 to 73.63 [20]. By chance, this analysis was atypically weighted towards blockbuster drugs, which represented five of the nine drugs studied. Nonetheless, these data highlight the variability in both cost and benefit, and also demonstrate that there may be some risk to pharmaceutical companies of a negative profit margin for the study of less economically viable products. However, it is also important to recognize that 80% of written requests issued by the FDA have been sponsor-initiated. While the FDA must first determine if there is a need to study these drugs in the pediatric population, sponsors obviously prefer to study drugs with the greatest potential financial gain. Consequently, 'blockbuster drugs' may have been disproportionately represented, at least in the early years of the program. An analysis of trials conducted between 2002 and 2004 under the pediatric exclusivity program noted that 13/59 (22%) products studied were 'blockbuster' drugs [20].

Although the financial benefit to pharmaceutical companies has been significant, it is also important to consider the overall cost benefit of improved pediatric drug dosing and safety. Cost savings to the health care system solely from a modest 2% reduction in adverse events for children have been estimated to be in the range of $152–708 million annually, based on the overall annual cost of adverse events and the incidence of adverse events in children [5]. To further quantify these gains for Congress, the FDA examined hospitalization rates for five serious illnesses (asthma, HIV/AIDS, cancer, pneumonia and kidney infections) and found significantly higher rates for children than for middle-aged adults. The agency hypothesized that some of the difference in hospitalization rates might be due to fewer informed drug therapies and less adequate data on drug dosages in children. The FDA calculated that eliminating 25% of these differentials for just these five illnesses would lead to direct medical cost savings of $228 million annually, and would account for approximately a third of the total costs of the exclusivity program over the next 20 years, with increased gain likely beyond that time frame [108]. Thus, the potential financial gain from improved pediatric drug dosing, safety and efficacy is likely significant. The fact that the BPCA program received near unanimous congressional support and was renewed without sunset in 2012, despite the financial and

political climate, highlights the major importance of drug and device development for child health and suggests that there is broad agreement among stakeholders that the long-term financial and public health benefits outweigh the associated costs.

Misaligned objectives

Another criticism of the BPCA program is that labeling changes are not the best means to improve safety and effectiveness of drug therapy. Physicians often do not use the drug label, typically preferring prescriber drug references including the Harriet Lane Handbook or Neofax. Neither of these resources indicate when dosing is recommended for off-label indications or age groups. In a limited analysis for an Institute of Medicine report, these prescribing resources often did not include the latest labeling information [4].

Furthermore, there is an evident discrepancy between labeling changes and actual need within the field. This is because study is only mandated for new ingredients, indications, regimens, or routes of administration and because there is only financial incentive to study on-patent drugs. Consequently, only one study sponsor has ever accepted an FDA-issued written request to study an off-patent drug; therefore, some of the most commonly prescribed pediatric drugs are neglected. As an example, in 1994 when the pediatric rule was first proposed by the FDA, ten drugs were identified as the most commonly prescribed off-label pediatric medications [108]. Four of those ten drugs – clotrimazole/betamethasone, fluoxetine, cromolyn sodium, and sertraline – remained on-patent, and all four were quickly studied following passage of the exclusivity provision. By the time of the FDA's first status report to Congress in 2001, all four had been granted patent extension [108]. The remaining six drugs were all off-patent – ampicillin, albuterol (for use in ages <2 years), antipyrine/benzocaine otic, promethazine, methylphenidate, and metaproterenol sulfate. To date, only methylphenidate has received a labeling change, and this was accomplished via an application for a new dosing regimen for an extended-release capsule [117]. Therefore, the sponsor qualified for patent extension. In a 2010 analysis, the Government Accountability Office reported that 17 off-patent written requests had been declined by sponsors and therefore referred to the NIH for further study. The NIH has funded studies of 11 of these agents, but at the time of the 2010 review, none of the studies had yet satisfied the requirements of their written request, and to date none of these studies has resulted in a labeling change [104,117].

The reasons behind this limited ability to study off-label therapeutics are primarily financial. The annual budget for the NICHD was $1.1 billion when Prilosec® received its patent extension, resulting in an estimated $1.4 billion in additional profits to AstraZeneca. Considering the financial implications, it is clear that under the current system, on-patent agents, and particularly more profitable agents, will be prioritized by study sponsors. As an example, of the 192 drugs listed on the FDA website as having received pediatric exclusivity through July 2012, 20 (10%) are antihypertensive agents including six different ACE inhibitors and four different angiotensin receptor blockers. Many of these agents are rarely prescribed by pediatric providers. Meanwhile, three commonly prescribed off-patent antihypertensive agents – sodium nitroprusside, furosemide and spironolactone – were included on the initial BPCA priority list in 2003, and a fourth agent, hydrochlorothiazide, was added with the first update in 2009. None of these off-patent agents have received labeling changes. In the interim, other drugs that have received pediatric exclusivity include eight cholesterol-lowering agents (including six different statins), six anti-reflux agents (including four different proton pump inhibitors), and four different antidepressants (three serotonin selective reuptake inhibitors and a serotonin–norepinephrine reuptake inhibitor) [118].

No allocated funding for off-label drugs

In the absence of a financial incentive to study off-patent agents, it is clear that funds must be allocated or privately raised. In 2002, with passage of BPCA, Congress authorized appropriation of $200 million for the fiscal year dedicated to the Program for Pediatric Studies of Drugs and for "such sums as are necessary for the five succeeding fiscal years" [102]. In essence, this was the monetary estimate that they felt would be necessary to study off-patent agents (for which the Program for Pediatric Studies of Drugs was designed). These funds were initially to be raised by the 'Foundation for the National Institutes of Health,' a private, not-for-profit foundation established by Congress [102,104]. However, the foundation has not provided funds for study of any off-patent agent, and they are no longer tasked with raising funds related to BPCA. In fact, no funds have ever actually been allocated by Congress for the BPCA program, and instead the funds must be provided from the internal NIH budget, therefore decreasing the pool of money available for study in other pediatric initiatives.

Limited neonatal studies

Another criticism of pediatric studies conducted under BPCA and PREA is a relative lack of neonatal trials [21]. By the end of 2011, only 6% of labeling changes enacted under BPCA applied to neonates [4]. Neonates (age <28 days) are the most neglected of all pediatric subpopulations, and by some estimates over 90% of medications are used off-label in this group [4]. The 2007 BPCA reauthorization included language to encourage neonatal

study and required a subsequent review of neonatal studies [101]. Of 37 written requests issued after 2007, only one required a neonatal study while three requested neonatal studies but gave the sponsors the option of excluding neonates. Since 2007, only eight drugs with written requests issued prior to 2007 have received neonatal-specific labeling changes, and of these, only two have been for new drug applications [104].

There are several reasons for the relative paucity of studies in neonates. New drug studies are often not required by the PREA mandate because the requirements apply only to the specific indication included in the application, and this indication typically applies to adults and/or older children. Similarly, the incentive structure has also been less successful in neonates. This is because pediatric exclusivity is often granted after study of the drug in children ages >1 month. Once exclusivity has been granted, there is no remaining incentive for sponsors to go back and conduct neonatal trials. In addition, the FDA has sometimes agreed to waive neonatal study requirements because there have been safety or ethical concerns with conducting these studies.

There are, in fact, unique challenges to clinical trials in neonates. These include scientific challenges relating to:

- The novel diseases and physiology of neonates;
- The heterogeneity of diseases and drug responses between neonates of differing gestational ages;
- The need for long-term and therefore costly follow up to assess drug effects on neurodevelopment;
- Limited availability of blood for sampling.

There are also unique ethical challenges. For example, balancing risk and benefit is complicated in an extremely premature neonate for whom any form of unnecessary intervention could be construed as harmful. In addition, there may be ethical concerns with obtaining informed consent and enrolling neonates in clinical trials as parents are under duress with limited time between presentation and initiation of drug therapy [21,22].

These ethical and scientific challenges have historically limited neonatal clinical trials and serve as a major barrier to improved drug study. However, important stakeholders now recognize that it is also unethical to practice neonatal medicine without adequate data on drug safety or efficacy. In an open letter to US senators in April 2012, the American Pediatric Association, American Pediatric Society, Association of Medical School Pediatric Department Chairs, and the Society for Pediatric Research all strongly encouraged regulatory provisions to advance neonatal drug studies in the 2012 BPCA/PREA reauthorization. In the same letter, they recommended that a neonatologist be permanently added to the FDA Office of Pediatric Therapeutics [107]. These changes were recently incorporated into the 2012 reauthorization, but it remains to be seen if they will help circumvent some of the unique challenges inherent to neonatal clinical trials.

Lack of publication

Publication of trial results ensures transparency and is also the most effective mechanism for dissemination of information to the greater pediatric community. While publication is the traditional benchmark for trial completion in academic circles, it is not a critical performance end point for industry. This may explain why relatively few trials conducted for pediatric exclusivity have been published in peer-reviewed journals. In an analysis of trials conducted between 1998 and 2004, only 44% were ultimately published, including only 33/100 trials that resulted in an important labeling change. This practice has been challenged as ethically unacceptable [23].

Conclusion

Since the 1990s, there has been an increasing awareness of the public health consequences of inadequate pediatric drug study. Regulatory changes have attempted to address these concerns by providing incentives as well as mandates to increase study and to improve labeling of agents for use in neonates, children and adolescents. By all accounts, these efforts have been enormously successful at stimulating pediatric research. Industry has injected much needed capital into pediatric trials, and, as a result, >400 labeling changes have been made. Undoubtedly, these efforts will improve the safety of pediatric medicine. However, the 'financial windfall' for industry remains a significant criticism. This financial gain comes largely at the expense of the US taxpayer. While the public health cost will ultimately be offset by savings as a result of improved pediatric drug dosing, safety and efficacy, many feel that industry should not be the ultimate financial benefactor. Furthermore, the money invested could potentially have achieved greater net-benefit, particularly in the realm of off-patent drugs, which are some of the most frequently prescribed pediatric drugs and yet remain vastly understudied. Nonetheless, after decades of relatively futile efforts to improve pediatric labeling, there have finally been substantive gains.

Future perspective

After decades of relative stagnation, it is clear that legislation is an effective means to stimulate change. Industry has responded to legislative mandates and incentives, and the resultant investment has led to greater progress than at any other time in the history of pediatric drug research. Early legislative shortfalls have been addressed during the reauthorization process, and the FDA and Congress have continually refined their efforts to appropriately stimulate pediatric drug

study. These refinements have been important and have resulted in critical improvements, including development of the priority list, establishment of branches at the NIH and FDA, and a renewed interest in training a future generation of clinical pharmacologists. However, pediatric drug study remains limited relative to that seen in adults. For example, there is no mechanism or incentive to encourage new drug development specifically for childhood diseases. Instead pediatric providers must continue to rely on 'trickle down' from the adult armamentarium.

Now that the 2012 BPCA reauthorization has been approved without sunset, there is no longer an automatic timeline for future refinements. Therefore, the onus will fall on the pediatric community to ensure continued procedural improvements to optimize alignment of investment and objectives. To this end, pediatric specialists should be included in key decision-making roles (e.g., at the FDA and NIH) and should have input into trial design, objectives, interpretation of results, and decisions regarding labeling. The most important future priority should be to improve study of off-patent agents. To this end, the incentive structure is limited, and, despite greater need, off-patent drug study has been relatively neglected. Recent efforts by the NIH are encouraging – particularly investment in infrastructure such as trial networks (e.g., Pediatric Trials Network) devoted to pediatric drug/device study. It is important to capitalize on these infrastructure gains but, more importantly, to encourage further

Executive summary

Off-label drug use in children

- Historically, approximately 80% of drugs have not been labeled for use in children.
- There are numerous examples of serious adverse events as a result of drugs used to treat children without prior study of dosing, safety or efficacy.
- Despite widespread recognition of this problem, prior to the 1990s there had been little improvement in pediatric drug labeling in over two decades.

Major regulatory changes mandating or incentivizing pediatric study

- US FDA Modernization Act (1997) – Introduced 'pediatric exclusivity' providing a potential 6-month patent extension for studies in response to an FDA-issued written request.
- Best Pharmaceuticals for Children Act (2002) – Reauthorized pediatric exclusivity and initiated a process for study of off-patent agents, including development of a priority list.
- Pediatric Research Equity Act (2003) – Mandates pediatric-specific study of all New Drug Applications, including submissions for new ingredients, new indications, new dosage forms, new regimens and new routes of administration.

The current process for pediatric drug study

- On-patent agents – The FDA issues a written request and, if sponsor accepts and completes the required studies, then it can qualify for pediatric exclusivity.
- Off-patent agents – Rarely studied by the sponsor as there is no financial incentive and therefore typically referred to the NIH (National Institute of Child Health and Human Development) to initiate study.
- New Drug Applications – Pediatric Research Equity Act regulations require pediatric study for the specific drug indication included in the application.

Major successes over the past 15 years as a direct result of regulatory changes

- Over 700 clinical trials conducted in children.
- Over 400 pediatric-specific labeling changes that have improved dosing, enhanced safety, extended age indications or included information on efficacy.
- Intellectual gains, including improvements in pediatric trial design and conduct, as well training of clinical pharmacologists with pediatric expertise.
- Infrastructure gains including establishment of the FDA Office of Pediatric Therapeutics and the Obstetric and Pediatric Pharmacology Branch at the NIH.
- Trial networks (e.g., Pediatric Trials Network) developed to study off-patent drugs.

Critiques

- Patent extension is a 'financial windfall' for drug companies.
- On-patent agents have been disproportionately prioritized with less study of important off-label agents.
- Although neonates are perhaps the most vulnerable pediatric population, only 6% of all labeling changes have included neonatal information.

Future perspective

- Regulatory changes have improved safety and labeling of pediatric therapeutics; however, the process can be refined to achieve a better cost–benefit margin.

investment in pediatric research. Billions of industry dollars were required to stimulate the >400 labeling changes for on-patent agents. A similar investment will be needed to encourage similar gains for off-label therapeutics.

Acknowledgments

The authors would like to thank A McMillan of the Duke Clinical Research Institute for her editorial assistance.

Financial & competing interests disclosure

K Hill has received a research grant from Pfizer Inc. PB Smith has served as consultant for Pfizer Inc., Astellas Pharma and GlaxoSmithKline and has received a research grant from Cubist Pharma. MC Wolkowiez has received a research grant from Pfizer Inc.; he has also served as consultant for Pfizer Inc. and Johnson & Johnson. DK Benjamin serves as a consultant (generating personal income) to Astellas Pharma US, Biosynexus, Cubist Pharmaceuticals, Johnson & Johnson Pharmaceutical research and development, Merck and Co., Pfizer Inc. and The Medicines Company. He has research grant from Astellas Pharma US, AstraZeneca and UCB Pharma. He also receives support from the US government for his work in pediatric and neonatal clinical pharmacology (1R01HD057956–02, 1R01FD003519–01, 1U10-HD45962–06, 1K24HD058735–01, and Government Contract HHSN267200700051C under the Best Pharmaceuticals for Children Act), the non-profit organization Thrasher Research Foundation for his work in neonatal candidiasis, and from industry for neonatal and pediatric drug development (For more information see: www.dcri.duke.edu/research/coi.jsp).

J Li does not have any conflicts of interest to report. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

References

Papers of special note have been highlighted as:

- ■ of interest

1 Shah S, Hall M, Goodman DM *et al.* Off-label drug use in hospitalized children. *Arch. Pediatr. Adolesc. Med.* 161, 282–290 (2007).

- ■ **An analysis of off-label drug prescribing habits among hospitalized children in the Pediatric Health Information Systems database.**

2 Wilson JT. An update on the therapeutic orphan. *Pediatrics* 104(3 Pt 2), 585–590 (1999).

3 Gilman JT, Gal P. Pharmacokinetic and pharmacodynamic data collection in children and neonates. A quiet frontier. *Clin. Pharmacokinet.* 23, 1–9 (1992).

4 Institute of Medicine. *Safe and Effective Medicines for Children. Pediatric Studies Conducted Under the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act*. Field MJ, Boat TF (Eds). The National Academies Press, Washington, DC, USA (2012).

- ■ **An Institutes of Medicine review of aspects of pediatric studies and changes in product labeling that resulted from Best Pharmaceuticals for Children Act and Pediatric Research Equity Act and their predecessor policies.**

5 Ward RM, Kauffman R. Future of pediatric therapeutics: reauthorization of BPCA and PREA. *Clin. Pharmacol. Ther.* 81, 477–479 (2007).

6 Breslow LH. The Best Pharmaceuticals for Children Act of 2002: the rise of the voluntary incentive structure and congressional refusal to require pediatric testing. *Harvard J. Legis*. 40, 133–193 (2003).

- ■ **An excellent review of the history of pediatric drug legislation.**

7 Choonara I, Rieder M. Drug toxicity and adverse drug reactions in children – a brief historical review. *Paediatr. Perinat. Drug Ther.* 5, 12–18 (2002).

8 Weiss CF, Glazko AJ, Weston JK. Chloramphenicol in the newborn infant. A physiologic explanation of its toxicity when given in excessive doses. *N. Engl. J. Med*. 262, 787–794 (1960).

9 Benjamin DK Jr, Smith PB, Sun MJ *et al.* Safety and transparency of pediatric drug trials. *Arch. Pediatr. Adolesc. Med*. 163, 1080–1086 (2009).

10 US FDA. Specific requirements on content and format of labeling for human prescription drugs: revision of "pediatric use" subsection in the labeling. *Fed. Regist*. 59(238), 64240–64250 (1994).

11 Department of Health and Human Services US FDA. Regulations requiring manufacturers to assess the safety and effectiveness of new drugs and biological products in pediatric patients: FDA final rule. *Fed. Regist*. 63(231), 6366632–6366672 (1998).

12 NIH. Best Pharmaceuticals for Children Act (BPCA) priority list of needs in pediatric therapeutics. *Fed. Regist*. 776(63), 18228–18229 (2011).

13 Vanchieri C, Butler AS, Knutsen A. *Addressing the Barriers to Pediatric Drug Development: Workshop Summary. Institute of Medicine Forum on Drug Discovery, Development, and Translation*. The National Academies Press, Washington, DC, USA (2008).

14 Rodriguez W, Selen A, Avant D *et al.* Improving pediatric dosing through pediatric initiatives: what we have learned. *Pediatrics* 121, 530–539 (2008).

- ■ **A review of the various labeling changes that resulted from the study of drugs in response to a US FDA-issued written request.**

15 Benjamin DK Jr, Smith PB, Jadhav P *et al.* Pediatric antihypertensive trial failures: analysis of end points and dose range. *Hypertension* 51, 834–840 (2008).

- ■ **An analysis of factors contributing to success or failure of trials of pediatric anti-hypertensive agents that were conducted in response to a written request.**

16 Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Department of Health and Human Services. *Obstetric and Pediatric Pharmacology Branch (OPPB), National Institute of Child and Human Development, Report to the National Advisory Child Health and Human Development Council, January 2008*. US Government Printing Office, Washington, DC, USA (2008).

17 Hartling L, Wittmeier KD, Caldwell P *et al.* StaR child health: developing evidence-based guidance for the design, conduct, and reporting of pediatric trials. *Pediatrics.* 129(Suppl. 3), S112–S117 (2012).

18 Pasquali SK, Burstein DS, Benjamin DK Jr, Smith PB, Li JS. Globalization of pediatric research: analysis of clinical trials completed for pediatric exclusivity. *Pediatrics* 126, e687–e692 (2010).

19 Nelson RE, McAdam-Marx C, Evans Ml *et al.* Patent extension policy for paediatric indications: an evaluation of the impact within 3 drug classes in a state medicaid programme. *Appl. Health Econ. Health Policy* 9, 171–181 (2011).

20 Li JS, Eisenstein EL, Grabowski HG *et al.* Economic return of clinical trials performed under the pediatric exclusivity program. *JAMA* 297, 480–488 (2007).

■ **Analysis of the costs associated with pediatric exclusivity.**

21 Ward RM, Kern SE. Clinical trials in neonates: a therapeutic imperative. *Clin. Pharmacol. Ther.* 86, 585–587 (2009).

22 Baer GR, Nelson RM; Ethics Group of the Newborn Drug Development Initiative. Ethical challenges in neonatal research: summary report of the ethics group of the newborn drug development initiative. *Clin. Ther.* 28, 1399–1407 (2006).

23 Benjamin DK Jr, Smith PB, Murphy MD *et al.* Peer-reviewed publication of clinical trials completed for pediatric exclusivity. *JAMA* 296, 1266–1273 (2006).

■ Websites

101 Full text of the US FDA Amendments Act of 2007.
www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FoodandDrugAdministrationAmendmentsActof2007/FullTextofFDAAALaw/default.htm
(Accessed 5 October 2012)

102 Full text of the Best Pharmaceuticals for Children Act (2002).
www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/ucm148011.htm
(Accessed 5 October 2012)

103 Full text of the Pediatric Research Equity Act (2003).
www.gpo.gov/fdsys/pkg/PLAW-108publ155/html/PLAW-108publ155.htm
(Accessed 5 October 2012)

104 United States Government Accountability Office Report to Congressional Committees: Pediatric Research – products studied under two related laws, but improved tracking needed by FDA (2007).
www.gao.gov/new.items/d11457.pdf
(Accessed 5 October 2012)

105 Public Citizen. Patently offensive: congress set to extend monopoly patents for Cipro and other drugs (2001).
www.citizen.org/congress/article_redirect.cfm?ID=6435
(Accessed 5 October 2012)

106 Full text of the US FDA Modernization Act (1997).
www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FDAMA/FullTextofFDAMAlaw/default.htm
(Accessed 5 October 2012)

107 Letter to US Senators from the American Pediatric Association, American Pediatric Society, Association of Medical School Pediatric Department Chairs, and the Society for Pediatric Research (2012).
www.ambpeds.org/public_policy/pdf/2012_04_20BPCAneonatesLetter.pdf
(Accessed 5 October 2012)

108 US FDA. Status Report to Congress on the Pediatric Exclusivity Provision (2001).
www.fda.gov/downloads/drugs/developmentapprovalprocess/developmentresources/ucm049915.pdf
(Accessed 5 October 2012)

109 American Academy of Pediatrics Pediatric Drug and Device laws reauthorization summary (2012).
www.aap.org/en-us/advocacy-and-policy/federal-advocacy/Documents/PediatricDrugDeviceLawsReauthorizationSummary.pdf
(Accessed 5 October 2012)

110 US FDA. Breakdown of FDAAA completed pediatric studies (2012).
www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm190622.htm
(Accessed 5 October 2012)

111 Best Pharmaceuticals for Children Act Scientific Prioritization Meeting, sponsored by the Obstetric and Pediatric Pharmacology Branch (OPPB), Center for Research for Mothers and Children (CRMC), Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), NIH, and US Department of Health and Human Services (HHS) (2008).
http://bpca.nichd.nih.gov/about/process/upload/Scientific-Prioritization-063008-final-073108-mm-ln.pdf
(Accessed 5 October 2012)

112 National Institutes of Child Health and Development. Extramurally supported clinical research networks.
www.nichd.nih.gov/health/clinicalresearch/NICHD.cfm
(Accessed 5 October 2012)

113 The Pediatric Pharmacology Research Units Legacy.
www.ppru.org/
(Accessed 5 October 2012)

114 Pediatric Trials Network.
www.pediatrictrials.org/
(Accessed 5 October 2012).

115 European Medicines Agency. Paediatric investigation plans, waivers and modifications.
www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000293.jsp&mid=WC0b01ac0580025b91
(Accessed 5 October 2012)

116 WHO. Essential medicines for children website.
www.who.int/childmedicines/en/
(Accessed 5 October 2012)

117 US FDA. Office of Pediatric Therapeutics pediatric labeling information database.
www.accessdata.fda.gov/scripts/sda/sdNavigation.cfm?sd=labelingdatabase
(Accessed 5 October 2012)

118 US FDA. Drugs to which FDA has granted pediatric exclusivity for pediatric studies under Section 505A of the Federal Food, Drug, and Cosmetic Act (2012).
www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm050005.htm
(Accessed 5 October 2012)

119 US FDA. Medical, statistical, and clinical pharmacology reviews of pediatric studies conducted under Section 505A and 505B of the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the FDA Amendments Act of 2007 (2012).
www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049872.htm
(Accessed 5 October 2012)

120 US FDA. Breakdown of FDAAA Completed Pediatric Studies (2012).
www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm190622.htm
(Accessed 5 October 2012)

121 US FDA. New pediatric labeling information database (2012).
www.accessdata.fda.gov/scripts/sda/sdNavigation.cfm?sd=labelingdatabase
(Accessed 5 October 2012)