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Orphan Drugs: the Cost of Adoption (**)

Orphan products are drugs or devices or diagnostic agents potentially useful but unavailable because of lack of commercial interest.

This definition is comprehensive of a large variety of products like:

— Drugs for uncommon diseases;

— Drugs for diseases common in poor countries;

— Drugs of potentially widespread use, but not patentable or with a patent life near expiration.

In all these cases the main reason for the status of orphanage is an economic one. And at the deep basis of the orphan condition is the type of socioeconomic model followed in the scientifically and technically advanced countries for the discovery and the introduction of new drugs in therapeutic use. It is well known that drug research is comprehensive of all the scientific and technical activities involved in the discovery and development of new drugs. The basic researches performed in universities or other public or private organizations have certainly an important role in furnishing new concepts or models for the ideation and development of new drugs. But it is to be pointed out that the accomplishment of the various steps necessary for the long (8-12 years) and expensive (several million dollars) pathway from the identification of a new product active in laboratory tests to its introduction in therapy is the result of the coordination of the work of many scientists and of a series of selective decisions that only the pharmaceutical industry is in a condition to perform. Each industrial research laboratory concentrates its activity in certain areas of therapy, according to criteria which obviously differ from one laboratory to another, but generally selected on the basis of the following evaluations:

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Medical needs
Scientific capability
Competition
Probability of therapeutic success
Probability of economic success.

The last parameter has probably the major influence in the selection of the area of research to be pursued.

For this reason it is not surprising that, for example, the total world expenditure on research and development in the area of tropical diseases was in 1976 only 2% of the sum spent in cancer research. And out of a total of some 5000 million dollars spent by the industry in R and D in 1980 only one percent was spent on diseases which are relevant for the Third World. Despite the fact that some parasitic diseases, such as malaria, schistosomiasis, filariasis, each affect more than 200 million people with high rates of incapacitation and death, the research efforts made to find more effective drugs, adequate for the socioeconomic conditions of the countries where these diseases are widespread, are relatively small (only 2-5% of the research done in the area of antibacterial chemotherapy, where many effective drugs are already available). It is clear that this distribution of research efforts in the various fields of therapy is unfortunately determined by the probability of commercial success more than by the real medical needs of humanity.

Therefore we are facing conflicting aspects in drug research:

a) There is no doubt that the research activities for the introduction of new drugs in therapeutic use have found their optimization process in the frame of the pharmaceutical industry, as demonstrated by the important successes obtained in the last decades.

b) No other organization seems capable to fill the role of the pharmaceutical industry in the drug development process.

c) The pharmaceutical industry has a unique expertise, and duplication of this expertise, through government and private initiative, would only increase development costs.

d) In many cases, industry has made available for patients also drugs of limited commercial value (public service drugs).

e) In case of rare diseases, it should be pointed out that a large involvement of public funds could be criticized because also for rich countries the concept is generally valid that the available resources should provide as much health as possible to as many as possible. There is the painful dilemma between the protection of individuals or minorities and protection of large communities.

f) On the other hand the exclusive role of the pharmaceutical industry in the drug development process is not the ideal solution in some specific cases, and it is the main reason for the abandonment of certain research areas and drugs.

Confronting all these facts, it seems that the only possibility of adoption of orphan products resides in the industry, provided clear incentives and rules

be given in order to establish adoption guarantees for the adopting bodies and to make certain areas of drug development attractive for the industry from both the scientific and financial points of view.

Incentives and rules should take in consideration the adoption costs, which vary very largely according to the status of orphanage of the product.

A rough breakdown of the R + D costs for a new drug gives the following approximate percentages of cost:

a) search for new potential drugs (synthesis, natural products, pharmacological screening up to the indication of a product of potential interest): 30%;

b) development of this new product through animal data involves 30% of the cost of the entire project; efficacy/safety in man: 20%; galenic, analytical, process development and assembly of all the documents for an NDA: 18%;

c) for a product already in the market, the studies for a new clinical indication for a rare disease could be of the order of 1-2% of the entire project.

Therefore, if we suppose the cost of an entire project for a new drug to be of the order of 50 million dollars, the cost of adoption of an orphan project could be from 1 million dollars if the product is already in the market and requires only additional clinical studies for a rare illness, to 50 million dollars if there is the need to start from the beginning, e.g., from the search for new potential drugs. Therefore the adoption costs could be of any order of magnitude between these two extremes according to the status of advancement of the project.

I have said that the projects on orphan drugs should be made attractive for the industry. Therefore, if the commercial interest in the final product is low, the contribution of public labs, foundations, public and ptivate grants should be proportionally high. A system should be studied where non-industrial funds are practically exclusive in the early phases of the project, with increasing participation of industrial partners in the development phases. For example, the cooperation between industry and the National Institute of Neurological and Communicative Disorders and Stroke for the development of a new antiepileptic drug is based on these general concepts.

Incentives are needed during all the development phases, but especially after the introduction of an orphan drug in the market. In this regard, the Orphan Drug Act operating in the US provides four incentives for drug companies: three during the R + D phases and one after marketing:

— Tax credit of 50 percent for the expenses of the clinical trials performed prior to marketing approval;

— Protocol assistance by FDA;

— Grants and contracts;

— A 7-years *exclusive* marketing license for unpatentable drugs.

The last incentive is very important.

The system of exclusive marketing license non-dependent on patent rights should be studied in more details and introduced in the legal procedures in various countries.