Good afternoon. My name is Dr. Kathleen Neville and I am delighted to be here today to address the issue of over-the-counter (OTC) drug regulation on behalf of the American Academy of Pediatrics (AAP). The AAP is a professional organization of over 62,000 primary care pediatricians, pediatric medical subspecialists, and pediatric surgical specialists dedicated to the health, safety, and well-being of infants, children, adolescents, and young adults.

I currently serve as the chairperson of the AAP Committee on Drugs. In my clinical role, I am director of the Experimental Therapeutics in Pediatric Cancer program at Children’s Mercy Hospital and Associate Professor of Pediatrics at the University of Missouri-Kansas City School of Medicine.

I am pleased to be here today to discuss the Food and Drug Administration (FDA)’s OTC drug monograph process. Promoting safe and effective drugs for use in children is among the Academy’s highest priorities and as such we strongly support an effort that would revisit and hopefully modernize the process by which new warnings or new safety and efficacy information can be reflected in OTC drug labeling for all products used in children in a timely manner.

In my comments today I will discuss the shortcomings of the OTC monograph process for children and offer feedback on some of the suggestions for change identified by the FDA. While I will highlight our ongoing experience working with the FDA to revise the monograph that regulates cough and cold products for children, I would urge the agency not to let the discussion in this public hearing delay publication of the proposal to revise this important monograph. Too much work has already been done by the FDA on the revision of this particular monograph.

Put simply, the OTC monograph system does not serve children well. Many of the existing drug monographs were developed with little or no data on the safety and efficacy of monograph drugs in children. While it is now universally accepted that “children are not little adults”—and therefore adult data is insufficient to justify use in children—this principle unfortunately did not guide the development of pediatric indications and dosing for monograph drugs. The physiology of children is different than that of adults and this changes how they absorb, metabolize, eliminate and respond to medications. This necessitates the development of age-specific therapeutic data on safety and efficacy for children.
Since the development of the original OTC monographs, the world of pediatric therapeutics has drastically changed. Largely as a result of the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA), the percentage of drugs used in children without pediatric-specific labeling has dramatically declined. Prior to 1997, approximately 80 percent of drugs used in children lacked pediatric labeling, but today that number is less than 50 percent. Last year, an important milestone was achieved when the FDA approved the 500th pediatric label change as a result of BPCA and PREA. These laws have a remarkable record of achievement.

The monograph process is no longer consistent with current best practices in pediatric pharmacology science that underscore the fundamental principle that drugs used in children be first studied for safety and efficacy within the pediatric population. While many monograph drugs are safe and effective for use in a children—and some are even mainstays of pediatric practice—others continue to be labeled for children and heavily marketed to parents despite safety concerns and newer data showing a lack of efficacy in children.

As noted by the FDA and as we have experienced with the pediatric cough and cold monograph, the process for changing a monograph is not well-adapted to address new safety or efficacy issues with the speed and nimbleness necessary to protect the public health. The AAP has been working with the FDA since 2007 to improve cough and cold product labeling for children. While we are appreciative of the progress made within the agency on this important initiative, it is frustrating to pediatricians that the FDA has yet to publish a proposal to amend the monograph.

Most of the pediatric cough and cold preparations on the market today are regulated under the Cough, Cold, Allergy, Bronchodilator, and Antiasthmatic Drug Products monograph. Even though the panel that developed the monograph concluded in 1976 that “data on the use in children of most drugs in [cough and cold preparations] are negligible or nonexistent,” the monograph permits these drugs to be considered “generally recognized as safe and effective” for all children age two and older. The monograph also did not require “do not use” warnings for children under two.

In March 2007, seven years ago this month, a group of pediatric experts submitted a citizen petition to the FDA asking that cough and cold products be relabeled to advise against use in children under 6 years of age. The petition challenged the
efficacy of these products in children and raised concerns about child injuries and deaths caused mostly by accidental overdose.

In response to many of the important points made in the citizen petition, the AAP acknowledged that although some cough and cold products were studied in children prior to their introduction on the market, the trials available at the time did not meet today’s standards, and that all well-conducted subsequent studies have found the products to be ineffective in children. In the face of evidence of no effectiveness and certain evidence of harm, the AAP recommended that cough and cold products be relabeled.

In October 2007, the FDA convened a joint meeting of its Pediatric Advisory Committee and Nonprescription Drugs Advisory Committee to consider the issues raised in the citizen petition. The joint committee voted unanimously that adult data on cough and cold products should not be extrapolated to establish efficacy of the drugs in children under 12. They also voted to recommend that the FDA immediately take cough and cold drugs off the market for children under 6 years of age.

Subsequently, the FDA began a process to revise the monograph that regulates these drugs. In October 2008, the FDA held what is referred to as a “Part 15” hearing to solicit public input on the FDA’s revisions to the monograph for these products. At the time and ever since, the AAP has said that OTC cough and cold products should, at a minimum, be re-labeled to recommend against use in children under six years. The AAP also recommends studies to demonstrate effectiveness for all pediatric subpopulations. These included pharmacokinetic studies in a variety of age groups, double-blind, placebo-controlled efficacy trials with clinically meaningful endpoints, and rigorous post-marketing surveillance efforts. Although manufacturers pledged as early as 2007 to engage in a comprehensive research program to generate clinical evidence proving the efficacy of these products in children, the AAP is aware of no new efficacy data to justify the use of these products in children.

Despite the recommendations of the AAP, FDA’s own advisory committees and calls from congress, revisions to the OTC cough and cold monograph have yet to be published. The only tangible progress that has been made so far in updating the labeling of these drugs has been through voluntary industry responses to mounting public and agency pressure.
In 2007, industry voluntarily relabeled the products to advise against use in children under 2, and in 2008, voluntarily relabeled them again to advise against use in children under 4. While these are steps in the right direction, they are voluntary, unenforceable, and ultimately they fall short of an FDA revision of the monograph based on the current state of the evidence.

Recent data show that the voluntary actions have improved child health, but that more progress can only be accomplished through the revision of the monograph. A 2013 study that analyzed the impact of the voluntary label changes on pediatric emergency department (ED) visits showed that relabeling for children under 2 resulted in a 41% reduction in the proportion of adverse drug event-related ED visits attributed to cough and cold products among children under 2. Subsequent relabeling for children under 4 resulted in a 32% reduction in the proportion of adverse drug event-related ED visits attributed to cough and cold products among children 3-4. What this shows is that relabeling is an effective strategy in reducing ED visits related to these products.

Unfortunately, the study showed no reduction in the proportion of adverse drug event-related ED visits for children 4 to 5 and 6 to 11, suggesting that labeling revisions do matter. In the absence of a revised OTC cough and cold monograph, it is questionable whether we will see changes in cough and cold drug-related ED visits for pediatric populations not covered by industry’s voluntary actions.

It is also worth noting that while there were reductions in drug event-related ED visits, the actual number of these ED visits still remains quite high. In the absence of a revised OTC cough and cold monograph published by the FDA that reflects the safety and efficacy of these products, parents will continue to give these products to young children. And pediatricians will continue to be on the front lines educating parents who are worried about these products.

Therefore, the AAP strongly recommends that the FDA move quickly to publish a revision to the pediatric cough and cold monograph. In doing so, the agency should conduct a comprehensive re-evaluation of the cough and cold monograph to determine whether the continued marketing of these products to children provides a benefit to children that outweighs the risks. This evaluation should take into consideration the impact of a revision on all pediatric subpopulations. Pediatricians, parents and children cannot afford to wait for what will likely be a lengthy, albeit important, conclusion of the OTC monograph reform process.
In the long-term, the AAP would agree with the FDA’s assessment that any comprehensive solution to modernizing the OTC drug review process use modern standards for safety and efficacy. The AAP appreciates the agency’s specific recognition that any such overhaul of the current system allow FDA to easily and quickly require additional information or data necessary to develop pediatric labeling. The FDA correctly notes that current best practices for determining pediatric dosing now call for pediatric-specific pharmacokinetic (PK) data. However, we caution the FDA that developing new labeled dosing for pediatrics is not as simple as gathering new PK data. Without new efficacy data, any attempt to add or revise pediatric dosing for monograph drugs must include a de novo review of the appropriateness of extrapolating adult efficacy to pediatric subpopulations.

A key component of the success of BPCA and PREA at providing meaningful pediatric data for drug labeling is that the FDA reviews and approves study protocols, issues Written Requests, and, thanks to newly added provisions of the Food and Drug Administration Safety and Innovation Act (or FDASIA), has enforcement authority to ensure the completion of required pediatric studies. Similarly, FDA needs to have the authority and mechanisms to revise OTC drug labeling to reflect emerging safety or effectiveness concerns and to respond to innovative changes to drug products.

For example, the AAP has continued concerns about the public health impacts of allowing OTC drug manufacturers to produce combination products consisting of multiple monograph drugs, particularly for cough and cold products. Effective and widely recommended antipyretics for children such as acetaminophen and ibuprofen are frequently mixed with ineffective cough and cold products. Single-ingredient antipyretics are too often mistakenly administered to children who are also given combination products with the same active ingredient, resulting in increased toxicity and adverse events related acetaminophen and ibuprofen.

The AAP notes its strong support for the new drug application (NDA) process. The NDA is the gold standard for the review and approval of drugs based on robust clinical trials and modern standards of evidence. Only drugs submitted under the NDA process, for instance, are subject to the full scope of the pediatric drug laws, BPCA and PREA.
While the FDA has offered a number of potential options that could hasten changes to an OTC monograph, we would note that FDA should have the authority to relatively quickly require the transition of a product from an OTC monograph to an NDA when significant concerns about safety and/or efficacy arise, even if those concerns may occur in a particular subpopulation. Using a risk-based approach, the FDA should determine which monograph drugs would be more appropriately regulated under an NDA and either immediately remove a product from the monograph or allow manufacturers a finite period to develop new data and submit an NDA before ultimate removal of the drug from the monograph.

Thank you for the opportunity to speak to you today on this important issue for child health. The AAP looks forward to continuing to work the FDA to improve drugs for children. I’d be happy to answer any questions you may have.