

American Academy
of Pediatrics



DEDICATED TO THE HEALTH OF ALL CHILDREN™

Remarks by

Michael R. Anderson MD FAAP

On behalf of the

American Academy of Pediatrics

Before the

Presidential Commission for the Study of Bioethical Issues

May 17, 2012

Madame Chairwoman, distinguished members of the Commission, thank you for inviting me to speak to you today. The topic you are undertaking is vitally important to the safety and well-being of our nation's children. My name is Mike Anderson, MD FAAP, and I am representing the American Academy of Pediatrics (AAP), a non-profit professional organization of more than 62,000 primary care pediatricians, pediatric medical sub-specialists, and pediatric surgical specialists dedicated to the health, safety, and well-being of infants, children, adolescents, and young adults.

I am Vice President and Chief Medical Officer for University Hospitals Case Medical Center and Associate Professor of Pediatrics at the Case Western Reserve School of Medicine in Cleveland, OH. I am also a practicing pediatric critical care specialist at Rainbow Babies & Children's Hospital where I serve as Chief Medical Officer. In my capacity as a practicing clinician, I have been active at the local, state, and national level in pediatric disaster readiness and response. In 2008, I was appointed by President George W. Bush to the National Commission on Children and Disasters (the Commission). I had the distinct honor of serving as the Commission's Vice Chair until its termination in early April 2011.

By way of training, I am board certified in Pediatrics and Pediatric Critical Care by the American Board of Pediatrics, and I earned my undergraduate and medical degrees from John Carroll University and Case Western Reserve University School of Medicine, respectively. I completed my pediatric residency at the Children's Hospital of Michigan, a fellowship in Pediatric Critical Care at Rainbow Babies & Children's Hospital, and I am currently enrolled in the Health Care Executive MBA program at Kent State University School of Business.

HISTORICAL CONTEXT FOR THE NEED FOR PEDIATRIC RESEARCH

Many of the laws which led to the formation of the Food and Drug Administration (FDA) as we know it today came as the result of therapeutic tragedies in children. The Biologics Control Act of 1902 established the Center for Biologics Evaluation and Research after the deaths of 22 children from contaminated vaccines. Following the deaths of 105 patients in 1937, many of whom were children, from a sulfanilamide elixir which was compounded with diethylene glycol, the Food, Drug and Cosmetic Act was the first to require premarket approval for safety. Twenty-five years later, thousands of children were born with birth defects after in utero exposure to thalidomide, leading to the Kefauver-Harris Amendment of 1962 which for the first time required manufacturers to prove efficacy as well as safety. While these legislative milestones all responded to pediatric problems, adults were the primary beneficiaries.

As recently as 1997, about eighty percent of drugs used in children were never studied for safety, dosing, or efficacy in children. So, while providers may have adequate information to inform the usage of drugs in adults, pediatric providers lack such information. The unapproved use of approved drugs, or so-called "off-label" use, is extremely prevalent among physicians who care for children. The term "off-label" use refers to a use of a drug that is not included in

the FDA-approved labeling for that drug. It is important to recognize that the term “off-label” does not imply an improper, illegal, contraindicated, or even investigational use. Rather, it means that substantial evidence to support efficacy and safety of the use has not been submitted by the drug sponsor to the FDA and approved by the agency. In most instances, qualified pediatric investigators, often without support of the branded drug or generic drug sponsor, have attempted to evaluate the safety and efficacy of a drug for an off-label use using non-standardized treatment protocols, in specific but limited pediatric populations who are likely to benefit from therapy. Data published in the medical literature under these circumstances are not as robust as data that would be generated by a drug sponsor at the request of the FDA if intended for package labeling for use in newborns, infants and children.

However, the absence of pediatric labeling information poses significant risks for newborns, infants, and children. Inadequate dosing information exposes pediatric patients to both the risk of adverse reactions that could be avoided with an appropriate pediatric dose, as well as the risk of providing an insufficient dose that would likely result in failed treatment, with associated increased suffering and possible death for the newborn, infant, or child being treated. The lack of pediatric safety information in product labeling exposes pediatric patients to the risk of age-specific adverse reactions unexpected from adult experience. Failure to develop a pediatric formulation of a drug or biological product, where younger pediatric populations cannot take the adult formulation, may also deny pediatric patients access to important new therapies, or may require pediatric patients to take the drug in extemporaneous formulations that may be poorly or inconsistently bioavailable.

AAP POSITION ON THE ETHICAL CONDUCT OF PEDIATRIC RESEARCH

In 1977 the AAP’s Committee on Drugs first published a landmark policy statement on “Guidelines for the Ethical Conduct of Studies to Evaluate Drugs in Pediatric Populations.” In this policy statement, the AAP, for the first time, said that it is unethical to adhere to a system which forces physicians to use therapeutic agents in an uncontrolled experimental situation virtually every time they prescribe for children. The Committee also said that it is not only ethical, but also imperative, that new drugs to be used in children be studied in children under controlled circumstances so the benefits of therapeutic advances will become available to all who need them.

This policy statement was most recently revised by the AAP’s Committee on Drugs and the Committee on Pediatric Research in 2010. In it, the Academy states that it is unethical to deny children appropriate access to existing and new therapeutic agents. Further, it is the combined responsibility of the pediatric community, pharmaceutical industry, and regulatory agencies to design, approve, and conduct high-quality studies in children and it is the responsibility of the general public to support the necessary research to ensure that all children will receive

treatment at the most appropriate dose in order to maximize efficacy and minimize toxicity, thereby providing optimal therapy to newborns, infants, and children.

The performance of research studies to evaluate drugs in children is critical for determining the safety and efficacy of medications in children. Without this type of research, medication use in children will be limited to extrapolation from adult studies or off-label use for indications that have not been studied in children, thereby putting children at increased risk of adverse effects. Growth and maturation can alter the kinetics, end-organ responses, and toxicities of drugs used in infants, children, and adolescents compared with adults. Without proper drug studies in children, children may not benefit from and may even be harmed by drugs that are available to adults. It is morally imperative, therefore, to formally study drugs in children so that they can enjoy appropriate access to existing and new therapeutic agents.

Understanding and protecting the needs of human subjects is particularly critical when research involves vulnerable populations, such as children. Research that involves children carries with it additional responsibilities for the investigator, the institutional review board (IRB), and product sponsor. While I will not go into detail on the Federal laws and regulations governing the protection of human subjects in research, with which you are no doubt familiar, I will highlight a couple of areas: determination of benefits and risks, IRBs, and informed consent.

Federal law requires that IRBs review clinical investigations that involve children and approve only those that satisfy one of several specified conditions. Regulations stratify the levels of research risk for children ranging from minimal risk to greater than minimal risk but offering the prospect of direct benefit to participants or offering the opportunity to understand or alleviate a serious child health problem. The risks include the known and predictable risks of the drug being studied as determined from previous animal and human studies in addition to the inherent risks of the research procedures themselves. In addition, there is always the risk of a heretofore unrecognized complication or adverse event from any drug being studied. Thus, all drug-study protocols in children must be scrutinized carefully for all potential risks, including those that are not necessarily a concern in adult studies. These risks include discomfort; inconvenience; fear; pain; separation from parents, family, or friends; effects on growth and development; and size and volume of biological samples being collected.

The type and number of invasive tests must be minimized and scientifically sound, and creative methods to obtain needed information noninvasively must be sought. Minimizing risk requires careful design of pediatric studies. Because children are a vulnerable population, they deserve the highest standards for monitoring safety during a drug study. Given the possible risks to children enrolled in a pre-event study of anthrax vaccine adsorbed (AVA) in children, the AAP supports compliance with the 21 CFR 50.54/ 45 CFR 46.407 federal review process which provides the opportunity for public review and comment. Consultation with pediatric subject matter experts in the design of a pre-event study of AVA in children as well as post-event care, follow-up and medical countermeasure distribution is critical.

The overarching responsibility of the scientific community in the IRB process is to carefully consider the proposed research protocol from the perspective of the potential human subject. It is imperative that all IRBs that review proposals for investigations in children include members with pediatric expertise who are knowledgeable about the special medical, psychological, ethical, and social needs of child research subjects.

The processes of informed consent and pediatric assent are central elements in all clinical research, indispensable for upholding the ethical principle of autonomy, and for ensuring the protection of human subjects. In pediatric clinical research, the informed consent process is complemented by the pediatric assent process, and its importance is magnified by the inherent vulnerability of pediatric research subjects. However, best practices for the informed consent and pediatric assent processes have never been defined. As a corollary, there is wide variation in informed consent and pediatric assent practices across the country, and IRBs vary in the criteria they require for approval of informed consent and pediatric assent procedures. Therefore, the AAP supports research to define best practices for both the informed consent process and the pediatric assent process.

Children as a group are underrepresented in clinical research, including research involving medical countermeasures. It is of vital importance that children be permitted to serve as participants in clinical research so that they may gain from both the personal benefits of participation (such as that afforded by access to new therapeutic agents and vaccines only available through clinical trials, or through access to clinical trials that are associated with heightened clinical monitoring that leads to improved clinical outcomes) as well as the benefits that accrue to all children as a group (i.e., so that new therapeutics and diagnostics can be developed and evaluated that will benefit children).

PUBLIC POLICIES TO PROMOTE PEDIATRIC DRUG RESEARCH

Since the publication of the 1977 policy statement, the Academy has advocated strongly that children deserve the same standards of therapeutic evidence as adults. The first step forward in public policy solutions to the lack of pediatric drug research came in 1997 when Congress passed the Food and Drug Administration Modernization Act. This law contained the first authorization of pediatric exclusivity, an incentive to study drugs in children. This program was reauthorized as the Best Pharmaceuticals for Children Act (BPCA) in 2002. In 1998 FDA published the Pediatric Rule which, for the first time, required that manufacturers of certain new and marketed drugs and biologics conduct studies to provide adequate labeling for the use of these products in children. The Pediatric Rule was struck down by the courts in 2002, but in 2003, Congress passed the Pediatric Research Equity Act (PREA), giving FDA the authority to require pediatric studies of drugs and biologics.

Finally in 2007, BPCA and PREA were reauthorized together, creating an integrated system for pediatric research incentives and requirements. In 2010, Congress extended BPCA to biologics for the first time. Reauthorizations of BPCA and PREA are currently being considered by Congress and both chambers are seeking to make these vital drug testing laws for children permanent.

BPCA and PREA work together as an effective two-pronged approach to generate pediatric studies. 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. These studies include off-label uses of drugs that may not result in new labeling indications for children, but result in knowledge shared with the medical community for those off-label uses studied at the request of the FDA. PREA provides FDA the authority to require pediatric studies of drugs when their use in children is for the same indication as for adults. Pediatric studies under PREA can be waived or deferred post-market under certain circumstances. Since 2007, all pediatric studies conducted by pharmaceutical companies under BPCA and PREA have resulted in labeling changes.

BPCA and PREA 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 little. Through BPCA and PREA we have gained more useful information on drugs and biologics used in children than we had in the seventy years prior to their enactment. Since 1997, more than 438 drug labels have been updated with pediatric information including 147 under BPCA, 181 under PREA, 50 under both BPCA and PREA, and 48 under the precursor to PREA, the Pediatric Rule. With these advancements, off-label use of drugs for most pediatric subpopulations has been reduced to around fifty percent. Despite this tremendous progress, for neonates from birth to age one month (including extremely premature infants who may weigh only one pound at birth), off-label use remains around ninety percent.

While BPCA and PREA apply to pediatric studies of drugs and biologics that are still on-patent, many products used in children are off-patent and lack data on safety, efficacy, and dosing for children. Some of these products are among the most commonly-used in pediatric care. To address this need for pediatric data and labeling, BPCA tasked the National Institute for Child Health and Human Development (NICHD) and the National Institutes of Health (NIH) with creating a priority list of pediatric therapeutic needs in off-patent products and conducting those needed studies. Several of the items on NICHD's priority list are medical countermeasures, and some of those studies are already underway. NICHD's program, including the formalization of the Pediatric Trials Network, has grown into a promising effort to increase pediatric labeling, with more than a dozen clinical trials completed or ongoing and dozens more awaiting funding to initiate the trials.

As mandated by BPCA and PREA, FDA's Pediatric Advisory Committee (PAC) must evaluate safety information reported in the year following a labeling change resulting from studies conducted under BPCA or PREA. Congress mandated this requirement as a response to concerns about long-term safety of products with pediatric labeling. According to the FDA, the one-year safety reviews by the PAC have resulted in routine safety monitoring, additional labeling changes, and other actions.

As a clinician, I cannot overstate the importance of what we've learned through the pediatric studies generated by these laws. Pediatric studies conducted under BPCA and PREA challenged what was previously thought about therapeutics in children. In many cases, studies and resultant labeling altered the dosages we give our patients. In others, drugs previously thought to be safe and effective in children proved not to be. And, pediatric studies have led to more effective formulations that are more palatable for children. To put it simply, the more we learn, the more we realize what we didn't know.

VACCINE RESEARCH

As noted by the tremendous success of BPCA and PREA at encouraging or requiring pediatric research, drugs, biologics, and vaccines as well as medical devices, and other products are routinely studied in children. Those studies involving children have yielded new information about the safety and effectiveness of products that have saved children's lives and, in some cases, prevented children from being exposed to drugs that do not work or to doses of medications that are inappropriate.

Unlike in drugs, pediatrics really drives vaccine research and development. From polio to pertussis to influenza, vaccines save children's lives. Vaccines prevent morbidity and mortality, and they help to enable children to reach their full potential. Virtually all vaccines licensed in the U.S. have approved pediatric labeling. In its report *Safe and Effective Medicines for Children*, the Institute of Medicine (IOM) found that of the 55 vaccines listed by FDA's Center for Biologics Evaluation and Research (CBER), only three products (5 percent) were not labeled for pediatric use, had waivers of the pediatric study requirements, and did not have pediatric studies registered at ClinicalTrials.gov. Those include adenovirus type 4 and type 7 vaccine which was developed under contract with the Department of Defense, a herpes zoster (shingles) vaccine, and an anthrax vaccine.

For most vaccines and drugs, adult safety and immunogenicity data is needed before the FDA will allow such products to be studied in children. While FDA does not require large-scale studies prior to the release of the seasonal influenza vaccine each year, the next generation vaccine technologies such as cell-based or genetically engineered vaccines will likely be required to undergo studies. Those studies will likely occur first in adults. As has been the experience under BPCA, FDA often will not issue a request for pediatric studies until the

product has been on the market in adults for some time so that the agency can monitor for any safety signals once it is in use by the general population.

PEDIATRIC MEDICAL COUNTERMEASURE RESEARCH

In general, the timing of the initiation of pediatric studies of drugs should be governed by a risk/benefit analysis that incorporates all relevant information on the drug under study as well as considerations related to the disease that is targeted for treatment and the availability of alternative therapies. For medical countermeasures, measuring risk and benefit also involves considerations of national security and threat assessments, information that may be classified or not publicly available. When considering medical countermeasure research, the mortality rate and difficulty of conducting research once the incident has taken place must be factors for consideration.

The U.S. Strategic National Stockpile (SNS) is the national repository of medical countermeasures including medications, vaccines and other critical medical equipment and supplies that are delivered to state authorities in a public health emergency. Analyses by the National Commission on Children and Disasters, the National Biodefense Science Board, and other experts have found that for threats that involve a chemical, biological, radiological or nuclear incident, the SNS not only is under-stocked with formulations of MCMs appropriate for children, but information also is lacking on pediatric dosing for MCMs. One of the key recommendations of the National Commission on Children and Disasters, on which I had the privilege of serving as Vice Chair, was that Congress, the Department of Health and Human Services, and the Department of Homeland Security/Federal Emergency Management Agency should ensure availability of and access to pediatric medical countermeasures at the Federal, State, and local levels for chemical, biological, radiological, nuclear, and explosive (CBRNE) threats.

Since the Commission regrettably terminated in 2011, some progress has been made by the Federal government to assess current gaps in existing medical countermeasures for children and quantities of stockpiled countermeasures for children, but availability of these countermeasures for twenty-five percent of the population, children, is not on par with those for adults. Legislation passed by the U.S. Senate would help ensure that children are a higher priority in the development and procurement of medical countermeasures for children.

In October 2010, the AAP, along with the Children's Health Fund, released the findings of a public poll that evaluated the public's views on disaster preparedness and response for children. The poll found that 92 percent of respondents agreed or strongly agreed that the U.S. should have readily available the same medical treatments for children as are available for adults for possible chemical, biological and nuclear agents that may be used in a terrorist attack. Seventy percent of respondents agreed or strongly agreed that the Federal government

should be better prepared to meet the physical and psychological needs of children in the aftermath of a disaster than it is for adults.

For CBRNE threats, children have unique vulnerabilities that must be accounted for and addressed. Children are subject to higher levels of exposure and harm following chemical and biological incidents. Children inhale more air and consume more water on a per-weight basis than adults. Because aerosolized agents (e.g. sarin and chlorine) are heavier than air, they accumulate close to the ground – right in the breathing zone of infants and children. Children are also much more vulnerable to agents that act on or are absorbed through the skin because their skin is thinner and they have a much larger skin surface-to-body mass ratio than adults.

In addition to the physical health vulnerabilities of children, during a disaster or emergency, children may be separated from their parents, they may be developmentally unable to communicate their needs with health care providers, they are vulnerable to exploitation and trafficking, and their mental health needs are both different from adults and may change over time.

Congress gave the HHS Secretary authority to approve a request for Emergency Use Authorization (EUA) once an emergency has been declared which may allow an approved product to be used for unapproved uses or may allow an unapproved product to be used, under certain circumstances, including when available information on the product's safety and efficacy allow the Secretary to determine that the benefits of use are likely to outweigh potential risks. Because use of a product under an EUA is not investigational, IRB approval and informed consent are not required. Multiple EUAs were issued during the H1N1 pandemic including products used in children such as oseltamivir for infants under one year of age. While EUAs are vitally important, they may have limited utility for children pre-event because, under current law, EUAs cannot be approved until an actual disaster or emergency has been declared. Additionally, the Federal government cannot purchase products to store in the Strategic National Stockpile if they are for unapproved uses unless that product has an approved EUA. So, under current law, there are significant challenges to stockpiling countermeasures for children unless those products have approved pediatric labeling.

The HHS plan for post-event prophylaxis (PEP) after inhalation exposure to anthrax is to offer all children 60 days of appropriate antimicrobial therapy in conjunction with three doses of the AVA. However, FDA has said that use of the AVA for PEP in pediatric populations, unlike adults which would be administered under an EUA, must be done under an Investigational New Drug (IND) application. An IND requires informed consent and IRB approval.

Given the difficulty of obtaining IRB approval and patient informed consent or assent during an actual disaster or emergency, it is important that the federal government collect the necessary pediatric data pre-event to enable the FDA to issue an EUA for AVA that includes pediatric uses, should that become necessary. Thought must be given to the potential loss of life or delays in

treatment that could accompany having to obtain IRB approval and informed consent post-event. Evaluating the safety and immunogenicity of vaccines which involves the collection and analysis of blood samples at one, two, and four weeks and may involve other requirements for follow-up care is simply not realistic during an emergency or disaster. Further, only a very small segment of the pediatric population would be able to participate in a standard vaccine-evaluation research study. For cities that may be exposed to anthrax, thousands of children would not be able to receive vaccine through research protocols, in contrast to the widespread availability of vaccine if sufficient preliminary data could be collected pre-event, to allow the Secretary to issue an EUA for AVA during an event. It is also worth noting that at least one of the antimicrobial therapies recommended by the federal government, ciprofloxacin, is not approved for children.

The collection of data pre-event may best be initiated using a tiered approach, one that begins with older pediatric age groups first. However, there will be challenges, challenges that could be significant, to initiating this research pre-event. Parents may be very unwilling to enroll their children in an anthrax vaccine research trial if they perceive the risk of exposure to anthrax to be minimal. They may see little to no benefit to participating in such research if they feel that their child or any child is not likely to be harmed by anthrax from a bioterrorism event.

There are vital national security reasons why the Federal government would not want to disclose what it believes to be the risk of an anthrax attack in the U.S. Similarly, there is an important need not to cause the kind of public panic disclosure of such a risk may create among the American people. However, should pre-event anthrax vaccine research in children go forward, the Federal government must present parents and potential enrollees enough information about the risk of an attack for them to assess for themselves that there is sufficient risk and benefit to participating in such research. Information about the recent anthrax attacks that have occurred in the U.S. should be provided.

For instance, in 2001, *Bacillus anthracis* spores were distributed intentionally through the U.S. postal system, causing 22 cases of anthrax, including five deaths. Among these cases was a 7-month-old child, who was suspected of being exposed during a visit to an office where an anthrax-tainted package was delivered. The child was hospitalized and fully recovered. Lessons learned from HHS' Dark Zephyr tabletop exercise which simulated an inhalational anthrax attack on a major metropolitan city in the U.S. should also be used to inform parents and potential enrollees. Finally, the fatality rate for inhalational anthrax is extremely high, approximately 75 percent, even with all possible supportive care including appropriate antibiotics. So, once an event has occurred, the availability of a vaccine that is safe for children, who account for 25 percent of the total population, will be critical to prevent massive loss of life, particularly if critical infrastructure to provide antibiotic PEP for all children is disrupted during an event, preventing the start of antibiotic therapy within twenty-four hours after exposure.

CONCLUSION

I would like to thank the Commission for inviting the Academy to participate in today's meeting. The Academy looks forward to providing additional insight and expertise at future Commission meetings. We offer ourselves as a resource to the Commission as it carries out its work.

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