

FDA Safety Reviews on Drugs, Biologics, and Vaccines: 2007–2013

Judith U. Cope, MD, MPH^a, Geoffrey L. Rosenthal, MD, PhD^b, Pamela Weinel, MS, MBA, RN^a, Amy Odegaard, MPH^a, Dianne M. Murphy, MD, FAAP^a

abstract

BACKGROUND AND OBJECTIVES: In 2002, Congress mandated that the US Food and Drug Administration (FDA) monitor postmarketing pediatric adverse events and present safety reports to the FDA's Pediatric Advisory Committee (PAC). These safety reviews play a critical role in the postmarketing surveillance and identification of pediatric safety issues. This article follows a previous review ending in 2007 and summarizes 6 years of recent pediatric safety reporting, recommendations by the PAC, and actions by the FDA, including labeling changes.

METHODS: An analysis of the FDA's PAC safety reviews performed from November 2007 through September 2013 was conducted. PAC recommendations for subsequent labeling changes, future studies, or other safety issues were reviewed.

RESULTS: There were 6930 serious adverse event reports in 181 reviews. These findings resulted in 33 (18%) recommended labeling changes, and 21 (64%) of these changes were adopted. For 10 products, information was added to the Warning and Precautions section of the label. The PAC also discussed or recommended additional studies for certain products.

CONCLUSIONS: This article highlights the importance of the FDA's ongoing pediatric postmarketing safety reviews of regulated products, advice from the PAC, and FDA actions in the best interest of pediatric patients. This mandated process facilitates detection of safety concerns that may not be identified in prelicensure clinical trials. It continues to identify critical safety concerns, including unlabeled adverse events, frequent off-label use, product misuse, and secondary exposures in children.

^aOffice of Pediatric Therapeutics, Office of Special Medical Programs, Office of the Commissioner, Food and Drug Administration, Silver Spring, Maryland; and ^bDepartment of Pediatrics, University of Maryland School of Medicine, Baltimore, Maryland

Dr Cope is the primary author who was involved in all team reviews and presented many of the safety review presentations; she wrote most of the article, conducted the initial analyses, and reviewed and made revisions to the manuscript. Dr Rosenthal is a Pediatric Advisory Committee member and was chair of the committee from July 1, 2007, through June 30, 2012. His input and chair perspective in the article were key; he was involved in the initial draft, analyses, and follow-up reviews. Ms Weinel drafted parts of the initial manuscript and reviewed and revised the manuscript; Ms Odegaard designed the database and conducted parts of the initial analyses, drafted parts of the initial manuscript, and reviewed and revised the manuscript; Dr Murphy assisted the primary author in the early drafts and analyses and subsequent revisions, continued edits, and follow-up reviews; and all authors approved the final manuscript as submitted.

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Address correspondence to Judith U. Cope, MD, MPH, FDA, White Oak Building 32, Room 5156, 10903 New Hampshire Ave, Silver Spring, MD 20993. E-mail: judith.cope@fda.hhs.gov

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WHAT'S KNOWN ON THIS SUBJECT: Earlier research studied postmarketing safety in children receiving drugs awarded market exclusivity extensions that were reviewed in expert panel meetings from June 2003 through April 2007.

WHAT THIS STUDY ADDS: This article reviews pediatric postmarketing safety surveillance efforts at the FDA from November 2007 through September 2013. It describes the identified safety signals, summarizes Pediatric Advisory Committee discussions, illustrates FDA actions, and includes input from a past PAC chair.

Beginning in 2002, Congress mandated the monitoring of postmarketing pediatric adverse events (AEs) to include reporting to the Pediatric Advisory Committee (PAC) of the US Food and Drug Administration (FDA). This legislation, including the Best Pharmaceuticals for Children Act of 2002,¹ the Pediatric Research Equity Act of 2003 and 2007,² and the Food and Drug Administration Amendments Act of 2007,³ created a regulatory framework to enhance postmarketing safety assessments of products studied in children. This legislation also required and incentivized studies of products in the pediatric population. The results of the studies, either negative or positive, were required to be included in labeling. This requirement is important because negative trial information is not usually included in labeling for adults. The legislation also mandated that 18 months after pediatric labeling changes, the FDA is to conduct pediatric postmarketing safety reviews of those products (drugs, vaccines, and biologic products) with presentations to the PAC. The 2012 Food and Drug Administration Safety and Innovation Act mandated the permanent continuation of this review process involving both internal and external experts and assessment by the PAC in an open, public forum.⁴ Smith et al⁵ reviewed the pediatric safety reporting of 67 drug products for the first 5 years after passage of the 2002 Best Pharmaceuticals for Children Act, highlighting the PAC's role in recommending labeling changes for 12 drug products (17.9%), continued monitoring for 10 (14.9%), and production of Medication Guides for 9 (13.4%). The present article summarizes the product safety reviews provided to the PAC and their recommendations and findings from November 2007 through September 2013.

METHODS

This study was an analysis of the pediatric-focused safety reviews prepared for each drug and biologic product presented to the PAC during the designated period. The drug product AEs were retrieved from the US Food and Drug Administration Adverse Event Reporting System (FAERS) database. This database comprises mandated reports of US and foreign AEs from manufacturers, hospitals, and user facilities, as well as voluntary reports from health care professionals and consumers.⁶ Narrative details are included in many reports. The Vaccine Adverse Event Reporting System database, cosponsored by the Centers for Disease Control and Prevention and the FDA, was used to capture vaccine-related AEs.⁷ In addition, drug use or prescribing data were provided to give estimates of the number of dispensed prescriptions and indications for use. These data from outpatient retail pharmacies, inpatient hospitals, or outpatient specialty clinics included an assessment of pediatric drug exposure incorporating prescribing specialty and diagnoses associated with use.

PAC Review Process

Pediatric safety reviews are conducted and prepared by FDA staff, including safety evaluators, medical reviewers, and epidemiologists. These reviews focus on serious adverse events (SAEs) such as death, life-threatening adverse reactions, hospitalization (initial or prolonged), disability, congenital anomaly/birth defect, and other serious important medical events as well as unexpected events that may be potentially related to the product.⁸ For drugs, pediatric age is usually defined as birth through 16 years. Drug utilization data provide an estimate of patient exposure in the pediatric population and an idea of the denominator and context in which to view the AE reports. To identify and assess

possible safety signals for previously unrecognized or unlabeled events, many factors are considered, including prescribing patterns, an assessment of the severity of the condition for which products are being used off-label, and exposure and confounding effects of concomitant medications. Drug class effects, drug interactions, and the natural history of the underlying conditions for which products are prescribed are all considered in the assessment of whether a reported AE is likely to be attributable to a certain product. An extensive literature review (medical, pharmacology, and toxicology), as well as an assessment of unpublished or incomplete studies submitted to the FDA by sponsors, is performed and presented to the PAC by FDA staff. The PAC discusses the FDA analyses and findings and then makes recommendations to the FDA on product labeling, product use, and/or additional needed studies.

RESULTS

During the study period, 14 PAC meetings were held with 181 pediatric-focused safety product reviews presented. The annual number of product reviews increased significantly in the 6 years (Fig 1) since biologic products and vaccines were added to the list of products mandated to have pediatric-focused safety reviews according to the 2007 Food and Drug Administration Amendments Act.³ A total of 6930 FAERS reports of SAEs were collected, including deaths that occurred in children with the use of these products. The top 3 specialties for the majority of products were infectious disease, ophthalmology, and pulmonary/allergy (Fig 2). The therapeutic product categories with the majority of SAEs were psychotropic and neurologic drugs.

For approximately two-thirds of the product reviews, the PAC recommended that the products return to ongoing routine FDA

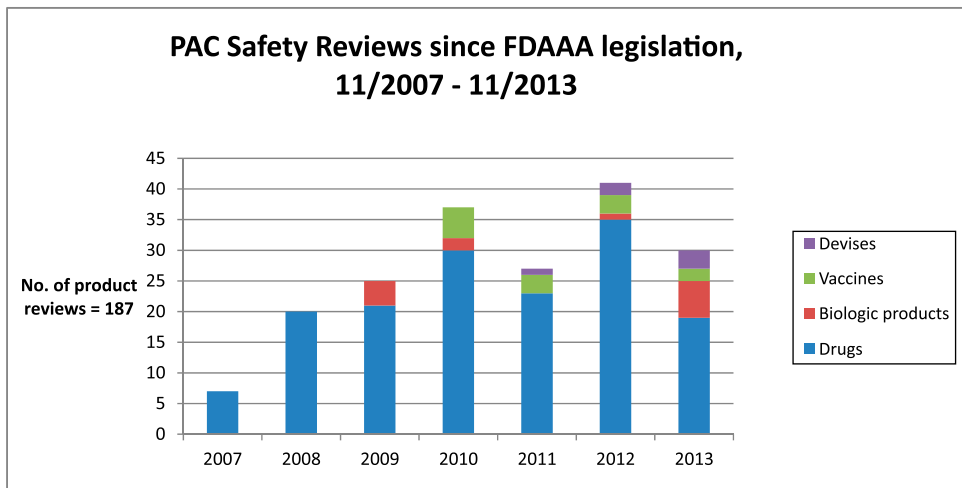


FIGURE 1

Pediatric-focused safety reviews for drugs, biologic products, vaccines, and devices presented to the PAC since passage of the 2007 Food and Drug Administration Amendments Act. This figure includes legislatively mandated safety reviews of pediatric devices from November 1, 2007, through September 30, 2013.

surveillance. This recommendation means that the FDA continues surveillance without a specific pediatric focus. The PAC recommended that 33 products (18%) have labeling changes. Twenty-one recommended labeling changes have been implemented for 20 products (Table 1). Ten of the label changes had information added to the Warnings and Precautions section of the label. For those products that had no labeling changes implemented, the FDA's clinical divisions concluded that the information was already adequately

provided in the labeling or that additional information, which was unavailable, would be needed before such a labeling change could be made. The PAC made several recommendations for additional studies (Table 2). Many of the important safety issues that were identified during the PAC reviews involved problems related to off-label use (eg, proton pump inhibitors, asthma and migraine medications), accidental secondary exposures (eg, AndroGel [testosterone gel]), behavioral and neuropsychiatric symptoms with nonpsychotropic

drugs (eg, Tamiflu [oseltamivir phosphate]), metabolic and endocrine events (eg, atypical antipsychotic agents), toxicity from active ingredients or excipients, especially in younger infants (eg, Kaletra [lopinavir/ritonavir]), and medication errors (eg, dispensing errors).

DISCUSSION

This article highlights the importance of ongoing pediatric-focused, postmarketing safety reviews of FDA-regulated products.⁹ Overall, pediatric AE reporting has comprised a small percentage of the total AE reports submitted to the FDA.¹⁰ Mandated pediatric-focused reviews with presentations to the PAC provide an opportunity for the detection of safety concerns that may not be identified in prelicensure clinical trials. Premarketing studies have limitations because of the small number of patients (excluding vaccines, attention-deficit/hyperactivity disorder, antibiotic, and asthma medications) usually enrolled in most pediatric studies. Compared with adult trials, studies required for demonstration of efficacy and marketing approval in children often involve a limited number of participants. The studies are short in

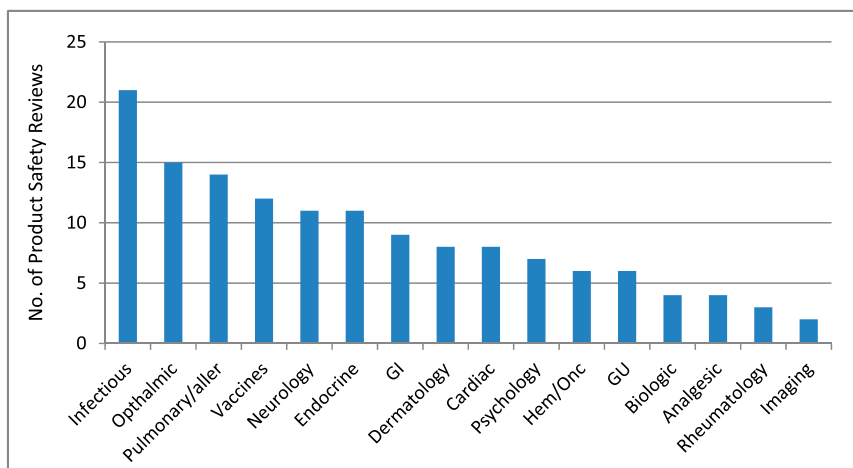


FIGURE 2

Number of product safety reviews according to pediatric specialty, November 2007 through September 2013. Aller, allergy; GI, gastrointestinal; GU, genitourinary; Hem/Onc, hematology/oncology.

TABLE 1 Completed PAC-Recommended Labeling Changes, November 2007 through September 2013 (N = 21)

| Drug | Recommended Labeling Changes |
|--------------------------------------|---|
| Abilify (aripiprazole) | Clarify potential for metabolic and weight effects in the pediatric population |
| Aldara (imiquimod) | Include information about the negative studies in children as well as local skin reactions in the genital area leading to "inability to urinate" |
| AndroGel (testosterone gel) | Include specific information about secondary exposure risk of pubertal development, virilization, and bone effects |
| Artiss (fibrin sealant, human) | Include information on specific ages of those studied in premarketing clinical trials |
| Asmanex (mometasone furoate) | Revise to clearly state that lactose is an ingredient in the excipient powder and harmonize the labeling for all dry product inhalers |
| Candidas (casposungin acetate) | Clarify that the hepatobiliary events have been reported |
| Epiduo (adapalene/benzoyl peroxide) | Include the potential for patient hypersensitivity to the product |
| Flovent HFA (fluticasone propionate) | Include dental caries and tooth discoloration to the postmarketing section of the labeling |
| Kapvay (clonidine hydrochloride) | Harmonize labeling with the clonidine IR labeling for AV block and hallucinations |
| Lamictal (lamotrigine) | Include information about suicidality |
| Provigil (modafinil) | Include information about the ADHD pediatric clinical trial data and stronger language that it is not approved for any pediatric indication because of safety issues |
| Retrovir (zidovudine) | Include information about dosing changes to reduce medication errors |
| Risperdal (risperidone) | Clarify potential for metabolic and weight effects in the pediatric population. Include additional information about pediatric use in this class of products |
| Sandostatin LAR (octreotide acetate) | Harmonize the LAR and injection solution versions of the label and include information that no causal association has been established |
| Serevent (salmeterol xinafoate) | Include information about the risk of serious asthma outcomes (asthma-related death, intubations, and hospitalizations) with the use of the class of the LABA |
| Suprane (desflurane) ^a | Include "cardiac arrest" in the postmarketing section of the labeling |
| Suprane (desflurane) ^a | Revised to clearly state that the use of maintenance of non-untubated pediatric patients be contraindicated |
| Tamiflu (oseltamivir phosphate) | Include information about neuropsychiatric events in the Warnings and Precautions section of the label and in the patient package insert |
| Topamax (topiramate) | Include information about AEs (eg, weight loss, bone mineralization, life-threatening episodes of epistaxis) as well as information about the results of sponsor's migraine studies in children |
| Valtrex (valacyclovir hydrochloride) | Clarify that central nervous system AEs have been reported in pediatric and adult patients |
| Zyprexa (olanzapine) | Clarify the potential for metabolic and weight effects in the pediatric population. Include information regarding pediatric use in this class of product |

ADHD, attention-deficit/hyperactivity disorder; AV, atrioventricular; IR, immediate release; LABA, long-acting β -agonist.
^a These changes resulted from 2 separate PAC meetings and recommendations.

duration, include a small select group of patients, and are typically not adequately powered to identify safety signals (especially rare but SAEs).⁵ Therefore, postmarketing reporting continues to be an important source of safety information for pediatrics. Children

may be especially vulnerable to product AEs. AEs that are unique to children, or that are either more severe or frequent than in the adult population, may not be detected until after a drug is approved and used in a larger pediatric population. This "real-world" population is

important in detecting safety signals. It allows for series of case reports of patients who may have a wide range of comorbidities, a variety of concomitant product use, and a broader spectrum of treated underlying conditions.¹¹ The narrative summaries of these case reports provide important clinical details (eg, patient characteristics and the presence of other risk factors) to allow an independent assessment of the causal role, if any, of a drug in the development of an AE.¹²

Lessons Learned: Neuropsychiatric, Behavioral, Metabolic, and Endocrine AEs in the Pediatric Population

Recent studies have shown that one-third of all adverse drug reactions reported in children were due to psychotropic drugs.¹³ In 2008 and 2009, when many of the atypical antipsychotic agents were reviewed by the PAC, a surprising number of AE reports of children with excessive weight gain was found. For example, the Abilify (aripiprazole) safety review had a report of a 6-year-old boy who gained 40 lb in 6 months and a 15-year-old girl who gained 13 lb in 1 to 2 months. On December 8, 2009, the PAC raised concerns about the potential for metabolic effects that may be more common or more severe in children, and they found that product labeling did not adequately reflect the risks. The PAC voted to recommend strengthening product labels regarding metabolic events and weight gain seen with atypical antipsychotic agents. Subsequently, the sponsors added a subsection to the Warning and Precautions section that included risks of hyperglycemia/diabetes mellitus, dyslipidemia, and weight gain and that these risks should be monitored. The PAC also discussed the need for more data on use in the pediatric population, as well as additional studies to provide better information on metabolic adverse reactions and the risk of type 2 diabetes.

TABLE 2 Examples of PAC Suggestions for Further Studies

| Product | Safety Concern | Recommended Safety Studies |
|---|--|--|
| AndroGel (topical testosterone gel) for adult males | Inadvertent secondary exposure in children | Further assess effects of low-level secondary exposures and transfer of drug product from inanimate objects to people |
| Atypical antipsychotic agents for schizophrenia and irritability with autistic disorder | Metabolic effects and off-label use | Long-term studies including registries and active surveillance systems to evaluate metabolic syndrome, growth, sexual maturation, and hyperprolactinemia; information about on-label and off-label use |
| Topical calcineurin inhibitors as second-line therapy for atopic dermatitis | Carcinogenicity | Long-term cancer registry data and review of the literature with special concerns for off-label use in very young children |
| Sandostatin (octreotide acetate) for acromegaly | High off-label use in neonates (eg, chylothorax) | Recommended that the FDA work with the NIH regarding systematic, prospective, and retrospective reviews of actual off-label use and AEs |
| Apidra (insulin glulisine recombinant) and NovoLog (insulin aspart recombinant) | Drug products administered with device technology | Postmarketing monitoring for AEs and medication errors for drug products used in association with device delivery systems; further study on device-related errors |
| Proton pump inhibitors for GERD and erosive esophagitis | High off-label use in very young infants | Further studies in the very young age group to understand risk/benefit profile and use of appropriate neonatal study end points |
| Kogenate FS (antihemophilic factor [recombinant]) used for hemophilia | Used for rare diseases with very small sample size | Need to develop databases to identify pediatric use for products such as Kogenate FS, which are intended to treat rare diseases |
| Flovent HFA (fluticasone propionate) for asthma | Increasing use in children <4 y | Recommended growth studies in young children, ages 0 to 4 y |

GERD, gastroesophageal reflux disease; NIH, National Institutes of Health.

Challenges of Determining if AEs Are Related to the Drug or Underlying Disorder

It is not always clear if AEs can be attributed to the drug, the underlying disease, or both. For example, the safety reporting for the antiviral medication Tamiflu (oseltamivir phosphate) revealed more neuropsychiatric events of abnormal behavior primarily in pediatric patients (particularly in Japan) that did not seem to be fully explained by influenza encephalopathy/encephalitis. These neuropsychiatric AEs of self-injurious behavior and suicidal ideation were added to the Precautions section of the Tamiflu labeling. In 2007, after further substantive analysis and data review of safety issues and additional drug sponsor and Japanese studies, the PAC voted to add wording to the labeling stating that patients with influenza may experience neuropsychiatric symptoms, including those taking Tamiflu. The FDA continues to review AE reports for the influenza products on a monthly basis during the influenza seasons and will report back to the PAC if important safety issues emerge.

Off-Label Use

Many drugs have never been studied in children, and there may be a lack of appropriate formulations. Off-label use

is common, and formal studies of drug usage in these settings are not frequently conducted, which increases the need for postmarketing safety monitoring.¹⁴ In 2009, when some of the atypical antipsychotic drugs were presented, the PAC discussed concerns about the off-label use for “attention deficit disorders,” which was the third most frequently associated indication for which the product was being prescribed. The expanded use of these medications for a wide range of clinical indications in children is a concern.¹⁵ The PAC requested that the FDA review the use data on atypical antipsychotic agents for children undergoing treatment for attention-deficit/hyperactivity disorder.

Toxicity of Product Excipients

The paucity of reports detailing SAEs of drugs should not be mistaken for proof that such effects do not occur. PAC safety reporting highlights the importance of conveying AEs of FDA-regulated products by submitting voluntary reports of these events to the FDA MedWatch program website.⁶ Even a handful of case reports in a special age group can suggest possible safety concerns. Kaletra (lopinavir/ritonavir), an antiretroviral oral solution, was presented to the PAC in 2009. At that

time, the safety review revealed SAEs, including cardiac events, some of which were already labeled. The FDA continued ongoing monitoring of SAEs and conducted an additional safety assessment of reports of premature infants, some with cardiac AEs, and some with increased lactate levels, central nervous system toxicity, and renal failure. This assessment ultimately led to identification of a possible safety signal with ethanol and/or propylene glycol excipient toxicity from this product. New labeling was instituted in February 2011 that Kaletra (lopinavir/ritonavir) should not be used in preterm neonates in the immediate postnatal period because of possible toxicities; the new labeling also stated that total amounts of alcohol and propylene glycol from all medicines that are to be given to infants should be taken into account to avoid toxicity from these excipients. A Drug Safety Communication and a Dear Health Care Provider Letter were also issued.¹⁶

Safety Concerns With Secondary Exposures to Drugs

Accidental exposures may be a special safety concern, especially in children who are particularly vulnerable. The topical testosterone product AndroGel

had been studied as replacement therapy in children with pubertal delay caused by primary or secondary hypogonadism. However, safety and effectiveness were not established. The mandated pediatric safety review with presentation to the PAC in June 2009 raised concerns about secondary exposures to young children from adult use. This exposure resulted in precocious pubertal development, enlarged genitalia, advanced bone age, and aggressive behavior. Clitoral reduction surgery occurred in some cases. These events led to a black box warning for AndroGel (testosterone gel). This example also illustrates how a few cases with adequate narrative details involving unusual AEs allowed the FDA to seek further information, which substantiated the concern.

Important Information From Pediatric Studies Added to the Label

One antiepileptic drug, Topamax (topiramate), was reviewed by the PAC in 2009 and again in 2011. In 2009, the PAC was informed that an adolescent study of Topamax (topiramate) had been conducted for migraine prophylaxis. The sponsor did not request that the indication and the pediatric information from the study be included in the labeling. Because the study was conducted before the 2007 legislation was enacted, pediatric study results were not required to be put into product labeling. However, the PAC strongly recommended that the information from the adolescent migraine study be added to the labeling. As a result, after an FDA request in 2011, the sponsor submitted the study data to the FDA as an efficacy supplement, and the important information from the clinical trial was ultimately incorporated into the product labeling.

Limitations

Although the FDA relies on FAERS data, reports frequently have limitations that can affect interpretation. These limitations include inadequate narrative detail, missing age facts, incomplete

dosage and route data, inadequate temporal information, and missing information about concomitant medication use.¹¹

FAERS reports often contain insufficient clinical details to enable an independent evaluation or determination of whether an AE occurred in the setting of off-label use. These data limitations, and the mostly voluntary nature of reporting into the system, create inferential limitations that the PAC considers carefully. Underreporting, reporting bias, samples not representative of those using specific products, and similar potential sources of bias are weighed by the PAC. Extensive off-label use of products for treating children further complicates our understanding of product safety in pediatrics.¹⁷

Pediatric cases, based on spontaneous reporting to the FDA, will not always result in a definitive conclusion about a product's safety, and additional epidemiologic or clinical studies may be needed to establish any causal relationship. De-challenge and re-challenge studies, as well as dose-response studies, are considered when they are available. However, observational pharmacoepidemiologic studies may have problems as well. Confounding by indication, lack of control for medical conditions and interventions, and other biases common to observational studies complicate the interpretation of observational studies used to inform product labels. Although clinical trials play an important role in defining a product's safety profile, they are not well suited for detecting AEs that occur rarely or any event that occurs less frequently than 1 in 100 or in the few hundred patients who represent the usual number of pediatric patients in most drug trials.

CONCLUSIONS

FDA pediatric-focused postmarketing safety reviews provide ongoing, comprehensive monitoring and

assessment of postmarketing pediatric product safety. Compared with earlier years, there has been an almost 3-fold increase in the number of products being presented to the PAC over the past 6 years. This legislatively mandated activity continues to enhance our understanding of the safety profile of products being used to treat children and helps ensure their safe use in the pediatric population. This outcome is particularly important for children who may be on therapies during important developmental life changes. The data analyses and surveillance program also validated the importance of legislation to drive effective and safe medications and therapeutic products for children. Although one cannot directly make attribution to changes in prescribing subsequent to new information provided in labeling, we do see a decrease in use of certain products after safety changes have been made or there has been an increase in public warnings. This process has also led to further epidemiologic and clinical studies, and highlighted the importance of the public's reporting to the MedWatch program.

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ABBREVIATIONS

AEs: adverse events
FDA: US Food and Drug Administration
FAERS: US Food and Drug Administration Adverse Event Reporting System
FDA: US Food and Drug Administration
PAC: Pediatric Advisory Committee
SAEs: serious adverse events

FINANCIAL DISCLOSURE: Dr Rosenthal works for the University of Maryland School of Medicine. He was cleared through the US Food and Drug Administration's conflict of interest process to participate in each of the safety reviews referenced in the article. The other authors are US Food and Drug Administration employees.

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