The assent of children

Pediatric trials promise benefits to juveniles and big bucks to Big Pharma.

BY MARK S. LESNEY

Pediatric clinical trials are, in principle, no different from adult trials in the potential for establishing the benefits of new drug therapies for a population at risk from a plentitude of diseases and conditions, many unique to a particular age group. But beyond the similar potential for benefits, the problem of implementation is very different—a host of unique ethical, regulatory, and scientific considerations arise in the testing of infants, children, and adolescents.

Historically, clinical trials research (beyond that directed toward diseases unique to juveniles) rarely considered children. Previous years of neglect forced family doctors into the unenviable position of performing de facto clinical trials on their younger patients by requiring them to determine child dosages and to monitor safety and efficacy for drugs tested only in adults. Sometimes, this cavalier attitude of dosing children as miniature adults (literally on a pound-per-pound basis) has led to tragedy. One example is "gray baby syndrome", in which chloramphenicol, even at the appropriate dosage, proved lethal to neonates because of their liver's inability to metabolize it.

Partly to address these issues, the U.S. Congress passed the Food and Drug Administration Modernization Act (FDAMA) in 1997. As an incentive to the pharmaceutical industry, it included a pediatric exclusivity provision that extended market exclusivity of a drug by six months if the manufacturer researched its use in children. The 1998 pediatric rule (63 F.R. 66632, Dec 8, 1998) that followed required manufacturers to assess the pediatric safety and effectiveness of drugs on a list compiled by the FDA in consultation with the medical profession and the pharmaceutical industry. In January 2002, the Best Pharmaceuticals for Children Act was passed to reauthorize the FDAMA provision and extend the role of the FDA in promoting drug research for children.

These laws have been given credit for a substantial increase in pediatric drug research. By April 2001, the FDA had dealt with 188 requests covering 155 drugs already on the market and 33 drugs not yet approved. The requests included 414 studies and more than 20,000 children as research subjects (*1*).

Toys for testing

As part of the Children's Health Act (Public Law 106-310) signed by President Bill Clinton in October 2000, additional constraints on pediatric trials were implemented (*2*). One of the unique results of the new law, building upon the long-fostered ethical tenet of informed consent, is to split the normal consent process into two parts—informed parental permission and child assent. The belief is that, although a child is incapable of giving informed consent by definition, the legal status of a child over seven years of age does not entitle the parents to give overarching permission for participation in a clinical trial above and beyond the child-subject's will or "assent". Assent is defined as "a child's affirmative agreement to participate in research."

Incentives to gain the child's assent have included a variety of techniques: certificates to Toys R Us, T-shirts, cash allowances, and child-attractive research centers—with many of the incentives being developed under the guidance of child psychologists. In fact, Robert Temple, associate director for medical policy at the Center for Drug Evaluation and Research (CDER), as quoted in *The Wall Street Journal* (*3*), described the recruiting efforts as a "frenzy" and stated, "If you have a hypertensive kid, hold on to him. He'll be in hot demand."

Of course, it must be remembered that in none of these cases are drugs known to be dangerous being tested on healthy children. The vast majority of pediatric clinical trials involve children with debilitating or life-threatening diseases for whom the development of effective drug therapies is of critical personal importance. For many children, these trials provide the only access to potential medications for diseases whose alternative prognosis can be permanent disability or death.

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It is precisely because these stakes are so high, however, that oversight of potential trial abuses must be strict.

Big drugs are big money, and lack of a sufficiently high pediatric enrollment in a trial can prevent a potential blockbuster drug candidate from getting out of the starting gate—or a current blockbuster from gaining that ex post facto six months of patent exclusivity. In a milieu highlighted by overworked Investigational Review Boards and growing reliance on contract-research organizations, the added financial pressure of government "carrots" pushing forward pediatric studies can provide both promise and peril for sick children across the globe.

References

(1) www.senate.gov/~labor/GAO.pdf.
(2) *Fed. Reg.* **2001,** *66* (79), 20589–20600.
(3) www.wsjclassroomedition.com/tj_052902_test.htm.

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▶clinicaltrialsweb

FDA/CDER pediatric site (www.fda.gov/cder/pediatric)
Contains extensive links to laws regarding pediatric clinical trials, the FDA's patent exclusivity lists, pediatric policies and guidelines, and presentations and press releases on the issues by CDER staff.

Clinicaltrials.gov (http://clinicaltrials.gov/ct/gui)
A searchable site that lists clinical trials, including those seeking recruits. It was launched in February 2000 and contains 6300 clinical studies sponsored by the NIH, other federal agencies, and the pharmaceutical industry in more than 69,000 locations worldwide. The site is a result of the FDAMA, and pediatric clinical trials can be identified by using search terms such as *pediatric*, *children*, or *neonatal*.