An Operative Subclassification of Orphan Drugs

Despite the enormous progress of medical research, we still do not cure most diseases which cause pain, physical disability or death. Some of these diseases are incurable. For others a potential treatment has been discovered or could be developed according to current scientific knowledge, but the drug is not made available to patients because pharmaceutical manufacturers or public agencies are not interested in it. These drugs are called orphan drugs.

Generally, orphan drugs are not developed because of their limited commercial value. In other words, their sales are not expected to recover the costs of developing and making available such drugs to the patient. The balance between expected sales and costs is what gives a drug its commercial value.

In developed nations, the size of the market is probably the most critical factor for the sales. In fact, the FDA guidelines for obtaining designation of a drug as an orphan drug refer to "disease or condition which occurs so infrequently in the United States that there is no reasonable expectation that the cost of developing and making available a drug for such disease will be recovered from sales of such a drug" [1]. In developing nations, the standard of living of the population, which often cannot afford the cost of medical treatment, is a more critical factor. In fact, in developing nations there are orphan drugs with a potential market of millions of patients, some of which are currently available in developed nations.

The costs of developing a drug depend on various factors, but the most critical one is the starting point of the development of a drug. There are orphan drugs which have already been tested and proved active in man; therefore, the costs of making them available to treat patients are limited to their production and distribution. It is of note that many pharmaceutical manufacturers already

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produce and supply some such drugs in the public interest without profit; in the United States, these "service drugs" include drugs for epilepsy, leprosy, myasthenia gravis and porphyria. With reasonable public support, the problem of this class of orphan drugs might easily be solved in most countries. In developing nations, this approach has in the past proved successful in the campaigns against malaria, smallpox and other diseases.

The development of new drugs from scratch is an entirely different enterprise. The investment needed to develop a major new drug was over 50 million dollars in 1976 [2] and will probably exceed 150 million dollars by the year 2000 [3]. In this subclass of orphan drugs the threshold for profitability is therefore much higher than in the above-mentioned subclass. It is unrealistic to expect that pharmaceutical producers invest millions of dollars to develop new drugs of no commercial value in the public interest; they would soon become bankrupt. This task is more suitable for public institutions, although their involvement in drug development creates difficulties as well.

Developing a new drug is not only an extremely expensive task, but it also requires a complex technology, decisional power and managing experience, which are seldom found in public institutions. Therefore, the successful development of orphan drugs from scratch is conditioned by the joint efforts of public institutions and pharmaceutical producers, possibly on an international basis; moreover, because of the high costs involved, success depends largely on whether or not these efforts are concentrated on specific and well selected targets.

There is another group of orphan drugs which are neglected, primarily because their scientific basis is too innovative to be accepted by the academic community and the management of the pharmaceutical industry. The conservative attitude of both the academic and pharmaceutical communities concerning drugs is not surprising. Most academic investigators submit the research programs to external committees for funding, and it is much easier and less risky to deal with well established activities and techniques rather than with a potential breakthrough in medicine. As a consequence, conventional research programs are preferred to innovative ones. The problem is quite similar for pharmaceutical manufacturers. Whereas the marketing potential of drugs in line with current therapeutic trends may be measured with reasonable accuracy, the marketing potential of innovation is as uncertain as gambling. Since millions of dollars are at stake, conventional drugs are generally preferred to innovative ones. To discuss the problem in practical terms, here again the stage of development of drugs should be carefully considered.

In some cases the novelty consists of the new use of an already available drug in medical practice; recent examples are vitamin C, which at high doses has been suggested to have an anticancer activity [4], and acetylsalicylic acid, for which an antcataract activity has been postulated [5]. Checking the real value of a new use of already existing drugs is generally feasible at reasonable costs. Unfortunately, more time and money are wasted in dissertations on the theoretical value of these drugs, rather than in planning and
conducting appropriate clinical trials such as the one which has recently been performed with vitamin C in cancer [6].

Because of the extremely high costs mentioned above, the development of innovative drugs from scratch is a difficult, although not impossible, task. Many years ago, while working in psychopharmacology as a pupil of Daniel Bovet, I began elaborating the idea that depression has some links with drug abuse and that the study of drug abuse could provide an insight into depression and its treatment. In the following years, this approach led not only to the hypothesis that the reduced threshold for the perception of unpleasant experiences is a pathogenic factor of depression but also to the development of an antidepressant agent called trazodone [7, 8]. At that time, MAO-inhibitors and tricyclics were the only antidepressants available. Since they share the ability to increase the activity of catecholamines and indoleamines at the synaptic level, this was proposed to be the mechanism of their antidepressant activity. At the same time, the hypothesis was postulated that depression is a “failure of vital energy” produced by a deficiency of central aminerergic mechanisms [9, 10]. Trazodone does not fit into the aminergetic hypothesis of depression; on the contrary, it worsens some behavioural responses which are associated with a deficiency of aminergetic transmission at the central level, whereas it increases the threshold for the perception of unpleasant stimuli. Because of its innovative features, it took more than 10 years to develop trazodone, but it is now a successful antidepressant in several countries, including the United States. Based on my personal experience, innovation requires patience and perseverance and is more congenial to small research teams than to big pharmaceutical producers.

In conclusion, I have stressed that orphan drugs are not a homogenous group and that their different features have some implications at the operative level. According to their stage of development, a distinction should be made between drugs which are already available for medical use and those which are still a scientific potentiality, namely, a drug to be developed from scratch. The orphan drugs of the first type can be made available to patients at a relatively low cost. Since they include several life-saving drugs, it is reasonable to suggest that efforts be concentrated on them. Developing an orphan drug from nothing is extremely expensive, and it is erroneous to expect that pharmaceutical manufacturers take on the problem alone. A joint effort of pharmaceutical producers and public institutions could probably lead to the development of new orphan drugs, provided that energy is concentrated on specific and well selected targets. It has also been stressed that, whereas the limited commercial value is commonly considered the main reason why orphan drugs are neglected, innovation is also a limiting factor because of the conservative attitudes of both the academic and pharmaceutical communities. Here again, orphan drugs should be classified according to their stage of development. Checking the new use of an already existing drug may generally be accomplished at a relatively low cost and it is recommended that this type of research be actively pursued. Developing innovative drugs from scratch is more difficult but is seemingly a philosophy which is suited for small research teams.
REFERENCES


