Essential Drugs for Infants and Children: North American Perspective

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“Essential Drugs for Children” implies that some drugs are not essential, which of course, is true. It also implies that essential drugs can and should be differentiated from “nonessential” drugs and targeted as a priority for development for pediatric use. With ~80% of the marketed prescription drugs in the United States not approved by the US Food and Drug Administration (FDA) for use by children, the goal of obtaining approval and labeling for all drugs currently not labeled for use by children is overwhelming. Therefore, drugs currently available must be prioritized for pediatric development so that available resources can be focused on those agents most important for pediatric use.

This is a daunting task. How is an essential drug defined? What are the criteria for selecting essential drugs? Is it the volume of use? Is it the number of children impacted by the drug? Is it the indication(s) for use? Is it the severity of the condition for which the drug is indicated? Is it a drug used to treat a life-threatening condition? For the child with bacterial meningitis, the appropriate antibiotic clearly is essential. For the child with HIV infection or cancer, drugs that will impede progression of the disease, prolong life, and mitigate suffering are essential. A drug used to treat a rare genetic disorder is essential for the child affected by that disorder, although it may have minimal impact on the health of the general population of children. In contrast, an effective vaccine will have profound direct benefit for the entire population.

A drug used to treat symptomatically the self-limiting pruritus associated with varicella or insect bites may be widely prescribed, although it is used to treat a relatively trivial condition. Each of some 30 odd subspecialties, if queried, undoubtedly would have its list of essential drugs. Advocates of treatments for rare diseases view certain drugs as essential, although they may be used in relatively few children and may not ensure long-term survival in all cases. How does one factor in these various considerations when developing criteria for prioritizing drugs for pediatric development? Determining how essential drugs are to be defined is a complex issue. At the same time, developing a definition and process for agreeing on the most important drugs for children is imperative when attempting to prioritize the plethora of drugs used by children but for which pediatric labeling and/or dosage formulations do not exist. This certainly is not a new or novel issue. Indeed, several abortive attempts have been made during the past 20 years to identify drugs most important to children.

In 1979, under a contract with the FDA, the American Academy of Pediatric (AAP)’s Committee on Drugs compiled a list of several hundred drugs in 33 therapeutic categories that were judged to be useful for pediatric patients but not labeled for pediatric age groups. This report was filed with the FDA in June 1979. No attempt was made to prioritize among the hundreds of drugs. No official action on the part of the FDA was ever taken.

The AAP Committee on Drugs, under contract with the FDA, compiled a second list of 103 drugs in 1984 that represented drugs used commonly in infants by parenteral routes but were not labeled for infants. This list included dexamethasone, diazepam, digoxin, dopamine, erythromycin, furosemide, gentamicin, indomethacin, morphine, naloxone, pancuronium, penicillin, phenobarbital, theophylline, vancomycin, and vitamins B12, E, K plus many more. Again, no attempt was made to prioritize within this list.

In response to the 1984 list, the FDA requested a list of the 10 most important parenterally administered drugs for neonates. This top 10 list was prepared and filed with the FDA in January 1985. Selection was based on two levels of criteria. Criteria for level I selection of drugs were 1) the drug was currently used in therapy of neonates; 2) it was anticipated that use would continue and therapeutic value was documented; 3) existing published data were available regarding dosage recommendations, therapeutic indications, and toxicity; and 4) current labeling for neonatal use did not exist. If these four conditions were met, level II priority assignment was based on 1) frequency of use; 2) low therapeutic index; and 3) significant or serious toxicities reported with drug. Drugs included on this list were phenobarbital, dopamine, dobutamine, theophylline, nitroprusside, calcium, pancuronium, ampicillin, caffeine, and indomethacin. This lead to modest progress; pediatric information subsequently was added to 5

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of these 10 drugs: theophylline (aminophylline), phenobarbital, nitroprusside, pancuronium, and indomethacin.

A special neonatal indomethacin formulation was developed for use in treating patent ductus arteriosus. However, the labeling for dopamine, dobutamine, calcium salts, and parenteral ampicillin still contain disclaimers regarding use in infants and children. In addition, there is no commercially available, FDA-approved caffeine formulation for infants on the market.

Clinical trials in infants and children on which labeling may be based typically have not included many of the major therapeutic categories. In 1990, Dr Chestin Berlin, then chair of the AAP Section on Clinical Pharmacology and Therapeutics, conducted a survey of US and Canadian medical schools to determine whether they were involved in pediatric clinical trials of drugs and, if so, in what therapeutic categories they had currently active protocols. Seventy-three schools responded, and 69 of the 73 reported at least one active clinical trial in children at the time of the survey. Twenty-five or more respondents reported studies in five therapeutic categories: surfactant (25); antibiotics (38); human growth hormone (25); antivirals (29); and cancer chemotherapy agents (34). If activity in clinical trials reflect essentiality, these are the therapeutic categories deemed most essential in the pediatric medical community at the time of the survey. Among the therapeutic categories least represented in pediatric clinical trials were diuretics (5); nonsteroidal antiinflammatory drugs (6); sedative/hypnotics (5); antiemetics (3); antifungals (5); antithrombogenic agents (1); antiarrhythmics (3); analgesics (7); calcium channel blockers (1); inotropes (5); biologics (2); and clotting factors (2). A number of other categories have not been given priority, at least as represented in clinical trials, although all of them are important therapeutic categories in pediatric medicine.

In 1992, I was invited to review the regulatory status of drugs used in critical care medicine in the annual fall meeting of the AAP. In doing so, I selected drugs in the therapeutic categories of analgesics, anticonvulsants, β-agonists, calcium channel blockers, corticosteroids, diuretics, gastrointestinal prokinetic agents, H₂-blockers, inotropes/pressors, neuromuscular blockers, sedative/hypnotics, and vasodilators. Among the drugs commonly used representing these therapeutic categories, I discovered the following were not labeled for use in children: dexamethasone, dopamine, dobutamine, albuterol, terbutaline, metaproterenol, midazolam, lorazepam, metoclopramide, ranitidine, ketorolac, propofol, nitroglycerin, and bumetanide. All these drugs clearly are valuable, if not essential, for the care of children in the critical care setting. Several of these drugs also are considered indispensable for the care of children outside the critical care setting. Among this group of drugs, parenteral midazolam was approved for children age 6 years and older in March 1997. However, the other drugs on the list remain labeled not for use in the pediatric population.

Where, then, does this disjointed history lesson leave us?

The problem is that there is no established systematic process, either in our regulatory or in medical structures, to establish criteria for identifying and prioritizing the most important drugs for pediatric use.

By default, drug development priorities tend to be driven primarily by political and economic influences, and the global needs of children receive secondary consideration. Several examples illustrate this.

A large quantity of resources, money, and effort currently is going into the development of drugs to treat HIV infection both in adults and in children. Although this is a laudable effort, the response to the HIV epidemic has tended to be highly politicized rather than managed as other serious life-threatening epidemics. Some would argue that this has resulted in an expenditure of resources that is disproportionate to the number of individuals affected in relation to the most common causes of morbidity and death in the population. On the positive side, it is the vocal lobby for the HIV-infected pediatric population that is primarily responsible for the recent public and congressional awareness of the general neglect of children in the drug-development process. But do new anti-HIV drugs represent the most essential drugs for the pediatric population in general? They certainly are considered essential for the limited population of children who may benefit from them.

Pharmaceutic investment in drugs for children is devoted disproportionately to antimicrobial agents, primarily driven by their market potential in the pediatric population. However, is another third-generation cephalosporin or another monobactam the most important drug for children, compared with inotropes, antiarrhythmics, and sedative/hypnotics that are neither labeled nor provided in appropriate formulations for children?

So how do we approach the daunting task of selecting those most important or essential drugs to be targeted for pediatric formulation and labeling?

A systematic coordinated process needs to be established with ownership and participation by the FDA and the industry representatives, and input from the medical specialty constituencies that provide care for children. The process first needs to provide for development of criteria to guide a selection process, followed by a thorough review of current drugs in each therapeutic category. Using established criteria, priorities can be established. This will need to be a dynamic ongoing process to include review of new chemical entities to ensure those most important to pediatric medicine are approved for use in infants and children as a part of the new drug development process. The drugs identified through this process then should be targeted by the FDA for pediatric labeling and development of appropriate pediatric dosage formulations.

Such an effort will require time and resources. Who or what should be the appropriate entity to lead the way and make this happen? One possibility is the...
FDA through its Pediatric Committee (known as PEDIACOM). The AAP, through its Committee on Drugs and respective specialty sections, also should play a major role. A task force could be established within the Department of Health and Human Services with representation from all appropriate public and private parties to develop a priority list of drugs for pediatric use. Another possibility is to contract this task to the USP to be conducted with the advice and oversight of the USP Pediatric Advisory Committee. Regardless of who assumes or is assigned primary responsibility, little will happen without adequate resources.

The implementation of this process undoubtedly would be expedited by a Congressional mandate, coupled with appropriated funding, requiring the FDA in conjunction with the appropriate specialty groups and advisory bodies to integrate this process into the drug approval regulatory process.

Whatever the approach, such a structural coordinated process will be necessary to identify the essential drugs for children. It always will be a political process with economic implications. Nevertheless, the process must be driven primarily by the therapeutic needs of children if drugs essential to the health needs of children are to be provided in child-friendly formulations and labeled for infants and children.
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