

Pediatric Labeling

PHOTOCOPY
PRESERVATION

PEDIATRIC LABELING FOR DRUGS

BACKGROUND

Children suffer from most of the same diseases as adults, and by necessity, are treated with many of the same drugs as adults. Manufacturers of drugs are not currently required to study and label their products for use in children, even where they can anticipate that the products will be prescribed for children. Although pediatric studies are conducted for some drug classes and by some manufacturers, the majority of drugs and biological products that pediatricians use have not been tested by their manufacturers in pediatric populations. As a result, product labeling frequently fails to provide directions for safe and effective use in children. The absence of pediatric labeling information poses a serious risk of inappropriate dosing and unexpected adverse effects in children. It also may result in failure to provide children with optimal treatment in cases where physicians are reluctant to prescribe potentially toxic drugs to children before the drugs have undergone pediatric testing.

Despite these risks, pediatricians often have no choice and the use of drugs that have not been adequately labeled is widespread. An FDA survey of drugs prescribed during 1994 identified the ten drugs prescribed most frequently to children without adequate labeling. Together, these ten drugs were prescribed to children more than 5,000,000 times in one year (see Tab 1). The pediatric physician community has therefore urged FDA to take steps to ensure that drug labels provide information on the safe and effective use of the drugs in children.

In recent years, FDA has undertaken several initiatives to encourage the voluntary addition of pediatric use information to drug labels. FDA implemented a "Pediatric Plan" designed to focus attention on, and encourage, voluntary development of pediatric data during drug development. As part of the Plan, FDA staff meets with manufacturers at several stages of drug development and encourages them to conduct pediatric studies of their drugs. FDA has also identified the top ten drugs used in children without adequate labeling instructions, and has written the manufacturers of these drugs requesting that they submit supplemental applications to add pediatric use information to their drug labels. In 1994, FDA issued a new rule that allowed pediatric use information to appear on labels on the basis of substantially less data than required before. The rule also required manufacturers to survey existing data to determine whether there was sufficient information to support pediatric use information on the drug's label.

These voluntary efforts to increase the amount of pediatric use information on labeling have not resulted in significant gains. The response to the 1994 rule has not been encouraging. Moreover, efforts to date have not increased the number of new drugs entering the marketplace with adequate pediatric labeling. As shown in the chart below, a comparison of new molecular entities (NME's) approved in 1991 through 1996 shows no improvement in the percentage approved with adequate pediatric labeling. While approximately 56% of the drugs approved in 1991 with potential use in children had some pediatric labeling, 37% of those approved in 1996 with potential use in children had pediatric labeling. The data also suggest that commitments by manufacturers to conduct pediatric studies after approval frequently do not result in pediatric labeling.

FDA estimates that pediatric studies are needed for approximately 10-15 products per year that would not otherwise have been studied in children. This figure includes an estimated 10-13 new drugs and biological products and two already marketed products.

Status of pediatric labeling/studies for NME's approved in 1991-1996	1991	1992	1993	1994	1995	1996	Total
Total number of NME's approved	30	25	25	22	28	53	183
Those with potential use in children (pediatric studies needed)	16	14	14	15	14	40	113
Label included some pediatric use information or pediatric studies complete at time of approval (as a percent of NME's needing pediatric studies)	9 (56%)	4 (29%)	5 ¹ (36%)	6 ¹ (40%)	5 (36%)	15 (37%)	44 (39%)
Post-approval pediatric studies promised or requested	7	10	10 ²	10 ^{2,3}	10 ²	17	64
Pediatric labeling added after approval	1	0	1	0	0	0	2

REGULATORY STRATEGY

The absence of adequate pediatric labeling continues to pose a significant public health issue. New approaches to the problem are needed. Financial incentives may be successful in generating pediatric labeling for some drugs, but there is no assurance that such incentives will work since they would leave it up to the manufacturer's discretion to conduct the studies. In addition, FDA's experience shows that a significant minority of manufacturers conduct needed pediatric testing without financial incentives. Providing exclusive marketing rights to companies that would have conducted pediatric studies without incentives may impose

¹ In one case, pediatric use information provided for one of two approved indications.

² In one case, pediatric data requested for second of two approved indications.

³ In one case, pediatric data requested for additional age groups.

unnecessary costs on prescription drug consumers, and on governmental and third party payers in the form of more expensive drugs.

The adequacy of pediatric labeling can be substantially improved by imposing a limited pediatric study requirement applicable only to the drugs and biological products needed most urgently by children. Pediatric studies would be required for certain innovative new drugs and never-before approved biological products if they (1) provide a meaningful therapeutic advance to children over existing treatments, or (2) are likely to be widely used in pediatric patients. The requirement could be deferred until after approval if, for example, it was appropriate to delay pediatric studies until sufficient data were collected in adults, or if imposition of the requirement would delay the availability of an important new therapy. Where deferral was permitted, a deadline for submission of the studies could be established. The study requirement could be waived altogether if among other things, the product was likely to be unsafe or ineffective in pediatric patients, pediatric studies were impossible or highly impractical, or reasonable efforts to develop a pediatric formulation had failed.

The pediatric study requirement would also, in compelling circumstances, apply to manufacturers of already marketed drugs and biological products to support pediatric use labeling for already approved indications. Appropriate circumstances would be (1) where the marketed product is widely used in children and the absence of pediatric labeling presents significant risks to children, and (2) where the product offers a meaningful therapeutic benefit over existing therapies, but additional dosing or safety information is needed to permit safe and effective use in children.

In the event that a manufacturer failed to carry out a required pediatric study, the drug would not be disapproved or withdrawn, because such an action would deprive adult patients of important therapies. Instead, an order from a Federal court requiring the manufacturer to conduct or fund the needed studies would be sought.