American Academy of Pediatrics

TESTIMONY OF
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on behalf of the
AMERICAN ACADEMY OF PEDIATRICS

before the

COMMITTEE ON ENERGY AND COMMERCE
SUBCOMMITTEE ON HEALTH

UNITED STATES HOUSE OF REPRESENTATIVES

MAY 22, 2007

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Chairman Pallone, members of the committee, I am Richard Gorman, MD, FAAP, a practicing pediatrician who has taken care of infants, children and adolescents for over 25 years. I am here today representing the American Academy of Pediatrics (AAP) in my official capacity as chair of the AAP Section on Clinical Pharmacology and Therapeutics. It is through my practice, Pediatric Partners in Ellicott City, Maryland where I see first-hand the pediatric therapeutic benefits of increased information on drugs used in children. With over 80,000 pediatric visits annually in four clinical sites in three counties in Maryland, my partners and I can attest to the importance of pediatric drug studies legislation. I would also like to express the Academy's strong support for new legislation to improve access and safety of medical devices used in children.

The pediatric academic research community that includes the Ambulatory Pediatric Association, American Pediatric Society, Association of Medical School Pediatric Department Chairs, and the Society for Pediatric Research also supports and endorses the Academy's testimony. These societies comprise academic generalist pediatricians, pediatric researchers, and full-time academic and clinical faculty responsible for the delivery of health care services to children, the education and training of pediatricians, and the leadership of medical school pediatric departments.

THE SUCCESS OF BPCA AND PREA

I am here today on behalf of the American Academy of Pediatrics to discuss the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA), which represent critical public policy successes for children. I begin my testimony today by saying enthusiastically and without reservation that in the last decade we have gained more useful information on drugs used in children through BPCA and PREA than we had in the previous seventy years.

The Senate has recently voted by 93-1 to reauthorize BPCA and PREA. AAP applauds the Senate's action. These two pieces of legislation have advanced medical therapies for infants, children, and adolescents by generating substantial new information on the safety and efficacy of pediatric pharmaceuticals where previously there was none. It is vitally important for infants, children and adolescents that these laws be reauthorized.

In previous testimony before Congress, I have described children as "the canaries in the mineshafts," acting as early warning of unknown dangers. Legislative progress on drug safety for all Americans has most often been made after the tragic injuries or deaths of children. Despite this history, little progress was made in the effort to include the pediatric population in therapeutic advances until passage of the pediatric studies provision of the Food and Drug Administration Modernization Act of 1997 (FDAMA). This provision was later reauthorized as BPCA in 2002, and PREA was enacted in 2003. With the passage of this legislation, we have started to remedy the alarming lack of pediatric drug labeling and information available to pediatricians and other health professionals.

BPCA and PREA work together as an effective two-pronged approach to generate pediatric studies. PREA provides FDA the authority to require pediatric studies of drugs when their use for children would be the same as in adults. BPCA provides a voluntary incentive to drug manufacturers of an additional six months of marketing exclusivity for conducting pediatric studies of drugs that the FDA determines may be useful to children.

Since the passage of FDAMA over a decade ago, FDA has requested nearly 800 studies involving more than 45,000 children in clinical trials through a written request. The information gained from these studies resulted in label changes for 128 drugs.[1] By comparison, in the seven years prior to FDAMA, only 11 studies of marketed drugs were completed, though 70 studies were promised. While similar data tracking PREA's effectiveness is not been publicly available, FDA's website credits 55 label changes to PREA. AAP hopes this year's reauthorization will improve tracking and reporting of PREA's results.

As a clinician, I cannot overstate the importance of what we have learned through the pediatric studies generated by these laws. Children's differing metabolism, growth and development, and size have very large effects. The performance of medications in children's bodies is even more dynamic and variable than we anticipated. Indeed, we have really learned, once again, that children are not just small adults. And the more we learn, the more we realize what we didn't know.

For example, pediatric studies and resultant labeling have:

- given pediatricians the ability to give the correct dose of pain relief medicine to children with chronic pain that were previously under dosed (Neurontin®);

- warned ICU physicians that a drug used for sedation in ICUs had twice the mortality rate as another drug combination (Propofol®);

- given pediatricians and child psychiatrists important information on both the relative effectiveness and serious side effects of anti-depressant medication in adolescents (Prozac®, Paxil®, et al.);

- given children increased relief of pain from medicines taken by mouth, breathed into the lungs, given through the vein, and absorbed through the skin; and,

- alerted both pediatricians and parents about unexpected side effects of medications that have allowed for a more complete discussion of both the risks and benefits of a particular therapeutic course.

What a tremendous improvement over the shrugging shoulders and the resigned look and the soft sigh when we had to say: "I'm sorry, we just don't know enough about this drug in children."

[1] American Academy of Pediatrics. Pediatric studies lead to more information on drug labels. *AAP News*. 2007;2:20-25

If a drug is not labeled for children, pediatricians are faced with two difficult choices: 1) not using a medication that could provide relief and help to the child because it is not labeled for use in pediatrics or 2) using the medication off-label based on limited studies and/or the clinical experience of health professionals. BPCA and PREA have given pediatricians more information to avoid this necessary but inadequate practice.

Better labeling has lead to better therapeutics for children, reducing medical errors and adverse effects. Lack of proper information for pediatric patients related to dosing, toxicity, adverse effects, drug interactions, etc. can and has lead to medical errors and potential injury. Medication errors produce a variety of problems, ranging from minor discomfort to substantial morbidity that may prolong hospitalization or lead to death. Another important factor underscoring the need for better labeling is the increasing effort of private and public payors to limit reimbursement for drugs prescribed off-label.

Increased pediatric studies also encourage the creation of child-friendly drug formulations. Even the most effective drug cannot improve a child's health if the drug is unavailable in a formulation that a child can take (e.g., pills vs. liquid) or if the taste is unpalatable. Compliance with a prescription often relies on the formulation. If a parent has to struggle with the child every time a dose is needed, the likelihood of completing the full prescription to obtain maximum benefit is greatly reduced. Again, here BPCA and PREA have been successful in informing what pediatric formulations are effective for children.

BPCA AND PREA ARE STILL ESSENTIAL TOOLS

Despite the advances resulting from BPCA and PREA, there remains much progress to be made. Children remain second-class citizens when it comes to drug safety and efficacy information. Currently, nearly two-thirds of drugs used in children are still not labeled for children.[2] Almost 80% of hospitalized children receive at least one drug prescribed to them for an off-label use.[3] For children, off-label use is the rule, not the exception, because of the scarcity of prescribing information for this population. Therefore, both BPCA and PREA are still crucially important and must be reauthorized this year, including needed improvements.

New drug safety legislation has been passed in the Senate and similar legislation has been introduced in the House. Such legislation is a needed complement to the tools provided by BPCA and PREA and will enhance, not duplicate, the available information families and providers have about drugs used in children. The studies generated under BPCA provide information far beyond safety and produce information on dosing, efficacy – and importantly – lack of efficacy in off-label use. PREA created a new presumption that all new drugs would be studied in children at the time of application thus preventing the need for a safety problem to trigger studies after the drug is on the market.

[2] United States Government Accountability Office. Pediatric Drug Research. (GAO-07-557); 1.
[3] Shah SS, Sharma VS, Jenkins KJ, Levin JE. Off-label Drug Use in Hospitalized Children. *Arch Pediatr Adolesc Med.* 2007;161:282-290

This year is the first time BPCA and PREA will be reauthorized together, providing Congress with an historic opportunity to pass a well-coordinated and effective package of legislation for the benefit of all children. We recommend the following improvements.

Increase the dissemination, transparency, and tracking of pediatric drug information. Dissemination of pediatric information to families and healthcare providers should be increased in both BPCA and PREA. If families choose to involve their children in a clinical trial for a drug, should not then the drug label reflect that study? The Government Accountability Office (GAO) found that about 87% of drugs granted exclusivity under BPCA had important label changes.[4] This is good news, but it is our view that every drug label should reflect when a pediatric study was done (either through BPCA or PREA) and the results of the study, whether the results are positive, negative, or inconclusive. Moreover, FDA and drug sponsors must do more to communicate these label changes to pediatric clinicians. FDA should continue and expand its periodic monitoring of adverse events for both PREA and BPCA as this has been a useful tool to evaluate drug therapies after approval.

The transparency of BPCA's written request process can be improved. Increased transparency will be beneficial to pediatricians, sponsors and families. AAP recommends that written requests be made public at the time FDA awards exclusivity and that each written request be allowed to include both off-label and on-label uses. Moreover, because we recognize that FDA has improved the pediatric study written requests since 1997, we recommend that the Institute of Medicine be engaged to review a representative sample of all written requests and pediatric assessments under PREA. This scientific review will provide recommendations to FDA to continue to improve the consistency and uniformity of pediatric studies across all review divisions within the FDA's Center for Drug Evaluation and Research.

Information regarding the number of written requests issued as well as information regarding pediatric studies and label changes made as a result of BPCA is tracked and posted at FDA's website. This information is key to understanding the operation of the law for children, and we recommend that FDA also be required to track this information for PREA and make such information available.

Integrate and strengthen BPCA and PREA administrative processes. In general, BPCA and PREA processes are working well at FDA but more often as parallel programs than one administratively integrated pediatric study program. AAP supports the expansion of the existing internal FDA pediatric committee to include additional kinds of expertise within the agency and an integrated approach to the oversight and tracking of all pediatric studies requested or required by FDA, including the ability to require labeling changes.

Expand study of off-patent drugs. BPCA and PREA work well for new drugs and other on-patent drugs for which increased market exclusivity provides an appropriate incentive. However, for generic or off-patent drugs, BPCA and PREA have had a less effective reach. At the last BPCA reauthorization, Congress tasked the National Institute for Child Health and Human

[4] GAO 2007; 16

Development (NICHD) with creating a list of off-patent drugs needing further study in children and with conducting those needed studies. Although Congress never appropriated any funding to NICHD for this purpose, NICHD nevertheless has made significant progress identifying important off-patent drugs in need of study and starting clinical trials to study these drugs. AAP recommends that the role of NICHD be expanded in the current reauthorization to include study of the gaps in pediatric therapeutics in addition to generic or off-patent drugs. We also recommend PREA be strengthened so that needed pediatric studies can be conducted while drugs remain on patent.

BPCA also contains a mechanism through which pediatric studies of on-patent drugs declined by the sponsor can be referred to the Foundation for the National Institutes of Health (FNIH). FNIH is given authority to collect donations from pharmaceutical companies to fund such studies. Unfortunately these donations were not forthcoming, and, as reported in the GAO report, no studies have been completed using this mechanism. AAP recommends retaining the legal authority of FNIH to maintain an emphasis on children and raise money from drug companies for important pediatric needs, such as training pediatric clinical investigators, building pediatric research networks and studying pediatric disease mechanisms. However, the FNIH mandate to conduct pediatric studies of on-patent drugs should not be continued.

Maintain quality and number of pediatric studies while addressing "windfalls." Providing drug companies 6 months of additional marketing exclusivity has been enormously successful in creating pediatric studies. The studies and label changes highlighted earlier in my testimony demonstrate this. Recent data shows that for the large majority of drugs, the return to companies for responding to a written request has not been excessive. The Journal of the American Medical Association published a study in February that showed the return to companies for performing pediatric studies varies widely.[5] Most companies who utilize BPCA made only a modest return on their investment in children.[6] However, for the about 1 out of 5 companies with annual sales greater than $1 billion, the returns garnered through exclusivity have been very generous. Concerns regarding the returns to these "blockbuster" drugs have been voiced by several members of Congress and a number of proposals have surfaced to limit or change the patent extension.

Any proposal to amend the pediatric exclusivity provision must not reduce quality and number of pediatric studies. AAP has pledged to review any proposal for limiting the exclusivity awarded under BPCA using two criteria: first, any change must not reduce the number of drugs studied in children. GAO found that drug sponsors agreed to conduct studies in response to a written request from FDA 81% of the time.[7] Any proposal that will decrease the number of companies responding favorably to a written request from FDA would undermine the essential goal of BPCA. We now have data to show that simply cutting the incentive from 6 months to some

[5] Li JS, Eisenstein EL, Grabowski HG, et al. Economic Return of Clinical Trials Performed Under the Pediatric Exclusivity Program. *JAMA*. 2007;297:490-488
[6] The median annual sales of a drug receiving pediatric exclusivity were $180 million with a return on investment of 1.5 times the cost of the study.
[7] GAO 2007; 12

lesser number across-the-board will certainly reduce pediatric studies and we cannot support such proposals.

The second criterion is administrative simplicity. Proposals for using complicated formulas are likely to bog down the administration of the program by FDA and give rise to endless disputes between sponsors and the agency—including litigation. We cannot risk deterring or delaying important information getting into the hands of families and their health care providers. Every additional variable that Congress gives FDA to evaluate, when considering awarding the incentive, adds an additional level of complexity and moves FDA further from its core regulatory expertise.

However, this does not mean that this issue should not be addressed. When this committee acts to reauthorize the exclusivity extension, we encourage you to make changes that are straightforward and as clear as possible, targeting only those "blockbuster" drugs for which an appropriate reduction in the exclusivity will not reduce acceptance and successful completion of written requests. The exclusivity adjustment crafted by Senator Dodd in S. 1082 meets AAP criteria and we urge the Committee to adopt this approach.

Make PREA a permanent part of the Food and Drug Act and continue to reevaluate BPCA. The FDA currently has the permanent authority to ensure the safety of drugs used in adults. Children deserve the same. When PREA is reauthorized, it should be made permanent. Congress need not debate every few years whether we should continue to require safety and efficacy information on drugs used children. It is useful, however, to reevaluate the exclusivity program periodically to ensure that the incentive offered achieves its desired goal despite changes in the dynamic pharmaceuticals market. Congress should have the opportunity every 5 years to analyze whether BPCA continues to strike the right balance between achieving critical pediatric information and providing an appropriate incentive to maintain the number and quality of pediatric studies for on-patent medication.

SUPPORT FOR H.R. 1494, THE PEDIATRIC MEDICAL DEVICE SAFETY AND IMPROVEMENT ACT

I also express AAP's strong support of H.R. 1494 and our sincere gratitude to Representatives Markey and Rogers for championing this important legislation necessary for achieving safe and effective medical devices for all children. We also thank Representatives Capps, Eshoo, Grijalva and Ramstad for cosponsoring the bill.

The Pediatric Medical Device Safety and Improvement Act of 2007, H.R. 1494, will help children get the safe medical and surgical devices they need by strengthening safety requirements and encouraging research, development, and manufacture of pediatric devices. This bill strikes the right balance between new incentives and increased postmarket surveillance and puts forward a comprehensive package that serves a critical step forward for children.

Defining the need for pediatric devices. The bill streamlines federal agency processes by creating a "contact point" at the National Institutes of Health (NIH) and requires FDA, NIH, and

the Agency for Health Quality and Research to work together on identifying important gaps in knowledge and improving pediatric medical device development.

Facilitating pediatric device development and manufacture through mentorship. The bill also establishes six-year demonstration grant(s) to support nonprofit consortia to provide critically needed support in helping the innovators with pediatric device ideas to navigate "the system" successfully and bring new pediatric devices to market. The consortium will match inventors with appropriate manufacturing partners, provide mentoring for pediatric device projects with assistance ranging from prototype design to marketing, and connect innovators with available federal resources. The consortia will also coordinate with the NIH "contact point" for pediatric device development and the FDA for facilitation of pediatric device approval.

Improving the Humanitarian Device Exemption (HDE). The Humanitarian Device Exemption (HDE) was meant to be a tool for approving devices intended for a small populations (less than 4,000 patients), which often included children and those with rare conditions, but the profit restriction on HDE-approved devices limits the effectiveness of the provision by forcing device manufacturers to only recover their research and development costs. By eliminating the profit prohibition for children, the bill increases the incentive for companies to manufacture pediatric devices, especially the small manufacturers who are likely to embrace an affordable pediatric device development pathway with definable, affordable regulatory requirements.

Tracking pediatric device approvals and streamlining device development. H.R. 1494 makes needed improvements in the way FDA tracks the number and type of devices approved for use in children or for conditions that occur in children. At present, FDA cannot satisfactorily produce data on the number and type of devices marketed for pediatric uses. The bill requires FDA to track new devices granted premarket approval or approved under the humanitarian devices exemption and report on the number of pediatric devices approved in each category.

Strengthening postmarket safety. The Institute of Medicine (IOM) studied post-market safety for pediatric medical devices for more than a year and produced a strong report in 2005 entitled, "Safe Medical Devices for Children." The IOM found flaws in safety monitoring and recommended expanding the FDA's ability to require post-market studies of certain products and improving public access to information about post-market pediatric studies. The IOM reported:

> [T]he committee must conclude that FDA has lacked effective procedures to monitor the fulfillment of postmarket study commitments. The agency has lacked a basic, searchable listing of devices for which further studies were specified as a condition of their approval for marketing. Furthermore, it has not maintained any system for systematically monitoring the status of these study commitments based on periodic reports or updates from either its own staff or sponsors.[8]

[8] Field MJ and Tilson H. eds. Safe Medical Devices for Children, Committee on Postmarket Surveillance of Pediatric Medical Devices, Board on Health Sciences Policy; Institute of Medicine of the National Academies, 2005, p. 195.

> FDA can ask for clinical studies prior to clearing devices, although clinical data are submitted for only a small percentage of devices that go through clearance. FDA cannot, however, order postmarket studies as a condition for clearance. It can (but rarely does) order studies subsequent to clearance through its Section 522 authority. Studies that are ordered subsequent to the approval or clearance of a device are limited to 3 years (which often means a shorter period of evaluation for most individual study subjects). This may be too short a period for certain safety problems or developmental effects to be revealed.[9]

As recommended by the IOM, this bill grants the FDA increased authority to ensure that approved medical devices are safe for children. Under this law, the FDA would be able to require postmarket studies as a condition of approval or clearance for certain devices under section 522, if used frequently in children. This legislation also allows the FDA to require a study of longer than 3 years if necessary to ensure that the study is long enough to capture the effect of a child's growth on the safety and efficacy of a medical device. New post-market authority can address the current limited amount of available data on devices for children and create a mechanism for ensuring that needed pediatric studies are conducted for a sufficient length of time.

CONCLUSION

I would like to thank the committee again for allowing me the opportunity to share with you the strong support of the American Academy of Pediatrics for reauthorization of BPCA and PREA as well as H.R. 1494. We urge swift passage by this committee for the sake of all children throughout the United States.

I would be happy to answer any questions you may have.

Richard L. Gorman, MD, FAAP

[9] IOM, p. 226.

THE OFFICIAL NEWSMAGAZINE OF THE AMERICAN ACADEMY OF PEDIATRICS

AAP News

DEDICATED TO THE HEALTH OF ALL CHILDREN

Volume 28 • Number 2
February 2007
www.aapnews.org

Pediatric studies lead to more information on drug labels

Children, parents and medical practitioners are now benefiting from information on the many new pediatric drug labels approved by the Food and Drug Administration (FDA) as part of a national initiative to ensure that there is scientific information on the safe and effective use of drugs in children.

Useful new pediatric information is now part of product labeling for 119 drugs (as of September 2006). This information was generated by more than 300 studies in pediatric patients conducted under the pediatric exclusivity incentive program established by the Food and Drug Administration Modernization Act of 1997 (FDAMA) and reauthorized by the Best Pharmaceuticals for Children Act of 2002 (BPCA).

The cumulative list of all labeling change summaries resulting from FDAMA and BPCA can be found at www.fda.gov/cder/pediatric/labelchange. htm. *AAP News* published previous listings of labeling changes in April 2001 and August 2003.

This article describes *select* subsequent pediatric labeling changes made due to the incentive program. The labeling changes for the drugs described here represent changes that affect a large number of children because they mitigate serious and life-threatening diseases and/or treat very common childhood diseases or provide vital new information on the use of the product in children. In addition, drug approvals that affect vulnerable populations such as neonates or children with other chronic and/or underlying health issues (e.g., neurological impairment, mental illness) also are highlighted.

Common pediatric conditions

Obesity, headaches, depression and behavioral issues related to attention-deficit/hyperactivity disorder and seizures are common reasons for pediatric office visits. Labeling changes for orlistat, sumatriptan, methylphenidate, mixed amphetamine salts and levetiracetam will assist the practitioner in choosing therapies and counseling patients regarding the safe use of these products.

Xenical (orlistat) for obesity management is supported in adolescent patients ages 12 to 16 years based on studies in adults with additional safety and efficacy data from a yearlong trial in obese adolescent patients. Since treatment with orlistat can reduce the absorption of fat-soluble vitamins, all patients should take a daily multivitamin supplement.

In contrast, data from pediatric studies of **Meridia (sibutramine)** were inadequate to recommend use of sibutramine for the treatment of obesity in pediatric patients. The risk of suicidal behavior or thinking in pediatric patients treated with sibutramine is unknown.

Imitrex (sumatriptan) Nasal Spray studies for the treatment of migraines in adolescents ages 12 to17 years did not show drug effectiveness compared to placebo. The use of sumatriptan in patients younger than 18 years is not recommended. Serious adverse events have occurred, similar in nature to those reported rarely in adults, including stroke, visual loss and death. Imitrex is approved for the treatment of migraines in adults.

Effexor (venlafaxine), Remeron (mirtazapine), Paxil (paroxetine), Serzone (nefazodone), Zoloft (sertraline) and Celexa (citalopram) are among the antidepressants recently studied in pediatric patients for which efficacy was not demonstrated when used to treat depression. Boxed warnings regarding suicidality were incorporated into labeling for antidepressants in this class based on results from BPCA studies. Of these, only sertraline is approved for use in pediatric patients. Sertraline is indicated for the treatment of obsessive-compulsive disorder in children 6 to 17 years. Monitor patients for clinical worsening, suicidality and unusual changes in behavior; growth also should be monitored in children receiving sertraline.

Concerta (methylphenidate hydrochloride) is approved to treat attention-deficit/hyperactivity disorder (ADHD) in children 6 to 17 years of age. Studies in adolescents 13 to 17 years old resulted in a higher maximum recommended dosage for adolescents compared to 6- to 12-years-olds for patients new to methylphenidate because of an increased apparent oral clearance in the older adolescent. In contrast, the maximum recommended dosage of **Adderall XR (mixed amphetamine salts)** for adolescents is lower than that for children 6 to 12 year olds.

Keppra (levetiracetam) approval for adjunctive therapy in the treatment of partial onset seizures in children was extended down to age 4 years. Behavioral symptoms and somnolence were observed in a higher percentage of pediatric patients treated compared with adults. Similarly, the age range for **Trileptal (oxcarbamazepine)** was extended down to 2 years of age for the adjunctive treatment of partial seizures.

HIV

Even though therapies for HIV are being studied in children, obtaining information on the effects of therapy in the youngest children and neonates has remained problematic. Developmental changes in infants, such as changes in the metabolism of drugs related to maturation of kidney function or liver enzyme systems, affect pharmacodynamics and potentially drug dosing. Thus, con-

ducting studies to determine appropriate dosing in neonates and young children is essential.

HIV-infected infants younger than 12 months are considered at high risk for disease progression. Combination therapy is recommended for all infants, children and adolescents who are treated with antiretroviral agents. When compared with monotherapy, combination therapy slows disease progression and improves survival, results in a greater and more sustained virologic response, and delays development of viral resistance to the antiretroviral agents being used.

Treatment with the protease inhibitor class of antiretrovirals became common practice in the treatment of HIV-infected pediatric patients in the late-1990s. Since then, there have been several FDA-approved formulations appropriate for infants and children who cannot swallow pills. Both nelfinavir and ritonavir, listed below, have approved formulations appropriate for young children.

Viracept (nelfinavir) is a protease inhibitor that can be used in combination therapy for the treatment of HIV infection. Nelfinavir was the most frequently used protease inhibitor from 1998-2002, and in 2003, was the second most frequently used (27.3%). The studies performed under BPCA provided information on twice-daily dosing and three-times daily dosing in pediatric patients, and demonstrated that under the age of 2 years, it is difficult to establish a reliable effective dose.

Norvir (ritonavir) is another protease inhibitor used in combination with other drugs to treat HIV-infected pediatric patients. Pediatric studies extended the age range down to 1 month. Ritonavir is mainly used now to increase the serum concentrations and decrease the dosage frequency of other protease inhibitors.

Cancer

Studying products to treat cancer in children is challenging because of the limited numbers of cases and numerous types of pediatric cancers that manifest themselves differently in children than in adults. For example, while clofarabine is effective in the treatment of pediatric cancer, irinotecan has not proven to be effective. Ondansetron is useful for treating or preventing chemotherapy-induced nausea and vomiting.

Clolar (clofarabine) is approved for the treatment of pediatric patients 1 to 21 years of age with relapsed or refractory acute lymphoblastic leukemia. A single arm study conducted in pediatric patients, who had relapsed after and/or were refractory to two or more prior therapies, provided information on proper dosing, PK parameters and the adverse event profile of the drug. The product was shown to increase survival or provide other clinical benefits.

Camptosar (irinotecan) studies demonstrated that the product should not be used in children with rhabdosarcoma based on a greater mortality and a more rapid progression of disease when on drug.

Zofran (ondansetron) Injection studies established dosing for the prevention of chemotherapy-induced nausea and vomiting for children 6 to 48 months old. The pharmacokinetic trials revealed that children less than 18 years of age cleared the product faster than adults. On the other hand, in children 1 to 4 months of age, clearance was slower than in patients who were 4 to 24 months of age. Pediatric studies also established dosing for the prevention of postoperatively induced nausea and vomiting for children 1 to 24 months old.

Infectious diseases

Infectious diseases are one of the most frequent reasons for pediatric office visits or hospitalization. Antiviral therapies such as oseltamivir and antibacterials such as ciprofloxacin, ertapenem and linezolid are important additions to the pediatric armamentarium.

Tamiflu (oseltamivir) is indicated for the prophylaxis and treatment of uncomplicated acute influenza and was studied in pediatric patients down to 1 year of age. Oseltamivir is not recommended for children younger than 1 year of age due to safety concerns. Additional post-marketing information also has raised the issue of unusual and sometimes injurious behavior in some children after receiving this product.

Cipro (ciprofloxacin), while indicated for complicated urinary tract infection and pyelonephritis, is not a drug of first choice due to increased adverse events compared to controls, including events related to joints and/or surrounding tissues.

Invanz (ertapenem) is indicated for the treatment of serious infections, including complicated intra-abdominal infections, complicated skin infections, community acquired pneumonia, complicated urinary tract infections and acute pelvic infections. However, pediatric studies demonstrated that this antibiotic should not be used in meningitis because the drug did not sufficiently penetrate the central nervous system.

Zyvox (linezolid) is used to treat infections caused by bacteria that are resistant to other antibiotics (e.g., *Staphylococcus aureus* (MRSA), other methicillin-resistant staphylococcus species (MRSS) and penicillin-resistant *Streptococcus pneumoniae* (PRSP)). These infections occur in children with ventriculoperitoneal shunts but unfortunately in these patients, drug levels were not high enough in the brain to treat central nervous system infection. Thus, linezolid is not recommended for the treatment of pediatric patients with central nervous system infections.

Vulnerable subpopulations

In the past, investigators have been reluctant to perform studies in vulnerable subpopulations such as neonates and children with neurological disorders, chronic pain, anorexia nervosa and orphan conditions. As a result of BPCA, trials are being conducted in children with these conditions, and important information regarding therapies for these conditions has been generated.

Dosing guidelines for maintenance of anesthesia in patients from birth to 2 months for **Ultiva (remifentanil)** have been incorporated into labeling. Safety and efficacy have been established from birth to 1 year and older.

Detrol LA (tolterodine) is indicated for the treatment of adults with overactive bladder with symptoms of urge urinary incontinence, urgency and frequency. However, a study in children ages 5 to 10 years revealed an increased number of urinary tract infections, aggressive, abnormal and hyperactive behavior, and attention disorders in patients treated with this drug when compared to placebo. In addition, the studies did not demonstrate efficacy. Therefore, tolterodine is not approved for use in children.

Duragesic (fentanyl) is indicated in the management of chronic pain in opioid-tolerant children 2 years and older who require continuous opioid analgesia for pain. Studies provided information for dosing in pediatric patients, and the one year post-exclusivity safety review demonstrated serious safety concerns when this drug was

inappropriately used for acute pain (such as post-surgical pain) in opioid naïve patients.

Ortho Tri-Cyclen (norgestimate/ethinyl estradiol) use in adolescent females with anorexia nervosa to improve bone mineral density is not recommended since in clinical trials no significant difference in bone mineral density was observed. The drug is approved for birth control and the treatment of acne in patients 15 years and older.

Fosamax (alendronate) use in children with severe osteogenesis imperfecta is not recommended based on studies in children ages 4 to 18 years old. In these trials, treatment with alendronate did not reduce the risk of fracture.

The cumulative list of all labeling change summaries resulting from FDAMA and BPCA can be found at www.fda.gov/cder/pediatric/labelchange.htm. An excerpt from this list containing details of the labeling changes that are highlighted here as well as labeling summaries approved from January 2005 to September 2006 appears below:

Pediatric Exclusivity Labeling Changes from August 1, 2003 through September 29, 2006

Exclusivity Granted/ (Labeled)	Product	Labeled Indications Resulting from Pediatric Studies	Labeling Changes
9/12/03 (12/12/03)	Orlistat Xenical (Roche)	Obesity management	• Use in 12-16 year olds is supported by studies in adults with additional data from a 54 week safety and efficacy study in obese adolescent patients. • Since orlistat can reduce absorption of fat soluble vitamins, all patients should take a daily multivitamin supplement containing fat soluble vitamins. • Adverse event profile in adolescent patients was similar to that seen in adults
3/15/00 (3/8/04)	Remifentanil Ultiva (Abbott)	Maintenance of anesthesia	• Safety and efficacy for the maintenance of anesthesia established from birth to 1 year of age • Recommended dosing guidelines for maintenance of anesthesia for patients from birth to 2 months • The clearance rate observed in neonates was highly variable – approximately 2 times higher than young healthy adults • Individual doses for each patient should be carefully titrated
9/4/03 (3/19/04)	Nelfinavir Viracept (Pfizer)	Treatment of HIV-1	• Safety and effectiveness established in patients 2–13 years of age • New twice daily dosing regimen and modified three times daily dosing for pediatric patients ≥2 years • A reliably effective dose not established in patients <2 years of age • PK information in pediatric patients from birth to 13 years of age • Highly variable drug exposure is a significant problem in pediatric patients • Adverse event profile was similar to that for adults
12/18/03 (3/25/04)	Ciprofloxacin Cipro (Bayer)	Complicated UTI and pyelonephritis	• Indicated for the treatment of complicated urinary tract infections (cUTIs) and pyelonephritis in pediatric patients 1–17 years of age • Not drug of first choice due to increased adverse events compared to controls including events related to joints and/or surrounding tissues • Information on PK and dose in pediatric patients 1–17 years of age • The most frequent adverse events observed within 6 weeks of treatment initiation during the cUTI clinical trial were gastrointestinal 15% compared to 9% and musculoskeletal 9.3% compared to 6% in ciprofloxacin-treated compared to control-treated patients, respectively

Exclusivity Granted/ (Labeled)	Product	Labeled Indications Resulting from Pediatric Studies	Labeling Changes
1/5/04 (4/14/04)	Tolterodine Detrol LA (Pfizer)		• Efficacy in pediatric population has not been demonstrated • The dose-plasma concentration relationship is linear in patients from 11 to 15 years • Parent/metabolite ratios differed according to CYP2D6 metabolizer status • 710 pediatric patients ages 5-10 years with urinary frequency and urge incontinence were studied in 2 randomized placebo controlled trials. Urinary tract infections were higher in patients treated with Detrol LA (6.6%) compared to placebo (4.5%) • Aggressive, abnormal and hyperactive behavior and attention disorders occurred in 2.9% of children treated with Detrol LA compared to 0.9% treated with placebo
Boxed Warning for Antidepressants			FDA required boxed warning for all antidepressants: Suicidality in (1/26/05) Children and Adolescents — Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of [insert established name] or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. [Insert established name] is not approved for use in pediatric patients **or** is approved for pediatric patients with [Insert approved pediatric indication(s)]. (See Warnings and Precautions: Pediatric Use) Pooled analyses of short-term (4 to 16 weeks) placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with major depressive disorder (MDD), obsessive-compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4,400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials.
12/2/02 (5/5/04) [2/18/05]*	Venlafaxine Effexor and Effexor XR (Wyeth)		• Effectiveness in pediatric patients has not been established • See Antidepressant Boxed Warning • 18% of Effexor XR treated patients (6-17 years) versus 3.6% of placebo treated patients experienced a weight loss of at least 3.5% in both MDD and the GAD studies • In an open-label study increases in weight were less than expected based on data from age and sex matched peers. The difference between observed weight gain was larger for children less than 12 years than for adolescents older than 12 years • During an 8 week placebo controlled GAD trial, Effexor XR treated patients ages 6-17 years grew an average of 0.3 cm, while placebo treated patients grew an average of 1 cm. In a 6 month open-label study, height increases that were less than expected based on data from age and sex matched pairs. The difference between observed and expected growth rates were larger for children less than 12 years than for adolescents older than 12 years • Decreased appetite observed in 10% of patients ages 6-17 years old receiving Effexor XR • Occurrence of blood pressure and cholesterol increases considered clinically relevant in pediatric patients similar to that observed in adults

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3/10/04 (6/24/04)	Irinotecan Camptosar (Pfizer)		• Effectiveness in pediatric patients has not been established • Adverse event profile from a Phase 2 trial with 170 children with refractory solid tumors comparable to that seen in adults; Grade 3-4 neutropenia experienced by 54 (31.8%) patients, neutropenia complicated by fever in 15 (8.8%) patients, Grade 3-4 diarrhea observed in 35 (20.6%) patients. • Accrual for phase 2 study with 21 children with previously untreated rhabdomyosarcoma halted due to high rate (23.6%) of progressive disease and early deaths (14%) • Adverse event profile seen in the 21 children different than that observed in adults; most significant Grade 3 or 4 adverse events were dehydration experienced by 6 patients (28.6%) associated with severe hypokalemia in 5 patients (23.8%) and hyponatremia in 3 patients (14.3%); in addition Grade 3-4 infection was reported in 5 patients (23.8%) (across all courses of therapy and irrespective of causal relationship) • PK parameters comparable to adults • Minimal accumulation of irinotecan and SN-38 (active metabolite) observed in children on daily dosing
3/22/04 (6/24/04)	Oseltamivir Tamiflu (Roche)	Treatment of uncomplicated acute illness due to influenza infection in patients 1 year and older	• Not recommended in pediatric patients less than 1 year of age because of uncertaintiesregarding the rate of development of the human blood-brain barrier and the unknown clinical significance of animal toxicology data for human infants
2/18/04 (10/13/04)	Sumatriptan Imitrex Nasal Spray (Glaxo)		• Five clinical trials evaluating oral sumatriptan in pediatric patients ages 12-17 years didnot establish the safety and effectiveness when compared to placebo • Postmarketing experience documents that serious adverse events (AEs) rarely reported in adults, including stroke, visual loss, and death have occurred in the pediatric population after use of subcutaneous, oral, and/or nasal sumatriptan. • Since clinical data to determine the frequency of serious adverse events in pediatric patients who might receive injectable, oral, and/or intranasal sumatriptan are not presently available, the use of sumatriptan in patients aged younger than 18 years is not recommended.
12/4/03 (10/21/04)	Methylphenidate Concerta (Alza)	ADHD	• Expanded labeling for 13-17 year olds including information on dose, PK parameters, and AE profile • Increase in age resulted in increased apparent oral clearance • For patients new to methylphenidate: higher maximum recommended dosage for adolescents compared to children 6-12 years of age • Data are inadequate to determine whether chronic use of stimulants in children may cause suppression of growth. Therefore, growth should be monitored during treatment • Safety and efficacy in children <6 years have not been established
7/14/04 (12/28/04)	Clofarabine Clolar (Genzyme)	Treatment of relapsed or refractory acute lymphoblastic leukemia after at least two prior regimens	• Labeling for patients 1 to 21 years old. This use is based on the induction of complete responses • Randomized trials demonstrating increased survival or other clinical benefit have not been conducted • Information on dose, PK parameters, and AE profile
(1/12/05)	Mirtazapine Remeron (Organon)		• Safety and effectiveness in the pediatric population have not been established • See Antidepressant Boxed Warning • Two placebo-controlled trials in 258 pediatric patients with MDD have been conducted with Remeron and the data were not sufficient to support a claim for use in pediatric patients

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6/27/02 (1/12/05)	Paroxetine Paxil (Glaxo)		• Safety and effectiveness in the pediatric population have not been established • See Antidepressant Boxed warning • Three placebo-controlled trials in 752 pediatric patients with MDD have been conducted with Paxil, and the data were not sufficient to support a claim for use in pediatric patients
6/27/02 (1/12/05)	Nefazodone Serzone (BMS)		• Safety and effectiveness in the pediatric population have not been established • See Antidepressant Boxed Warning • Two placebo-controlled trials in 286 pediatric patients with MDD have been conducted with Serzone, and the data were not sufficient to support a claim for use in pediatric patients
2/1/02 (2/18/05)	Sertraline Zoloft (Pfizer)		• Safety and effectiveness in the pediatric population other than pediatric patients withOCD have not been established • See Antidepressant Boxed Warning • Two placebo controlled trials in 373 pediatric patients with MDD have been conducted with Zoloft, and the data were not sufficient to support a claim for use in pediatric patients
7/12/02 (2/18/05)	Citalopram Celexa (Forest)		• Safety and effectiveness in the pediatric population have not been established • See Antidepressant Boxed Warning • Two placebo-controlled trials in 407 pediatric patients with MDD have been conducted with Celexa, and the data were not sufficient to support a claim for use in pediatric patients
11/17/04 (3/11/05)	Sirolimus Rapamune (Wyeth)	Prophylaxis of organ rejection in patients undergoing renal transplants	• Safety and efficacy established in children 13 years or older judged to be at low to moderate immunologic risk • Safety was assessed in a controlled clinical trial in pediatric (<18 years of age) renal transplant recipients considered high immunologic risk. The use of Rapamune in combination with calcineurin inhibitors and corticosteroids was associated with an increased risk of deterioration of renal function, lipid abnormalities, and urinary tract infections • Safety and efficacy have not been established in pediatric patients less than 13 years old or in pediatric renal transplant recipients considered at high immunologic risk • Information on PK parameters, adverse events and safety
12/1/04 (3/25/05)	Ondansetron Zofran (Glaxo)	Prevention of chemotherapy-induced and postoperative induced nausea and vomiting	• Established dosing for surgical patients down to 1 month from 2 years of age • Established dosing for cancer patients down to 6 months from 4 years of age • Surgical and cancer patients <18 years tend to have a higher ondansetron clearance compared to adults leading to a shorter half-life in most pediatric patients • The clearance of ondansetron in patients 1-4 months of age is slower and the half-life is approximately 2.5 fold longer than patients who are >4 – 24 months of age • Patients <4 months of age receiving this drug should be closely monitored • Additional information on dose, PK parameters, AE profile and safety
1/27/05 (4/26/05)	Gemcitabine Gemzar (Lilly)		• Effectiveness in pediatric patients has not been demonstrated • Phase 1 trial in pediatric patients with refractory leukemia demonstrated a maximum tolerated dose; however, no meaningful clinical activity observed in a Phase 2 trial of gemcitabine in 22 patients with relapsed acute lymphoblastic leukemia and 10 patients with acute myelogenous leukemia • Toxicities observed were similar to those reported in adults

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2/11/05 (12/19/02; 5/12/05)	Linezolid Zyvox (Pfizer)	Nosocomial pneumonia, community-acquired pneumonia, complicated and uncomplicated skin and skin structure infections, and vancomycin-resistant infections caused by susceptible strains (12/19/02)	• Extended age range down to birth for nosocomial pneumonia, community-acquired pneumonia, complicated skin and skin structure infections and vancomycin-resistant infections. Safety and efficacy extrapolated from studies in adults and supported by PK and comparator-controlled studies in patients from birth to 11 years • Extended age range down to 5 years of age for uncomplicated skin and skin structure infections based upon a comparator-controlled study in 5 to 17 year olds • Clearance of linezolid varies as a function of age; As age of pediatric patients increases, clearance gradually decreases, and by adolescence mean clearance values approach those observed in adults • Pediatric patients exhibit wider variability in clearance and systemic exposure (area under the curve) compared with adults • New every 8 hours dosing regimen for pediatric patients birth to 11 years of age and every 12 hours dosing regimen for pediatric patients 12 years and older • Information on PK parameters, AE profile, laboratory changes, dosing, and clinical studies (5/12/05) • PK data in pediatric patients with ventriculoperitoneal shunts showed variable cerebrospinal fluid (CSF) concentrations; therapeutic concentrations were not consistently achieved or maintained in the CSF • Use of linezolid for the empiric treatment of pediatric patients with central nervous system infections is not recommended • Additional information on efficacy in pediatric patients with infectious vancomycin-resistant *Enterococcus faecium*
12/18/03 (5/13/05)	Norgestimate/ ethinyl estradiol Ortho Tri-Cyclen (Ortho McNeil)		• No significant difference between Ortho Tri-Cyclen and placebo in mean change in total lumbar spine (L1-L4) and total hip bone mineraldensity in 123 adolescent females with anorexia nervosa in a double-blind, placebo-controlled, multicenter, one-year clinical trial
2/11/05 (5/18/05)	Ertapenem Invanz (Merck)	Complicated intra-abdominal infections; complicated skin and skin structure infections; community acquired pneumonia; complicated urinary tract infections; acute pelvic infections	• Approved for use down to 3 months of age. Efficacy extrapolated from studies in adultsand supported by PK and safety studies in pediatric patients • Not recommended in infants under 3 months of age as no data are available • Not recommended in the treatment of meningitis in the pediatric population due to lack of sufficient CSF penetration • Information on dose, PK parameters, AE profile and clinical studies
(6/21/05)	Levetiracetam Keppra (UCB Inc)	Adjunctive therapy in the treatment of partial onset seizures in patients with epilepsy	• Extended indication from adults to patients 4 years and older • Safety and effectiveness have not been established in patients less than 4 years of age • PK analysis showed that clearance increased with an increase in body weight • Approximately 22% increase of apparent total body clearance of levetiracetam when co-administered with enzyme-inducing anti-epileptic drugs (AEDs). Dose adjustment not necessary • 37.6% of pediatric patients reported behavioral symptoms compared to 13.3% in adults • Somnolence occurred in 22.8% in pediatric patients compared to 14.8% in adults • Information on dose, PK parameters, AE profile and clinical studies

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1/29/03 (5/20/03)	Fentanyl Duragesic (Alza)	Chronic pain in opioid tolerant patients	• Safety evaluated in three open-label trials in 291 patients 2 years through 18 years of age with chronic pain • New Warning: Duragesic should be administered to children only if they are opioid-tolerant and age 2 years or older • New information on pharmacokinetics, dosage and administration and patient information • Precaution to guard against accidental ingestions by children • Adverse Events: no apparent pediatric-specific risk associated with Duragesic use in children as young as 2 years old when used as directed. Most common adverse events were fever (35%), vomiting (33%), and nausea (24%) Public Health Advisory 7/8/05-changes in boxed warnings/warnings, contraindications, precautions and dosage and administration emphasizing: • Use only in opioid tolerant patients with persistent pain-contraindication in the management of acute, mild or intermittent pain (e.g., prn), post-operative pain, including use after out-patient or day surgeries (e.g., tonsillectomy) and for short-treatment periods because serious or life-threatening hypoventilation could occur
10/28/04 (7/21/05)	Mixed salts Amphetamines Adderall XR (Shire)	ADHD	• Expanded labeling for 13-17 year olds • On a mg/kg body weight basis children 6-12 years have a higher clearance than adolescents or adults. Body weight is the primary determinant • There was not adequate evidence that doses greater than 20 mg/day conferred additional benefit in a placebo-controlled study conducted in adolescents aged 13-17 with ADHD • In a single-dose PK study in adolescents, isolated increases in systolic blood pressure (SBP) were observed in patients receiving 10 mg and 20 mg Adderall XR. Higher single doses were associated with a greater increase in SBP • Sustained increases in blood pressure should be treated with dose reduction and/or appropriate medication • Information on dose, PK parameters, and AE profile
4/15/05 (8/11/05)	Meloxicam Mobic (Boehringer Ingelheim)	Relief of signs and symptoms of pauciarticular or polyarticular course juvenile rheumatoid arthritis	• Safety and efficacy established in patients 2 years of age and older • Clinical studies evaluated doses ranging from 0.125 mg/kg/day to 0.375 mg/kg/day. There was no additional benefit demonstrated by doses above 0.125 mg/kg/day in the clinical trials. The lowest effective dose should be used • Adverse events in children were similar to those in adults including skin reactions and gastrointestinal bleed risk • Information on dose, PK parameters, AE profile and clinical studies
5/24/05 (9/13/05)	Insulin aspart Recombinant Injection NovoLog (Novo Nordisk)	Diabetes mellitus	• In clinical studies comparing NovoLog to regular human insulin in patients 2 to 18 years with type 1 diabetes, NovoLog achieved glycemic control comparable to regular human insulin • The incidence of hypoglycemia was similar for both treatment groups
(9/28/05)	Emtricitabine – Emtriva (Gilead Sciences) Pediatric Formulation	Treatment of HIV-1 infection in combination with other antiretroviral agents	• Safety and effectiveness in pediatric patients 3 months and older supported by data from 3 open-label, nonrandomized clinical studies • Safety and effectiveness in patients <3 months have not been established • Relative bioavailability of Emtriva oral solution is approximately 80% of Emtriva capsules. Thus, maximum dosage is different for these 2 formulations: Solution max - 240 mg once daily; Capsules max - children weighing >33 kg one 200 mg capsule once daily • The AE profile in pediatric patients was comparable to that observed in adults • Information on dose, PK parameters, AE profile and clinical studies

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6/14/05 (10/6/05)	Ritonavir Norvir (Abbott)	Treatment of HIV-infection in combination with other antiretroviral agents	• Extended age range from 2 years down to 1 month • AE profile in the pediatric population was similar to that for adults • Information on dose and PK parameters
3/2/05 (10/28/05)	Oxcarbazepine Trileptal (Novartis)	Use as adjunctive therapy in children aged 2 years and above with epilepsy	• Extended adjunctive therapy age range from 4 years down to 2 years • No evidence drug was effective as adjunctive therapy in patients <2 years • In clinical studies as adjunctive therapy, apparent clearance (L/hr/kg) decreased when age increased such that children 2 to <4 years of age may require up to twice the dose per body weight compared to adults; and children 4 to ≤12 years of age may require a 50% higher dose per body weight compared to adults • Approximately 11% of pediatric patients <4 years discontinued treatment because of adverse events including convulsions, status epilepticus and ataxia • Information on dose, PK parameters, AE profile and clinical studies
5/24/05 (11/28/05)	Glimepiride Amaryl (Aventis)		• Data are insufficient to recommend pediatric use of glimepiride • In an active-controlled, single-blind, 24-week trial, 272 pediatricpatients aged 8 to 17 years with Type 2 diabetes were randomized to treatment with glimepiride or metformin. Trial suggested differences favoring metformin • AE profile in the pediatric population was similar to that for adults • Information on PK parameters
10/6/04 (12/8/05)	Sibutramine Meridia (Abbott)		• The data are inadequate to recommend the use of sibutramine for the treatment of obesity in pediatric patients • Efficacy in obese adolescents has not been adequately studied • Sibutramine's mechanism of action inhibiting the reuptake of serotonin and norepinephrine is similar to that of some antidepressants • It is unknown if sibutramine increases the risk of suicidal behavior or thinking in pediatric patients • In a study of adolescents with obesity in which 368 patients were treated with sibutramine and 130 patients with placebo, one patient in each group attempted suicide. Suicidal ideation was reported by 2 sibutramine-treated patients and none of the placebo patients
4/28/03 (12/21/05)	Alendronate Fosamax (Merck)		• Alendronate is not indicated for use in children • The efficacy and safety were examined in a randomized, double-blind, placebo-controlled two-year study of 139 patients, 4-18 years old, with severe osteogenesis imperfecta • Treatment with alendronate did not reduce the risk of fracture • There were no statistically significant differences between the alendronate and placebo groups in reduction of bone pain • Information on PK parameters, AE profile, and clinical studies
9/16/04 (3/16/06)	Irbesartan Avapro (Sanofi-Synthelabo)		• In a study at a dose up to 4.5 mg/kg once daily, irbesartan did not appear to lower blood pressure effectively in pediatric patients ages 6 to 16 years
12/15/05 (4/10/06)	Fluvastatin Lescol and Lescol XL (Novartis)	Heterozygous familial hypercholesterolemia as an adjunct to diet	• New indication in adolescent boys and girls (at least one year post-menarche) 10-16 years of age, with heterozygous familial hypercholesterolemia • Information on dose, AE profile and clinical studies

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1/12/06 (5/10/06)	Octreotide Sandostatin LAR (Novartis)		• Efficacy and safety of octreotide as a weight loss agent were examined in a randomized double-blind, placebo-controlled study in 60 patients aged 6 –17 years with hypothalamic obesity from cranial insult; mean BMI increased 0.1 kg/m2 in drug treated patients compared to 0.0 kg/m2 in control-treated patients • No unexpected AEs were observed; however, the incidence of new cholelithiasis in this pediatric population (33%) was higher than that seen in adult indications • Information on PK parameters and AEs
6/9/06 (9/27/06)	Imatinib mesylate Gleevec (Novartis)	Treatment of newly diagnosed pediatric patients with Philadelphia chromosome positive (Ph+) chronic myeloid leukemia (CML) in chronic phase	• Extended age range for the treatment of newly diagnosed CML down to pediatric patients • There are no data in children <2 years of age • Follow-up in children with newly diagnosed Ph+ chronic phase CML is limited • Information on hematologic toxicities, AE profile, clinical studies and dosing guidelines new for newly diagnosed pediatric patients
6/28/06 (9/28/06)	Brinzolamide Azopt ophthalmic suspension (Alcon)		• IOP-lowering efficacy was not demonstrated in a 3-month controlled clinical study in which brinzolamide was dosed only twice a day in pediatric patients 4 weeks to 5 years of age
6/28/06 (9/28/06)	Levobetaxolol Betaxon ophthalmic suspension (Alcon)	Treatment of elevated intraocular pressure	• Extended indication from adults to pediatric patients • The adverse event profile was comparable to that seen in adults and elderly patients
(9/29/06)	Enfuvirtide Fuzeon (Hoffmann-La Roche)	Treatment of HIV-1 infection in treatment-experienced patients with evidence of HIV-1 replication despite ongoing antiretroviral therapy	• Additional safety and efficacy data and AE information from clinical study in 5-16 year olds • Insufficient data to provide dosing recommendations in patients <6 years

Note: These labeling changes only reflect the pediatric changes for studies submitted in response to a written request and are not necessarily the most current label. More current labeling can be found at www.drugs@FDA.gov.