VALUE IN HEALTH 15 (2012) 1185–1191

Available online at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: www.elsevier.com/locate/jval

COMMENTARY

What Is Wrong with Orphan Drug Policies?

André Côté, PhD[1,*], *Bernard Keating, PhD*[2]

[1]*Faculté des sciences de l'administration, Université Laval, Québec, QC, Canada;* [2]*Faculté de théologie et de sciences religieuses, Université Laval, Québec, QC, Canada*

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 two unforeseen effects of orphan drug policies: 1) they provide unique business opportunities for manufacturers and 2) drugs approved through these policies are often inaccessible because of their high price. We identify six causes of this 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 c) they force third-party payers to make drugs accessible 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 heath needs. Finally, fairness requires that the barriers to access should be morally justifiable.

Conflict of interest: The authors declare that they have no competing interests.

* *Address correspondence to:* André Côté, Faculté des sciences de l'administration, Université Laval, Québec City, QC, Canada GIK 7P4. E-mail: Andre.cote@mng.ulaval.ca.

1098-3015 – see front matter Copyright © 2012, International Society for Pharmacoeconomics and Outcomes Research (ISPOR). Published by Elsevier Inc.

http://dx.doi.org/10.1016/j.jval.2012.09.004

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 [1,6,9,10,13,14].

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, Agalsidase 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 pharmacoeconomics 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
- Appreciable support for biotechnology companies
- Excessive stratification of therapeutic indications