# Changing Requirements for Evaluation of Pharmacologic Agents

Russell W. Chesney, MD*, and Michael L. Christensen, PharmD*‡

**ABSTRACT. Children sadly have been excluded from some of the therapeutic advances that have marked pharmaceutical drug development during the past 100 years. Most drugs in use today lack Food and Drug Administration approval for use in children or are restricted to certain pediatric age groups, predominately older than 12 years. Only a few of the new drugs approved each year have pediatric indications and dosing guidelines described in the drug labeling information. However, many of these drugs are used in children. The lack of suitable information places children at risk for over- or underdosing, and there is a lack of suitable dosage forms, which can result in improper drug administration. This lack of information on the safe and effective use of drugs in the most vulnerable patients—infants and neonates—is of greatest concern. Recent changes in the regulations that govern drug development has dramatically increased the number of drugs that undergo testing in children. This article reviews new laws that govern drug testing in children and the use of children in therapeutic research.** *Pediatrics* **2004;113:1128–1132;** ***Food and Drug Administration, drug studies, children in research, institutional review board.***

ABBREVIATIONS. FDA, Food and Drug Administration; FDCA, Food Drug and Cosmetic Act; FDAMA, Food and Drug Administration Modernization Act; NIH, National Institutes of Health; DHHS, Department of Health and Human Services; IRB, institutional review board.

Numerous problems have hampered clinical drug testing in children. Infancy and childhood are characterized by rapid changes in the physiologic processes that govern drug disposition and effect. Hence, studies must be conducted at multiple age ranges to ensure that adequate information is available in all applicable pediatric populations. Childhood usage is frequently a small proportion of a given drug's use, and a high cost is associated with obtaining pediatric labeling, estimated at $1 million to $4 million for each safety and efficacy study. There is not only an ethical concern about the use of children as study subjects but also how soon in the drug development process children should be included. It is crucial that the design of clinical trials take into consideration the unique characteristics of children, rapid physiologic changes, suitable controls, use of placebos, appropriate outcome measures, and the process of informed consent. Finally, most drugs lack a suitable dosage form for use in younger children, who cannot swallow large pills or capsules. The failure to evaluate drugs adequately in children has often left practitioners able to use only empiric therapeutic measures to treat their pediatric patients as "small adults." Practitioners must often choose between not treating a child with a potentially beneficial but not approved medication or treating them based on adult information and limited studies in children. In either case, children may not be prescribed appropriate therapy or have access to age-appropriate formulations.

From the Departments of *Pediatrics and ‡Clinical Pharmacy, Pediatric Pharmacology Research Unit, Center for Pediatric Pharmacokinetics and Therapeutics, University of Tennessee, Memphis, and Children's Foundation Research Center, LeBonheur Children's Medical Center, Memphis, Tennessee.

Received for publication Oct 7, 2003; accepted Oct 20, 2003.

Reprint requests to (R.W.C.) Department of Pediatrics, LeBonheur Children's Medical Center, 50 North Dunlap, Rm 306, Memphis, TN 38103. E-mail: rchesney@utmem.edu



## CHANGING REQUIREMENTS IN THE FOOD, DRUG, AND COSMETIC ACT

The evaluation of drug and other treatments to ensure safety has been a concern of the US federal government for nearly a century. The Food and Drug Administration (FDA) was created during the administration of Theodore S. Roosevelt to deal with adulterated medications that were then rampant in society. From the beginning of federal interest in drug safety, a concern for the "special status" of children has resulted in a fundamental dilemma: should children be protected from drug studies, or is it more important to evaluate adequately a medication in children of different ages? Put more bluntly, should we "avoid using children as guinea pigs"? Why should children not have the same extent of testing for proper drug dose, safety, and efficacy as adults receive? This controversy is not resolved and continues to receive considerable discussion.

Concern for the risk to public health of unsanitary food and adulterated drugs led to the Federal Food and Drug Act in 1906 (Table 1). The act prohibited interstate commerce in misbranded or adulterated food, drink, and drugs, and a key stimulus was adulterated quinine sold to the US Army in Mexico. The act was rewritten as the Food Drug and Cosmetic Act (FDCA) in 1938 after the death of 107 children from sulfanilamide elixir that was suspended in diethylene glycol.[1] No toxicity testing had been performed before marketing. The fundamental aspect of this legislation was that new drugs had to be safe before marketing. As well, new drugs had to have adequate directions for safe use by lay individuals included in the written materials that accompanied the drug, referred to as "labeling." A problem

**TABLE 1.** Major Changes to the Food Drug and Cosmetic Act

| | |
|---|---|
| 1906 | Drugs must not be adulterated or misbranded |
| 1938 | Drugs must be proven safe and have adequate directions for use |
| 1962 | Drug must also be effective in the intended population |
| 1979 | Pediatric labeling emphasized |
| 1994 | Final Rule clarifies pediatric labeling procedures |
| 1997 | FDA Modernization, Section 111 Pediatric Studies |
| 1998 | Final Rule: Pediatric Studies |
| 2002 | Best Pharmaceuticals for Children Act |

**TABLE 2.** Changes in Requirements for Children Involved in Clinical Investigation

| | |
|---|---|
| 1974 | National Research Act |
| 1978 | Recommendations for Research Involving Children |
| 1983 | Final Rule for the Protection of Human Research Subjects |
| 1998 | NIH Policy and Guideline on the Inclusion of Children |
| 2000 | Children's Health Act |
| 2001 | Interim Rule-Addition Safeguards for Children in Clinical Investigation of FDA Regulated Products |

with the requirement for adequate directions was that newer drugs that came onto the market were not safe for use except under medical supervision, and these drugs could not meet the adequate directions for use requirement. A 1951 amendment to the FDCA solved the problem by establishing 2 classes of drugs: 1) over-the-counter drugs that could contain adequate directions for use on the label and 2) prescription drugs used only under medical supervision. Another pediatric tragedy, fetal malformation from maternal ingestion of thalidomide, led to an amendment in 1962 that drugs not only had to be safe but also effective in the population for which they were to be marketed.[2,3] Established safety and efficacy in one population would not apply to another age range. Thus, safety and efficacy in adults cannot be transferred to children. Ironically, major changes to the FDCA unfortunately have been the result of therapeutic tragedies in children. Paradoxically, despite the recognized problem with the use of medications in children, the amendments to FDCA have seldom prompted increased study of drugs in children. Indeed, if anything, it has discouraged the evaluation of drugs in children because of perceived concerns over ethical issues, fears of "harming" children, and the perceived increased liability in "testing" drugs in children. That children also represent a small market share for most drugs often discourages sponsors from pursuing drug labeling for children.

The recognition that a distinct minority of drugs were labeled as safe and effective for use in children led to the 1979 FDA regulations that specific pediatric indications are described under the "Indications and Usage" section of the labeling, with appropriate pediatric dosage provided under the "Dosage and Administration" section.[4] The act also requires that recommendations for pediatric use be based on substantial evidence derived from adequate and well-controlled studies in the pediatric population, unless the requirement was waived. Although the "Pediatric Use" subsection was intended to encourage drug labeling in pediatric patients, it had, as did the 1962 amendment, the opposite effect. The requirement further discouraged pediatric labeling for most drugs because it required extensive data in the intended population. Several surveys have continued to show that the vast majority of newly approved drugs do not include pediatric labeling. The FDA, concerned that, without adequate information, practitioners may be reluctant to prescribe certain drugs for their pediatric patients or may prescribe them inappropriately, then implemented the 1994 Final Rule for pediatric labeling. This rule clarifies the FDA position on various pathways that can be used to obtain pediatric labeling of drugs. The 1994 Final Rule also places greater responsibility on the sponsor to justify why pediatric labeling should not occur. For instance, some drugs may be labeled for pediatric use on the basis of adequate and well-controlled studies in adults with pharmacokinetic and safety data in children. The 1994 Final Rule also recognizes the hazards that "inactive" ingredients can pose to pediatric populations.

The 1994 Final Rule did not impose a general requirement that manufacturers carry out studies if existing information were not sufficient to support pediatric labeling. Accordingly, this rule did not substantially increase the number of drugs for which there is adequate pediatric labeling. In 1991, 9 (56%) of 16 newly approved drugs considered by the FDA to have potential usefulness in pediatric patients had some pediatric labeling at the time of approval. By 1996, only 15 (37%) of 40 newly approved drugs with potential usefulness had some pediatric labeling at the time of approval. Hence, additional regulations were required to ensure the safe and effective use of drugs for pediatric patients. The FDA Modernization Act of 1997 requires that manufacturers of new drugs that may produce health benefits in the pediatric population to submit safety and effectiveness data on relevant pediatric age groups before approval.[5] This act is also intended to improve pediatric use information for drugs that are already on the market and for which there is a compelling need for more information. Drugs that meet the FDA guidelines for pediatric studies will receive an additional 6 months of exclusivity if a study is proposed. Exclusivity is a certain period of time of marketing protection enforced by the FDA. During the period of exclusivity, the FDA will not allow submission or approval of an application for an identical generic product. Updates on the statistics of the pediatric exclusivity provision including the drugs granted 6 months of additional exclusivity and the drugs that have had pediatric labeling changes can be found on the FDA web site (www.fda.gov/cder/pediatric/).

In 1998, the FDA issued a set of regulations: The Final Rule: Pediatric Studies. The Final Rule broadened the scope of Food and Drug Administration Modernization Act (FDAMA) to include marketed drugs and biological products.[6] The 1998 Final Pediatric Rule requires manufacturers of marketed drugs

to submit data on pediatric studies that represent meaningful therapeutic benefit or a significant improvement in therapy or has substantial use that has been defined as being used by >50 000 patients for the labeled indication. The FDA began requiring these pediatric studies in December 2000.

In 2002, Congress passed the Best Pharmaceuticals for Children Act, which extends the 6-month exclusivity provisions of the FDA until October 2007.[7] Important new provisions in the act are the creation of the Office of Pediatric Therapeutics within the FDA and creation of a Foundation of the National Institutes of Health (NIH) for the study of drugs in children. The Office of Pediatric Therapeutics will be responsible for coordination and facilitation of all activities of the FDA that may have any effect on a pediatric population or the practice of pediatrics or may in any way involve pediatric issues. The foundation will obtain funds through gifts, grants, and other donations for research and studies on drugs in children. Recently, there has been considerable debate over the need for the 1998 Final Pediatric Rule. In March 2002, the FDA indicated that it was suspending the 1998 Final Pediatric Rule for 2 years. The reason provided by the FDA for suspending the 1998 Final Pediatric Rule was to determine whether the reauthorization of the financial incentives of FDAMA would be adequate. This was met by an outcry from pediatric advocacy organizations, and the FDA acquiesced from suspending the 1998 Final Pediatric Rule in April 2002. There is now legislation pending in Congress to codify the provisions of the 1998 Final Pediatric Rule.

## CHANGING REQUIREMENTS FOR PEDIATRIC INVESTIGATION

The participation of children in research has been impeded because of regulatory requirements, economic deterrents, lower incidence of diseases, and complex developmental changes. Early initiatives to ensure the safe participation of children in research began in 1974 with the National Research Act. The report from the National Commission on Research Involving Children provided the foundation in 1978 for the federal regulations (Subpart D of Title 45 Code of Federal Regulations, Part 46, 45 CFR 46), Additional DHHS Protections for Children as Subjects in Research. The rule was codified in 1983. This rule applies to all Department of Health and Human Services (DHHS)-supported research. Studies that were supported by private industry and reviewed by the FDA were not subject to these regulations. However, the FDA generally followed these regulations as appropriate guidance for the conduct of pediatric studies. The FDA did classify children as vulnerable subjects but did not specifically address the involvement of children in clinical investigation. In 1998, the NIH instituted the Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects. The policy states that children must be included in all human subjects research that is conducted or supported by the NIH unless there are scientific and ethical reasons not to include them. The Children's Health Act of 2000 established a pediatric research initiative to increase pediatric biomedical research at the NIH, to enhance collaboration among institutes, to develop clinical trials in children to promote safer and more effective use of medications in children, and to bring the FDA into compliance with DHHS regulations that provide additional safeguards for children who are involved as subjects in research. The FDA issued these regulations in 2001 to comply with provisions of the Children's Health Act of 2000 and in recognition of increased participation of children in research as a result of the FDAMA and Best Pharmaceuticals in Children Act.[8]

### New Institutional Review Board Duties

The Interim Rule requires that institutional review boards (IRBs) review new and ongoing clinical investigations in which some or all of the subjects are children and approve only those that satisfy specific criteria depending on 3 risk categories (minimal risk, greater-than-minimal risk with prospect of direct benefit to the subject, and greater-than-minimal risk with no direct benefit to the subject that may yield generalizable knowledge). If the IRB determines that ongoing research falls within a fourth risk category (a clinical investigation that is not otherwise approvable but presents an opportunity to understand, prevent, or alleviate a serious problem in children), then the IRB should contact the FDA for additional guidance. If the IRB determines that research in progress does not fit any of the 4 risk categories, then the IRB has authority to suspend or terminate approval. Under the Interim Rule, the FDA has modified the language of subpart D of 45 CFR 46 for clinical investigations support by DHHS to apply to clinical investigations subject to FDA regulatory authority (Appendix 1).

### IRB Challenges

The FDA recognizes that IRBs may not always be able to know the level of risk to which a subject may be exposed in a particular investigation. Appropriate strategies for monitoring the level of risk may include establishing a data-monitoring committee to review ongoing data collection and recommend study changes or stoppage on the basis of safety information. Placebo-controlled trials are also recognized to create ambiguity in regard to the prospect of direct benefit to an individual subject. The FDA does support the use of placebo-controlled trials but has invited comment on the issue of conducting placebo-controlled trials in children.

Assent of the child is an important element of the additional safeguards. Assent is the child's affirmative agreement to participate in research, and mere failure to object to participation should not be considered as assent. The IRB must decide whether the child is capable of providing assent on the basis of their age, maturity, and psychological state. If the IRB decides that assent is required, then it must also determine how assent must be documented. The FDA also sets forth guidelines when an IRB may waive the assent requirement.

The FDA uses the term "parental permission" for their child to participate in a clinical investigation, because children cannot give consent themselves. For the first 2 risk levels, permission is needed from only 1 parent. For the last 2 risk levels, both parents must give their permission unless 1 parent is deceased, unknown, incompetent, or not reasonably available or when only 1 parent has legal responsibility.

### Clinical Study Design Issues

A number of important issues need to be taken into consideration. What constitutes disease in children? What are suitable controls? Should children with clinical disease be treated with placebo? What are the appropriate outcome measures? How early in the drug development process should clinical studies in children be initiated? How does one get informed consent from the parent/legal guardian and assent from the child? Which age groups need to be studied? When or is it appropriate to use healthy children as volunteers? Should all drugs be studied in a given drug class in which 1 agent has been shown to represent meaningful therapeutic benefit in children? The FDA, the NIH, and a number of pediatric organizations are currently discussing these and other issues. To assist the pharmaceutical industry in completing clinical studies in children, the FDA has begun to issue disease-specific guidance.

## CONCLUSIONS

The FDA Modernization Act, the Best Pharmaceutical in Children Act, and the Final Rule give pediatric practitioners real reason for optimism for increased numbers of clinical trials in children and the eventual increase in the number of drugs approved for use in children. The FDA has received 295 proposed pediatric study requests from the pharmaceutical industry and has issued 240 written requests for pediatric studies as of February 2002 (go to www.fda.gov/cder/pediatric/wrstats.htm). The Office of Pediatric Therapeutics has been created within the FDA. There are plans for the creation of a foundation at the NIH to obtain funds for research and studies on drugs in children. Finally, the Network of Pediatric Pharmacology Research Unit, established in 1994 by the National Institute of Child Health and Human Development, serves as a resource for the study of drug action and disposition in children and is in its ninth year; plans are under way for competitive funding for a third 5-year period. Currently, 13 units are actively working with the pharmaceutical industry to develop the necessary data to establish the safe and efficacious use of drugs in children. The evaluation of drugs in all populations for which there is potential requires cooperation among the drug industry, the NIH, the FDA, and these centers to accomplish this goal.

Although the Interim Rule allows IRBs broad latitude in determining what is appropriate with respect to these investigations, it also lacks precise standards, which can lead to uncertainty and precludes IRBs from defending themselves from enforcement by regulatory agencies. The most important protection is ample documentation to support a thorough review of a protocol and careful analysis applying the standards set forth in the Interim Rule. Because the Interim Rule is currently in effect, IRBs should review all current research studies involving children now, as well as revise all IRB policies and procedures to ensure compliance with this new rule.

## Appendix 1: FDA Risk Categories for Studies Involving Children

### Risk Category 1: Clinical Investigation That Do Not Involve Greater-Than-Minimal Risk (CFR 46.404, CFR 50.51)

Clinical investigations that do not involve greater-than-minimal risk may be approved by the IRB in which no greater-than-minimal risk is presented only when adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians. "Assent" is defined as the affirmative agreement to participate. Failure to object may not be construed as assent.

### Risk Category 2: Clinical Investigation Involving Greater-Than-Minimal Risk But Presenting the Prospect of Direct Benefit to the Individual Subjects (CFR 46.405, CFR 50.52)

Clinical investigations that involve greater-than-minimal risk but presenting the prospect of direct benefit to individual subjects may be approved only when the IRB finds and documents that 1) the risk is justified by the anticipated benefit to the subject, 2) the relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches, and 3) adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians.

### Risk Category 3: Clinical Investigation Involving Greater-Than-Minimal Risk and No Prospect of Direct Benefit to Individual Subjects But Likely to Yield Generalizable Knowledge About the Subjects' Disorder or Condition (CFR 46.406, CFR 50.53)

Clinical investigations that involve greater-than-minimal risk and no prospect of direct benefit to individual subjects but likely to yield generalizable knowledge about the subjects' disorder or condition may be approved if 1) the risk represents a minor increase over minimal risk; 2) the intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations; 3) the intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition that is of vital importance for the understanding or amelioration of the subjects' disorder or condition; and 4) adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians.

### Risk Category 4: Clinical Investigation That Is Not Otherwise Approvable But Presents an Opportunity to Understand, Prevent, or Alleviate a Serious Problem That Affects the Health or Welfare of Children

Clinical investigation that does not fall into 1 of the categories above may be approved by the IRB if 1) the IRB finds and documents that the clinical investigation presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem that affects the health or welfare of children; 2) the Commissioner of Food and Drugs, after consultation with a panel of experts in pertinent disciplines and after opportunity of public review and comment, determines either that the investigation in fact satisfies the conditions of 1 of the categories of clinical investigations set forth above or that the following conditions are met: a) the investigation presents a reasonable opportunity to

further the understanding, prevention, or alleviation of a serious problem that affects the health or welfare of children, b) the investigation will be conducted in accordance with sound ethical principles, and c) adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians. The Commissioner of the FDA must consult a panel of experts and allow an opportunity for public review before determining whether the clinical investigation is approvable.

## ACKNOWLEDGMENTS

Supported in part by a grant from PHS U01 HD-31326, by a Center of Excellence grant from the State of Tennessee, and a grant from the Children's Foundation Research Center.

## REFERENCES

1. Deaths due to elixir of sulfanilamide-Massengill: Report of the Secretary of Agriculture submitted to House Resolution 352 of November 18, 1937 and Senate Resolution of November 16, 1937. *JAMA*. 1937;109:1985–1988
2. Lenz W. A study of the German outbreak of phocomelia. *Lancet*. 1962; 2:1332
3. Taussig H. A study of the German outbreak of phocomelia. *JAMA*. 1962;198:1106–1114
4. Pediatric Use Supplement Rule. 21 CFR 201.57(f)(9)
5. Food and Drug Modernization Act, PL 105-115, 111 Statute 2296; 1997
6. Department of Health and Human Services, Food and Drug Administration. *Fed Reg*. 1998;63:66632–66672
7. Best Pharmaceuticals for Children Act, PL 107-109
8. Department of Health and Human Services, Food and Drug Administration. *Fed Reg*. 2001;66:20589–20600

# Changing Requirements for Evaluation of Pharmacologic Agents

Russell W. Chesney and Michael L. Christensen

*Pediatrics* 2004;113;1128

**Changing Requirements for Evaluation of Pharmacologic Agents**

Russell W. Chesney and Michael L. Christensen

*Pediatrics* 2004;113;1128