The Pediatric Pharmacology Research Unit (PPRU) Network and Its Role in Meeting Pediatric Labeling Needs

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ABBREVIATIONS. PPRU, Pediatric Pharmacology Research Units; NICHD, National Institute of Child Health and Human Development; PI, principal investigator; NDA, new drug application; FDA, US Food and Drug Administration.

This meeting marks a milestone in the quest for solutions to the phenomenon referred to by Harry Shirkey in this country 3 decades ago as the problem of the therapeutic orphan. I know that the European colleagues who have come to share their knowledge and experience have long concerned themselves with ways of overcoming this same phenomenon in their respective countries. The person who has been attacking this issue for the longest time in the United States is Sumner Yaffe, the progenitor of this meeting and the man responsible for the development of the Network of Pediatric Pharmacology Research Units (PPRU) from his position as director of the Center for Research on Mothers and Children of the National Institute of Child Health and Human Development (NICHD). I am indebted to Sumner for the opportunity to chair the PPRU Network Steering Committee and to Jeffrey L. Blumer, the principal investigator (PI) at the Cleveland PPRU site for planning today's watershed event.

There have been numerous reasons given by pharmaceutical manufacturers over the years for their failure to sponsor tests that would provide data sufficient to result in approved labeling for pediatric use when new drugs were introduced (for the purposes of this talk, I'll speak to the issues that we face in the United States only, but I recognize that similar issues exist in virtually every country represented at this conference). The advances made in several spheres of endeavor and the creation of the PPRU Network have primarily eliminated virtually all the arguments that have been used over the years to avoid the development of labeling for the use of most drugs for pediatric indications.

The most commonly used excuses for failure to provide the results of pediatric studies for labeling of new drugs, or for new pediatric indications for marketed drugs include: 1) the cost of the studies is too great compared with the size of the potential market among pediatric patients; 2) it is difficult to find enough patients to participate in studies that promise statistical significance; 3) a pediatric study might take too long and thereby prolong the approval process for an important new drug; 4) the ethical issues associated with studying children are too complex to permit such studies; 5) there are too few qualified pediatric pharmacology investigators and those who exist are difficult to contact and to meet on a reasonable timetable; and finally, 6) physicians who care for children will prescribe the drug once it is on the market, so why bother with pediatric studies.

The issue of the cost of conducting the additional studies necessary to label new agents for pediatric use is a difficult one, because the cost may vary widely depending on the nature of the drug and its physiochemical characteristics. Suffice to say, it is likely that the cost of the most difficult drug to formulate and study for pediatric use will almost certainly be very small compared with the cost of bringing the new entity to market for any indication. Furthermore, the potential cost to society of having potent, unlabeled new entities marketed for adults and then prescribed for use in children is also unknown, but perhaps even greater than the cost of conducting the necessary studies as a part of the new drug application (NDA) process.

The PPRU Network was established for several reasons, according to Dr Yaffe. One of the primary issues that PPRUs were designed to address was the availability of patients for clinical study. Indeed, by amalgamating seven institutions that have in aggregate >1 million ambulatory visits and >70,000 inpatient admissions each year, PPRU potentially provides access to a very large population of infants and children and subsumes the gamut of pediatric diagnoses. Furthermore, because they are each generally geographically unique, the issue of distributive justice, being mindful of the need to spread the benefits and the risks of clinical investigation across the whole breadth of the population, is likely to be addressed by such a consortium approach to pediatric clinical drug studies.

There is no need for the additional studies required for pediatric labeling to delay either the approval of the NDA or the general release of a drug. The studies necessary to label most drugs for pediatric use should be able to be completed at the same time as those done for general approval or, in a worst instance, should be able to be completed soon after
the approval of the NDA by prearrangement between the manufacturer and the regulatory agency. It is disingenuous and unseemly for representatives of industry to attempt to frighten legislators and regulators into ignoring the need to require pediatric studies by suggesting that important drugs will be delayed in the pipeline by the issuance of new pediatric regulations.

Numerous individuals and organizations have taken up the issue of the ethics of conducting studies of new drugs in minors over the past 35 years. The clear conclusion to be drawn from the treatises they produced is that there are ways to perform studies in children of all ages that meet the test of scientific rigor and also fall within general ethical precepts. Indeed, the American Academy of Pediatrics published its first set of such guidelines in 1977.2 These were modified and reissued in 1996.3 They form the backbone of the guidelines that are followed by ethical PIs and that are supervised by child-oriented institutional review boards. They are well established and are in use in virtually all major centers of pediatric research and education in North America. Although there must be constant vigilance to ensure that the rights of the minor research subject (or that minor’s family) are not taken advantage of in any way, there is no doubt that ethical restraint of pediatric drug studies has never been the factor impeding the conduct it was said to be and currently cannot be considered as a factor of any significance whatsoever.

The design of the PPRU Network has brought trained, experienced, and skilled pediatric pharmacologists together into a consortium arrangement that results in a whole that is greater than the sum of its parts. There are many other pediatric clinical pharmacologists in the United States, but the members of the PPRU act in concert to provide remarkable insights and strength to the development of protocols, the facilitation of patient recruitment and study completion, and the timely reporting of results.

Furthermore, each PPRU has the education and training of new investigators in this field an integral part of its mission. Thus, the lack of a large number of skilled investigators in this country can no longer be said to be a problem that militates against accomplishing studies of drugs in children, and the corps of trained pediatric clinical pharmacologists will be being expanded by virtue of the existence of the PPRU Network.

The PPRU Network is the legacy of the vision of Dr Yaffe, as I mentioned above. However, it is as well a product of the efforts of many, many persons over the years. Some of us in this room have been working toward the goal of achieving appropriate labeling for pediatric uses for almost as long as Sumner has. Allies in this effort were few and far between during those earlier years, but were easily found among consumer and parent groups during the mid-1980s. The US Congress began to take notice of the issue by the end of that decade.

The first glimmer of hope that an advance toward the goal of achieving pediatric labeling for new drugs that would likely be used in pediatric practice could occur before the beginning of the new millennium was sparked by the publication of the request for proposals to develop PPRU sites across the United States in 1992. The likelihood that real progress might be made was enhanced in December 1993 when the new Pediatric Rule was published by the US Food and Drug Administration (FDA). (It should be noted that the FDA had a special interest in enhancing the development of drugs and formulations for pediatric indications during the several years when David Kessler, a pediatrician, was its commissioner.) This initiative was of great importance because it was the first major attempt to deal directly with the inertia in both the FDA and the pharmaceutics manufacturing community. It was followed a month later by the funding of the first five PPRUs by the NICHD. There now are seven sites and a functioning Network that I have the privilege of chairing.

The leaders of NICHD have determined that they will fund the PPRUs for another 5-year period. The second RFP will likely be published before the end of 1997. How many sites will be selected and where they will be located remains in question at this time, but it is clear that the Network will continue to provide an important resource for the conduct of the clinical studies that will be required to achieve pediatric labeling for appropriate drugs in the future. Thus, it is especially timely that we are meeting at this point in the history of the PPRU Network, because it is both a landmark in the rapidly developing maturity of the network and also the time before its imminent transition to the second stage of the lifetime. It has been a pleasure to work with the outstanding PPRU site PIs who make up the Network Steering Committee, the FDA liaison persons, and the NICHD staff members who are integral to the work of the Network. We all look forward to closer interactions with our European colleagues now that we have been brought together for this special meeting to share our experiences and our concerns regarding the development of safe and effective pharmaceutics for infants and children regardless of their citizenship.

REFERENCES
Meeting Pediatric Labeling Needs

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