COMMENTARY

What Is Wrong with Orphan Drug Policies?

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ABSTRACT

The effects of orphan drug policies raise serious concerns among payer organizations and lead to often-tragic disappointment for patients who are denied much anticipated drug reimbursements. We evaluate the effects of orphan drug policies on the basis of this concern for real accessibility to drugs. We highlight six causes of the emergence of effects. The first four are the direct result of incentives included in orphan drug policies. The fifth cause is the “off-label” use of orphan drugs. These emergent effects have several implications: 1) they raise doubts about the equity of access to drugs, 2) they highlight the limitations of the cohort paradigm in medicine, and 3) they force third-party payers to make drugs affordable even when the prices of drugs are believed to be disproportionate to the clinical effects obtained.

Keywords: health policy, hospital and public health systems, orphan drugs, outcomes, stakeholder strategies.

Introduction

The United States, Japan, Australia, and the European Union have all adopted policies promoting the development and commercialization of drugs that target so-called orphan diseases. The stated purpose of these policies was to meet the needs of patients with rare diseases. Fiscal and economic incentives were put in place to ensure the development of market niches whose profit potential would have been close to zero had changes to legislative and regulatory frameworks not been made [1–3]. The will to ensure a fair access to treatment of patients, whatever the prevalence of their disease [4], is the moral foundation of these policies.

The prevalence threshold defining a rare disease, in order for it to benefit from the advantages of orphan status, is established, in relative terms, at fewer than 5 persons per 10,000 inhabitants (Europe) or, in absolute terms, at fewer than 200,000 persons (United States) [4–6]. To these epidemiological criteria are added economic considerations. A drug receives orphan designation if it is used to treat a disease whose prevalence is so low that, in absence of incentives, commercializing the drug would unlikely generate sufficient revenues to absorb the costs related to its development and marketing [4,7,8].

As for the second point, many authors point out that some drugs that received the orphan status have nevertheless had a financial return that significantly outmatched the investments involved [2,3,9]. For some, these cases remain exceptional and are nothing but evidence for the effectiveness of policies that have been put in place [10]. For some others, these instances are more and more numerous [2], and they think that some revisions are necessary to give back these policies their original spirit [7].

Nearly 30 years after the introduction of the first law, the Orphan Drug Act in the United States, a critical assessment is in order. Have these policies met their objectives as regards availability and accessibility? In other words, do they really ensure a fair access to treatment in agreement with the common will of the different governments that are involved?

Taking into account concerns about availability, accessibility, and fairness in access to treatment at the same time, we discuss the real effect of the incentives planned in the policies on orphan drugs. To do this, we will describe the main effects brought about by these policies. In the context of our discussion, we adopt the following definitions: availability refers to the drug being approved by a national authority. As for accessibility, it is defined as “The degree to which individuals are inhibited or facilitated in their ability to gain entry to and to receive care and services from the health care system. Factors influencing this ability include geographic, architectural, transportational, and financial considerations, among others.” In the medical setting, fairness is defined with respect to the aim of providing citizens with equal access to health resources, which matches their actual health. Fairness requires a positive action by the state when the market does not provide a good match between investments and health needs. Finally, fairness requires that the barriers to access should be morally justifiable.

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Subsequently, we will try to identify the reasons for the emergence of these effects. Finally, as the national governments cover a major part of the expenditures in health care, we will highlight several implications of orphan drug policies of our public health systems.

We opted for a research design of the qualitative and inductive type. Our methodological approach was grounded theory. Our empirical material consisted of a combination of objective/subjective and qualitative/quantitative data from three main sources: 1) the remarks and comments of practitioners, 2) statistical data, and 3) factual and analytical elements from the scientific literature. Analytical work was conducted simultaneously with empirical work.

The Beneficial Impact of the Policies on Orphan Drugs

The beneficial effects induced by the policies on orphan drugs are beyond dispute, especially as regards the availability of new molecules. In the United States, 353 orphan drugs were allowed to be marketed by the Food and Drug Administration (FDA) from January 1983 to May 2010 [11]. In Europe, 65 drugs received the same authorization from January 2010 to July 2011 [12].

Moreover, many authors stress the contribution of these policies, especially the extension of and improvement in quality of life, the acquisition of new knowledge about other types of illnesses, the considerable boon to the industry, especially in biotechnology, and the accelerated processing of drug approval applications [1,2,5,8,9,10,13,14].

Nonetheless, the availability of such molecules is limited to a few therapeutic families, namely, those that offer a significant turnover. Moreover, though they are available, these molecules are not necessarily accessible because of their high price. However, these policies turned out to be real business opportunities for manufacturers, especially in favoring the emergence of “Blockbuster” of a new kind. We will develop each of these three points in the next few paragraphs.

Concentration in Commercially Lucrative Therapeutic Areas

Classification by therapeutic class of 353 orphan drugs, approved by the FDA between January 1983 and May 2010, indicates that five therapeutic classes account for 75% of the market for orphan drugs. In fact, 95 are specifically from the oncology/cancer therapeutic class. This is followed, in descending order, by metabolic disorders (54), hematology (41), infectious diseases (41), and neurological disorders (30). The remaining 25%, 92 of the 353 orphan drugs approved by the FDA, are distributed among the other 11 therapeutic classes, which include psychiatric, musculoskeletal, gastrointestinal, dermatologic, respiratory, ophthalmologic, hepatic/biliary, immunology, cardiovascular, and genitourinary disorders, and drugs for the treatment of intoxications/envenomations. The concentration is even more significant in Europe, where 42 (65%) of the 65 orphan drugs approved are specifically from two therapeutic classes, oncology/cancer (29) and metabolic disorders (13) [12].

Gavel [15] provides an explanation of this phenomenon by showing that drugs used to treat cancer are, by far, the most profitable. Seachrist [16] and Casali [17] argue in the same direction, indicating that this profitability can be explained, at least in part, by the frequent off-label use of these drugs.

Also, according to our data, 33 of the 353 orphan molecules that received FDA market authorization between 1983 and 2010 were not marketed or were withdrawn for commercial or safety reasons. Note that 12 of these had no therapeutic equivalents in the target indication. As for the remaining 21, alternatives existed (same pharmacological agents) but were not approved for other therapeutic indications: 13 were approved under the same trade name, and 8 were available as generics.

Medicines Available But Not Accessible Because of Their High Price

Orphan drugs are extremely expensive. Cerezyme, developed by Genzyme for the treatment of Gaucher disease, is the example most often cited. This treatment, which in the case of the United States, targets approximately 2000 patients, is one of the most expensive in the world. In fact, it costs between $100,000 and $400,000 per year depending on the age of the patient (child or adult) [18]. Another example, Aliglaside Beta, marketed by the US company Genzyme under the name Fabrazyme and indicated for the treatment of Fabry disease, costs about $300,000 per patient annually [10].

These few examples are far from representing isolated cases. The prices charged for these new orphan drugs frequently exceed the usual pharmaco economics scales and the thresholds of social acceptability. Such escalation consequently raises concerns and leads to major problems: concerns by payer organizations, and tragic disappointment for patients who are denied much anticipated drug reimbursements. In fact, although drugs have received market approval, they may likely not be reimbursed, where consequently patients may not have access to them unless they pay for them themselves.

A Highly Lucrative Opportunity for Manufacturers

In a report titled Opportunities in Orphan Drugs—Strategies for Developing Maximum Returns from Niche Indications published for Business Insights Ltd., Thornton [11] suggests that manufacturers have an incentive to abandon the traditional business model based on the mass sale of drugs intended for general care treatment and to turn to targeted drugs with high commercial potential. The author bases his advice, on the one hand, on the increasing difficulty of manufacturers to market mass drugs and future “blockbusters,” and, on the other hand, on the high profitability of orphan drugs.

Compilation of the whole population of the orphan molecules indicates that several molecules that have benefited from incentives provided in the US Orphan Drug Act and/or the European Union orphan drug policy have received substantial return of investment. In fact, 43 trademarks, each for the treatment of at least one orphan designation, generated global annual sales exceeding $1 billion in 2008. Of these, 18 products were intended solely for the treatment of a rare disease and 11 achieved global annual sales equal to or greater than $1 billion during the 7-year exclusivity period granted by the FDA (Table 1). Furthermore, compilation indicates that 33 trademarks, each corresponding to at least one orphan indication, achieved global annual sales of $100 million to $999 million in 2008. Of these, 19 were approved for orphan applications, 7 had global annual sales of $100 million to $199 million, 9 had global annual sales of $200 million to $299 million, 5 had global annual sales of $300 million to $399 million, 3 had global annual sales of $400 million to $499 million, 5 had global annual sales of $500 million to $599 million, and 3 had global annual sales of $600 million to $999 million in 2008 (Table 2).

Some Explanatory Factors

We identified six factors that explain the deviation of the programs that originally aimed to restore fairness for people stricken with rare diseases toward unique business opportunities for manufacturers. These explanatory factors are as follows:

- Fast-tracking the development and marketing of these new molecules
- Appr e ci able support for biotechnology companies
- Excessive stratification of therapeutic indications
Opportunity to give new profitability to obsolete molecules

Pricing based on willingness to pay from patients and/or third-party payers

Off-label practice

Fast-tracking

Orphan drug policies represent a fast track for manufacturers eager to replenish their pipeline of new drugs. Since Merck’s withdrawal of Vioxx in 2004 and Pfizer’s withdrawal of Bextra in 2005, this avenue has become increasingly attractive. Indeed, since that time, regulatory agencies have tightened their criteria for marketing approval, requiring, in particular, an increased number of clinical trials. This tightening has been translated into both a longer time to complete clinical trials and an increased number of refusals or volunteer withdrawals [18].

Obtaining an orphan designation allows companies to overcome these obstacles. In fact, the FDA has shown considerable leeway in applying approval criteria for drugs intended for the treatment of serious and debilitating diseases that result in reserved vital prognoses and for which no other adequate therapy exists. Most orphan drugs meet these criteria. In such cases, manufacturers may invoke an emergency and request a review of compliance with conditions. The drug in question may obtain market authorization before the normally required end of clinical trials subject to compliance with the conditions set out in the compliance notice. Among these conditions, new clinical trials are usually required. When an emergency cannot be cited, manufacturers may, in the United States, benefit from the expertise of the FDA by taking advantage of the orphan drug approval assistance program provided by the Orphan Drug Act. The consequent exchange of information results in faster processing of both clinical trial evaluations and approval notices [19].
An Appreciable Support for Biotechnology Companies

Orphan drug policies also represent an opportunity for biotechnology companies, especially those involved in the development of proteins, enzymes, and antibodies. The heavy dependence of most young biotechs on private research and development (R&D) investment funds ensures that the promise of 7-year exclusivity remains attractive.

A biotech that obtains orphan designation attracts interest from investors because of the clinical potential of the molecule being developed, the financial incentives accompanying the designation (grants, tax credits), and the potential economic spin-offs [11]. Furthermore, through its Office of Orphan Products Development, the FDA provides various financial, technical, and information support services to orphan designation developers for the design of clinical trials and for assistance in the preparation of approval applications.

In this regard, our data indicates that of the 353 orphan drugs approved by the FDA, 178 were from the biotechnology industry and 175 were from pharmaceutical companies. It should also be noted that several biotechnology companies, including Amgen, Genentech, and Genzyme, began to do business following the approval of an orphan drug.

Excessive Stratification

The approval of a drug that has previously obtained orphan designation for several therapeutic indications significantly increases its profitability. It is, according to Thornton [11], “the main strategy for expanding revenues for drugs with orphan designation.”

Two possibilities are thus presented to manufacturers wishing to increase the number of indications of a drug and, consequently, significantly increase the number of patients likely to be prescribed the drug. The first is to expand the number of orphan indications. This approach allows companies to obtain product exclusivity for the treatment of specific diseases. This is the case of Glaive (United States) and Glove (Europe and Australia), a drug developed by Novartis (imatinib mesylate), which has one orphan indication for chronic myeloid leukemia and another for the treatment of gastrointestinal stoma tumors, two diseases considered rare.

Manufacturers may get approval for the same molecule for different therapeutic indications, whether orphan or routine. We cite the example of Epogen (epoetin alfa), the first drug marketed by Biotech Amgen in 1989. This medication is used to treat anemia during the terminal phase of renal failure. Despite a prevalence of fewer than 78,000 patients, Epogen generated sales

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Table 2 – Drugs obtaining at least one orphan designation and having sales between $100 million and $999 million in 2008.

<table>
<thead>
<tr>
<th>Trade name</th>
<th>Generic name</th>
<th>Year of orphan designation</th>
<th>Year of market approval</th>
<th>Number of therapeutic designations</th>
<th>Sales (million US $)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Replagal</td>
<td>Alpha-galactosidase A</td>
<td>1998</td>
<td>2006</td>
<td>1</td>
<td>176</td>
</tr>
<tr>
<td>Myozyme</td>
<td>Alpha-glucosidase</td>
<td>1997</td>
<td>2006</td>
<td>1</td>
<td>296</td>
</tr>
<tr>
<td>Activase/Cathflo</td>
<td>Alteplase</td>
<td>2003</td>
<td>2006</td>
<td>1</td>
<td>286</td>
</tr>
<tr>
<td>AmBisome</td>
<td>Amphotericin B</td>
<td>1996</td>
<td>1997</td>
<td>3</td>
<td>290</td>
</tr>
<tr>
<td>Strattera</td>
<td>Atomoxetine</td>
<td>2003</td>
<td>2004</td>
<td>2</td>
<td>207</td>
</tr>
<tr>
<td>Vidaiz</td>
<td>Azacitidine</td>
<td>2001</td>
<td>2004</td>
<td>3</td>
<td>199</td>
</tr>
<tr>
<td>Dysport</td>
<td>Botulinum toxin A</td>
<td>1989</td>
<td>2002</td>
<td>1</td>
<td>230</td>
</tr>
<tr>
<td>Subutex/</td>
<td>Buprenorphine</td>
<td>1994</td>
<td>2002</td>
<td>1</td>
<td>230</td>
</tr>
<tr>
<td>Suboxone</td>
<td>Ceramide</td>
<td>1988</td>
<td>2003</td>
<td>1</td>
<td>500</td>
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<tr>
<td>Fabrazyme</td>
<td>Ceramide trihexosidase</td>
<td>1988</td>
<td>2003</td>
<td>2</td>
<td>749</td>
</tr>
<tr>
<td>Erbitux</td>
<td>Cetuximab</td>
<td>2000</td>
<td>2006</td>
<td>2</td>
<td>749</td>
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<tr>
<td>Sensipar</td>
<td>Cinacalcet</td>
<td>2003</td>
<td>2004</td>
<td>1</td>
<td>597</td>
</tr>
<tr>
<td>Exjade</td>
<td>Deferasirox</td>
<td>2002</td>
<td>2005</td>
<td>1</td>
<td>531</td>
</tr>
<tr>
<td>Sprycel</td>
<td>Desatinib</td>
<td>2005</td>
<td>2006</td>
<td>2</td>
<td>310</td>
</tr>
<tr>
<td>Pulmozyne</td>
<td>Dornase alfa</td>
<td>1991</td>
<td>1993</td>
<td>1</td>
<td>305</td>
</tr>
<tr>
<td>Marinol</td>
<td>Dronabinol</td>
<td>1991</td>
<td>1992</td>
<td>1</td>
<td>190</td>
</tr>
<tr>
<td>Aromasin</td>
<td>Exemestane</td>
<td>1991</td>
<td>1999</td>
<td>1</td>
<td>465</td>
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<tr>
<td>Fludara</td>
<td>Fludarabine phosphate</td>
<td>1989</td>
<td>1991</td>
<td>2</td>
<td>140</td>
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<tr>
<td>Elaprase</td>
<td>Idursulfase</td>
<td>2001</td>
<td>2006</td>
<td>1</td>
<td>305</td>
</tr>
<tr>
<td>Intron A</td>
<td>Interferon alfa-2b</td>
<td>1987</td>
<td>1988</td>
<td>10</td>
<td>234</td>
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<tr>
<td>Somatuline</td>
<td>Lanreotide</td>
<td>2000</td>
<td>2007</td>
<td>1</td>
<td>170</td>
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<tr>
<td>Aldurayme</td>
<td>Lariondase</td>
<td>1997</td>
<td>2003</td>
<td>1</td>
<td>151</td>
</tr>
<tr>
<td>Liaida</td>
<td>Mesalamine</td>
<td>2008</td>
<td>2008</td>
<td>1</td>
<td>140</td>
</tr>
<tr>
<td>Peginterferon alfa-2b</td>
<td>Peginterferon alfa-2b</td>
<td>2008</td>
<td>2008</td>
<td>1</td>
<td>914</td>
</tr>
<tr>
<td>Rebetol</td>
<td>Ribavirin</td>
<td>2003</td>
<td>2003</td>
<td>1</td>
<td>260</td>
</tr>
<tr>
<td>Actonel</td>
<td>Risedronate</td>
<td>2006</td>
<td>2006</td>
<td>1</td>
<td>462</td>
</tr>
<tr>
<td>Humatrope</td>
<td>Somatropin</td>
<td>1986</td>
<td>1987</td>
<td>3</td>
<td>441</td>
</tr>
<tr>
<td>Genotropin</td>
<td>Somatropin</td>
<td>1994</td>
<td>1997</td>
<td>3</td>
<td>898</td>
</tr>
<tr>
<td>Nutropin</td>
<td>Somatropin</td>
<td>1987</td>
<td>1985</td>
<td>5</td>
<td>375</td>
</tr>
<tr>
<td>Nexavar</td>
<td>Sorafenib</td>
<td>2004</td>
<td>2005</td>
<td>3</td>
<td>647</td>
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<tr>
<td>Thalomid</td>
<td>Thalidomide</td>
<td>1995</td>
<td>1998</td>
<td>4</td>
<td>505</td>
</tr>
<tr>
<td>Tobi</td>
<td>Tobramycin</td>
<td>1994</td>
<td>1997</td>
<td>2</td>
<td>295</td>
</tr>
<tr>
<td>Remodulin</td>
<td>Treprostinil</td>
<td>1997</td>
<td>2002</td>
<td>1</td>
<td>270</td>
</tr>
<tr>
<td>Decapeptyl</td>
<td>Triptorelin pamoate</td>
<td>1990</td>
<td>1990</td>
<td>1</td>
<td>347</td>
</tr>
</tbody>
</table>
of $5 billion in 2001. This commercial success is explained by Amgen’s having the drug approved as well for high-prevalence therapeutic indications, including the recovery of red blood cells in patients suffering from bone marrow suppression caused by anti-HIV drugs or chemotherapy, and reducing the need for transfusions in surgery patients [10].

Compilation shows that of the 43 orphan drugs approved by the FDA whose global annual sales reached more than $1 billion, 18 had only one orphan designation, 15 had two, and 10 had three and more (Table 1), for 97 orphan indications. The picture is the same for 33 products achieving global annual sales of $100 million to 999 million in 2008 and used as the active pharmaceutical agent for 64 orphan indications (Table 1).

For example, the molecule interferon is marketed under nine brand names and has received 33 orphan designations. Three of these brands—Betaseron (Chiron), Avonex (Biogen), and Rebif (Pfizer)—received market approval from the FDA for six therapeutic indications, and all became blockbusters. The case is not unique (Table 1).

It is clear from our analysis that actual legislations trigger a three-step strategy: 1) apply for orphan designation, obtain substantial economic benefits during the development, approval, and marketing phases, and demand a high price because of the low prevalence of the initial target population; 2) after approval, convince doctors to use the drug in their practice; and 3) expand sales by obtaining new therapeutic indications, orphan or otherwise, while maintaining the initial price.

Opportunity to Give New Profitability to Obsolete Molecules

Manufacturers who recycle old drugs can benefit from the economic incentives provided for in orphan drug policies, in particular, 7-year commercial exclusivity. Note, in this regard, that Vioxx (rofecoxib) was granted a second life as an orphan drug for much more restricted indications. From 1983 to 2010, 26 active ingredients have been granted orphan designation. Fourteen of the 26 active ingredients in recycled obsolete orphan drugs have received market approval. While the benefits for patients are undeniable, the prices charged for recycled molecules are nevertheless surprisingly high in some cases. As an example, arsenic trioxide, an old inexpensive molecule used for treating cough, leprosy, and even syphilis, was shown to be effective in the second-line treatment of acute promyelocytic leukemia in the 1990s. The total cost of treatment is around $50,000. The same scenario is true for N-carbamylglutamate, a pharmaceutical agent used to compensate for a deficit in N-acetylglutamate synthase, which, since it was approved as an orphan drug, saw its price increase from $15 per gram to $367.30, or $5,611 to $132,774 per patient per year for life [20].

Pricing Based on Willingness to Pay from Patients and/or Third-Party Payers

To justify these high prices, manufacturers equally cite R&D investments, the cost of acquiring and processing the active ingredient, marketing costs, and weak demand [14,21,22]. The cost of developing Cerezyme, however, which offers the same properties as Ceredase using a recombinant that is much less expensive to produce, is valued at $30 million [1]. According to McCabe et al. [18], production and marketing costs are insignificant for this drug. Ceredase (alglucerase) was discovered and developed by scientists at the National Institutes of Health in the 1970s and was approved by the FDA following clinical trials conducted and funded by the latter [3].

In general, R&D costs for orphan drugs are 25% of the costs of standard drugs [11]. In addition, manufacturers can quickly recover their investment by obtaining a conditional approval for the orphan molecule [11]. The costs associated with clinical trials are also low due to the small number of patients involved. On the basis of information collected from the ClinicalTrials.gov database, Thornton [11] established at 124 the average number of patients recruited for phase III clinical trials of orphan drugs. Furthermore, Thornton states that some phase III trials are conducted with samples as small as 15 patients, while others are the result of combining a trial from a previous phase (e.g., combined phase II/III clinical trials) [11]. Costs associated with the sale of orphan drugs are also insignificant. Patients with rare diseases are, for the most part, referred to and followed by teams of specialists, doctors, and pharmacists in tertiary hospitals. Specialists are exposed to the marketing of orphan drugs on a regular basis through their clinical activities, teaching activities, and research activities, and through their participation in international meetings.

Finally, it is worthwhile to note the contribution of patient organizations in the funding, research, and development of orphan molecules. For example, the American Cystic Fibrosis Foundation has invested more than $300 million in the development of nearly all treatments approved in the United States for this rare disease. The foundation is actively involved in the subsidizing of 37 new molecules currently under development [11].

On the basis of these data, we conclude that pricing is based on what patients and/or third-party payers are willing to pay. Because orphan molecules are targeted at a captive market and have no therapeutic equivalents, third-party payer organizations have little room for maneuver and often resign themselves to accepting the manufacturer’s suggested price, all the more so because they are subjected both to the influence of the media and to pressure from patient associations [12].

Off-Label Practice

The use of drugs for therapeutic indications other than those specified in their monographs significantly increases the profitability of orphan molecules. It is estimated that nearly 20% of the prescriptions in the United States are off-label. This percentage increases to 50% for oncology and is even higher for pediatrics, especially pediatric oncology [23–25]. As noted previously, 95 of the 353 (27%) orphan drugs approved by the FDA between January 1983 and May 2010 are specifically from the oncology/cancer therapeutic class.

Cohen and Wilson [26] note that 10 of the 14 orphan drugs in their study of monoclonal antibodies include one or several additional off-label indications. The authors cite the example of infliximab, an orphan drug originally approved for the treatment of Crohn’s disease (1995) and later, in 2003, for treating patients with rheumatoid and psoriatic arthritis, ankylosing spondylitis, and ulcerative colitis. Likewise, infliximab is prescribed for various off-label therapeutic indications, some of which are in the process of approval, in particular for the treatment of juvenile idiopathic arthritis and uveitis.

Implications for Public Health Systems

We will now highlight several implications of orphan drug policies, some of which call into question the management, even the very foundations, of our public health systems. Our discussion will focus on three issues:

- Access to orphan drugs
- A prelude to individualized medicine
- An impossible “formula”

Access to Orphan Drugs

Until now, the refusal of public health programs to reimburse for drugs otherwise known to be effective has been, almost entirely, a moot issue. Today, this is no longer the case.
Because, in the health systems of most countries, fairness of access is regarded as a fundamental principle, access to orphan drugs is seen as a right by patients and families and, in return, an obligation for managers of public health programs. With technological and scientific advances, however, the number of treatments and treatable patients is rising. This, coupled with the high cost of treatment, has an increasingly significant impact on national budgets devoted to the reimbursement of drugs, so much so that one fears that it may jeopardize the viability of these programs. "The French and Dutch analyses predict that the total cost of ODs per country will reach 6-8% of total budgets by 2010" [12].

A Prelude to Individualized Medicine

By responding positively to the various requests made by patients affected by rare diseases, third-party payers are obliged to cover the astronomical costs of individualized medicine developed and evaluated in a system based on cohort medicine.

The selection criteria for choosing a molecule in cohort medicine are need, prevalence, and cost/benefit ratio. In this sense, public health programs choose among the available drugs that best meet the needs of target populations on the basis of pharmacoeconomic efficacy and value. In the case of rare diseases, cohorts recruited for research sometimes represent all the eligible individuals of a given target population. The small number of patients, and their concentration in tertiary facilities where research normally takes place, explains why target populations and research cohorts tend to be the same. In this context, patients responding well to treatment are known. It then becomes particularly odious to refuse reimbursement to these patients on the basis of a problem of efficacy within the cohort. In such situations, the criteria used in cohort medicine for selecting molecules are difficult to apply.

In other words, supply is justified by imposing accessibility criteria, whereas equitable access, often perceived as a right to unlimited access, would otherwise seem compromised. Moreover, governments risk giving the impression that they are insensitive to the suffering of citizens.

An Impossible "Formula"

Indeed, agencies that manage drug formularies are not obliged to include, in the formularies, all drugs approved by the national authority. The drawing up of the list of the Drug Formulary implies that choices must be made.

Three main factors guide these choices: medical necessity, efficacy, and cost. The paradigm governing these choices is evidence-based medicine. In general, this paradigm is valid for approval, inclusion, and prescription. However, approving agencies have special programs that allow “promising” products to be approved according to criteria that play in the favor of orphan drugs. Such programs respond positively to requests from patient groups seeking faster access to these products, even if it means assuming risk at an individual level. Products approved through these programs, however, risk being denied reimbursement because of weak evidence. The decision not to include a drug, when therapeutic alternatives exist, normally does not create many waves. This is not the case for serious diseases for which there is no specific treatment. The willingness to pay is high because of the seriousness of the disease, the absence of alternatives, and the possibility of identifying the individuals and families affected by the decision. The very possibility of improving the condition of patients seems, on the surface, to be justification enough.

The problem is even more glaring when it involves patients who after participating in a clinical trial continue treatment as part of a compassionate program. An approval following a refusal of reimbursement may mean the end of the compassionate program, because the company can claim to have fulfilled its obligation under the Helsinki Declaration to supply the drug for subjects who have responded positively to experimental treatment.

Such delays place intense pressure on tertiary centers that use these expensive drugs and may consider themselves morally obligated to ensure the continuity of treatment from their own budgets.

Conclusions

Throughout this article, we have highlighted the shortcomings of orphan drug policies in view of the original concerns of the legislator, namely, the availability and accessibility of therapies for the treatment of rare diseases as well as fairness in access to treatment. Our goal here was not to question the merits of such policies, but rather to seek to understand how programs that are presented, at first glance, as philanthropic or humanitarian programs have, in fact, changed into business opportunities.

Measures that aim to speed up commercialization allow manufacturers eager to replenish their pipeline of new drugs to escape new rules aimed at tightening approval criteria.

Some incentives, such as those based on the protection of intellectual property, promote the concentration of marketing activities in a few profitable therapeutic areas at the expense of others that are equally, if not more, important. Orphan drug policies have the paradoxical effect of creating new orphan patients!

These incentives also promote the creation of new drugs at prices that are so high that the actual accessibility of these drugs for patients is very often an illusion. Accessibility is determined by one’s economic status or one’s coverage by private or public health insurance. Citizens may perceive this inequality in access to these drugs as inequality among sickness areas. This inequality is perceived as violating fairness.

Finally, the combined effect of high prices, excessive stratification of therapeutic indications, off-label use of orphan drugs, and market exclusivity for 7 years provides manufacturers with yet another opportunity in their strategic arsenal for marketing extremely profitable molecules, indeed for developing new blockbuster.

In short, by eliminating manufacturers from the competitive arena, notably by granting them a 7-year period of commercial monopoly, do we not encourage them to pursue a policy of excessive pricing? Moreover, is it reasonable to grant 7-year market exclusivity for a product whose R&D costs are probably significantly lower in comparison with those required by a new molecule?

The observed effects are incompatible with the stated goals of orphan drug policies. These effects contrast with the image widely conveyed in the literature depicting orphan drugs as having little financial attractiveness [27].

That companies favor the most profitable niches seems inevitable. In fact, should we be surprised? On the other hand, in a perspective in which the priorities of orphan drug policies were determined by the number of patients affected, and adjusted according to the seriousness of the disease, would the targets favored by manufacturers be the same?

Moreover, in a perspective in which a society has a limited amount of resources and, therefore, must decide how to distribute these resources among its members, access to orphan drugs at a high price confronts managers of health systems with fundamental ethical questions insofar as our collective identity is defined by principles, which are here being undermined.

In conclusion, we believe that the development of a more integrative knowledge is desirable, even necessary, to better
understand these distortions and to restore to orphan drug policies the legitimacy of their primary objectives.

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