Therapeutic Orphans: European Perspective

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There are several factors to be considered when facing the problem of therapeutic orphans. First, there is the scientific one. We are all convinced that there is much need for more data concerning the use of drugs in children, infants, and neonates. Second, there is a regulatory factor involving political and technical institutions. Finally, we have to consider the economic interest of the pharmaceutics industry in investing money in research that would hardly generate sufficient return.

THE PROBLEM

There is no need to stress here that improved research in pediatric clinical pharmacology is required. Despite the fact that the number of clinical trials in children has increased, in many cases the use of drugs still depends on extrapolation of data from adults, and adequate scientific documentation for their use in children is lacking. We need additional studies to optimize dosages at various ages throughout childhood, and we still need studies on clinical efficacy and tolerability of drugs in children.

However, we must recognize that when the pharmaceutics industry has an economic interest in developing a drug for use in children, we generally have good clinical data and reasonably large studies. Just think of many studies on antibiotics or the many drugs used in the treatment of otitis media or pharyngitis.

But in many cases, there is simply no economic advantage for the pharmaceutics industry to conduct studies in children. These studies would be time-consuming, often necessarily multicentered, and costly. This is true for a number of drugs. We also must consider that negative results in children could reflect unfavorably on the use of the same drug in adults and limit the profit of the industry.

Performing such studies therefore would depend primarily on the economic support of nonprofit or governmental organizations. The example of the network of pediatric clinical pharmacology centers developed in the United States could find a European counterpart.

DIFFERENCES BETWEEN THE EUROPEAN AND THE US SITUATION CONCERNING PEDIATRIC PHARMACOLOGY

In the United States, pediatric clinical pharmacology seems a well established and recognized discipline. This is not the case in many European countries. Despite the fact that some European groups have been actively involved in the field in general, perhaps with the exception of France, most studies have been performed by general pediatricians or subspecialists with some interest in developmental or pediatric clinical pharmacology. If we wish to develop a network in Europe similar to that in the United States, we have to consider these different characteristics.

In the United States, there are federal agencies that can develop a common strategy, whereas in Europe this would depend on the European Union commissions. Although there are technical agencies to revise application dossiers and to grant European marketing authorizations, it is not the prerogative of these agencies to develop an orphan drug policy. This would be the object of a European commission with political privileges. We must admit that presently there is not a common view on the problem of orphan drugs. A commission has been established in Brussels to elaborate a European strategy but, thus far, there are no official documents. This commission has basically adopted the US policy developed since 1983 and in Japan since 1993, suggesting criteria for the definition of an orphan drug status and indicating the need for incentives for the pharmaceutics companies such as detaxation or obtaining exclusive market rights for a certain number of years during which part of the investment might be recovered.

Rare diseases, defined as diseases with a prevalence lower than 1 per 2000, have been identified as an action area. In contrast, medicinal products for life-threatening or seriously debilitating diseases, in particular diseases in children, should be eligible even when the prevalence is higher than 1 per 2000. The commission has thus far only advanced suggestions. These should be adopted by the European Parliament.

These European documents, however, have not yet addressed in more depth the question of drug studies in children. This is considered a particular aspect of the orphan drug problem, which cannot be tackled at present because the debate is far behind that in the United States.

Children as therapeutic orphans are not mentioned except in one document under the French presidency in 1992, which proposes a definition of...
orphan drugs, specific incentives for the pharmaceutics companies, improvement, and adapted marketing authorization application procedures. This document notes the particular case of drug studies in children recognizing that now marketing authorization does not require clinical trials in children, although the disease exists in children, leading to use by extrapolation (dosage and indication) that may cause potential problems regarding efficacy and toxicity.

It also is recognized that lack of pharmaceutical formulations for children and, in particular, for infants, and of unit of doses, notably in the case of drugs with a narrow therapeutic index, raises various kinds of problems of efficacy and safety.

As far as orphan drugs are concerned, the document stresses the need for a European bureau or a European Committee, as part of the European Union to deal with orphan drugs. It would be a joint structure of the European Agency for the Evaluation of Medicinal Products.

The function of the bureau would be:
• allocation of research funds;
• establishment of a European catalog of rare diseases;
• creation of an orphan drugs data bank;
• provision of information on orphan drugs to health care professionals and consumers; and
• creation of a register of research work in the area of orphan diseases and drugs.

The bureau also should make efforts to encourage public and private research in the development of orphan drugs. Such a bureau would work in coordination with national structures that may be set up to support the development of orphan drugs. It also is stated that this bureau should work in coordination with the United States and that the European Union should envisage a trans-Atlantic project with the American data bank where the Food and Drug Administration already has identified approximately 1000 rare diseases.

I assume that this bureau is also intended to consider the case of children as therapeutic orphans, but this is not clearly stated.

This seems to be the state of the art on therapeutic orphans in Europe. Thus, I believe that at the institutional level, the problem has not been considered adequately and that it will not have much consideration in the near future.

We are left with the existing rules in the single European countries. I tried to find out through the members of the European Society for Developmental Pharmacology whether in their countries there were specific programs. But the general answer was no, although in the United Kingdom there has been some preliminary approach between the British Pediatric Society and representatives of the pharmaceutics companies to establish rules for marketing drugs for children.

I conclude that at the institutional level, the European debate on therapeutic orphans is still in a very early stage, and I do not think that it will develop in a reasonably short time.

WHAT TO DO IN THE NEAR FUTURE?

Can we, as pediatric clinical pharmacologists, advance some proposal? One way would be to separate the problem of children as therapeutic orphans from the more general one of orphan drugs. The European Community should be convinced to fund and support political studies and collaborative projects between the United States and the European network for clinical pharmacology in children. Together, we should identify areas of interest, design protocols, and apply for grants.

The advantage of working from a European perspective is obvious. We should remember that Europe represents a population of 370 million, a variety of ethnic groups with specific problems concerning rare diseases, and diseases in children. I am certain that non-European Economic Community countries could be encouraged to join programs developed by such a commission. But for this, we need to be sponsored politically in the European Union.

Unlike Europe, the United States is a single country with a federal organization that can coordinate and sponsor multicenter studies. These studies may involve centers from outside the United States. For example, the National Institutes of Health has sponsored studies on the acellular pertussis vaccine that was performed in Sweden and Italy. This could be done in other cases for studies on drugs as well as on vaccines. National Institutes of Health studies could associate European centers. Many of these already have participated in studies, the results of which were used to present dossiers for marketing authorization in the United States. Thus, this is a feasible way.

A second proposal would be institutional. The National Institutes of Health could try to establish a formal cooperation with the European commission, asking to develop in Europe a network similar to that active in the United States. A possible third partner could be the European Society for Developmental Pharmacology, which therefore would be invested with an official responsibility.

The two ways are not mutually exclusive. Hence, I propose that in the near future, the US network could associate some European centers in its studies. Obviously this raises the question of funding. In the meanwhile, the National Institutes of Health on the one hand and the European Society on the other should look toward the possibility of establishing a European Commission for studies of drugs in children.
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