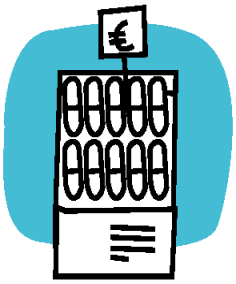
Unit 3: Are medicines an economic good like any other ?



7. Orphan drugs: legislation, controversy and prospects

I am Philippe Gorry a physician and researcher in innovation economics at the economic research center GREThA at the University of Bordeaux. Today, I will talk to you about orphan drugs. What is an orphan drug? What is an orphan drug? Orphan drugs are drugs used in the treatment of rare diseases and which have a particular status which includes financial incentives to encourage research and development in the pharmaceutical industry. As health or innovation economists we can consider how effective such legislation is on public health. Let's begin with a few definitions and some historical context before analyzing the current situation. The notion of a rare or orphan disease Rare diseases can refer to diseases with a number of different causes but their common denominator is their low prevalence. No treatment is available for most rare diseases. They are characterized by high mortality rates and often also by chronic incapacity and therefore significantly impact the quality of life of patients and their families. This is the case for more than 5,000 diseases which are considered orphan diseases due to the lack of available treatment. There has been limited development of drugs for these diseases due to a lack of understanding of their physiological mechanisms, the problems with clinical trials because of the low number of patients and the discouraging investment costs for research and development as the molecules have limited commercial potential. We use the term orphan drug to refer to drugs that treat these rare diseases. After the thalidomide scandal in the 1960s and 1970s regulations for drug commercialization in the United States became stricter. The pharmaceutical industry then began to concentrate on an economic model involving blockbuster drugs. Because of this, drugs developed for small numbers of patients which were not very profitable, disappeared from the market. In light of this an association of patients with rare diseases, called NORD the National Organization for Rare Disorders fought to get appropriate legislation adopted in the United States to encourage the development of these drugs. This legislation was enacted in the United States in 1983 followed by the European Union in 2000. The creation of this orphan status led to significant incentives for pharmaceutical companies to develop such drugs. The Orphan Drug Act in the US defines a rare disease as affecting less than 200,000 people. The European Medicines Agency (EMA) chooses to define a rare disease as one having low prevalence and affecting less than 1 person in 2,000, it must be serious and the drug must have significant benefits for patients. The status of orphan drug is separate from the MA or marketing authorization. Incentives for this status can be both regulatory and financial. On the regulatory side, companies can get market exclusivity independent from the monopoly granted by a patent. This exclusivity lasts for seven years in the United States and for ten years in Europe. On the financial side, there are research grants in the US awarded by the NIH, or National Institute of Health through the SBIR program, or Small Business Innovation Research. In Europe, EU research programs can also award grants. There can also be reduced regulatory fees for the marketing authorization or, in the US, access to a tax credit which will reimburse half of the cost of clinical trials. Health authorities can also help pharmaceutical companies to put together their MA applications. This is a regulatory process with two stages. At any point during the development of the drug sponsors, companies, universities, associations or natural persons can apply for the orphan status, but the benefits of this status will be applied only from the date of the MA.

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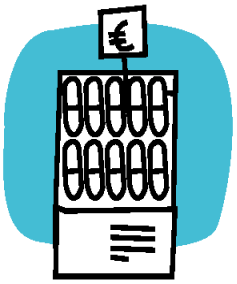

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A drug can have multiple orphan statuses one for each therapeutic indication and an orphan disease can be targeted by the development of several orphan drugs. Let's not forget that the market exclusivity awarded by this status differs from the monopoly of a patent. Depending on the development timeframe for the drug from seven to twelve years or more and the application date of the patent which protects the orphan drug, the market exclusivity granted could end up extending the company's monopoly by one or several years which would maximize the return on investment of the R&D. What are orphan drugs like today following US and EU legislation? After 35 years of US legislation on orphan drugs as well as 15 years of European legislation the FDA and the EMA have granted orphan status more than 4,000 times in the US and almost 2,000 in Europe. As seen on this graph the number of orphan designations starts out modest with about 50 applications per year shown here in blue until the turn of the millennium when there was a strong increase in applications in Europe shown in orange at the same time as an increase in applications in the US. However, only a small minority of these orphan drug applications actually resulted in an MA: over 600 in the US and about a hundred in Europe i.e. about 5-15% of applications. This legislation led to the development of innovative biotechnological products which can help patients who have various rare diseases. Adagen was the first enzyme replacement therapy commercialized in 1984 to treat severe combined immunodeficiency disease associated with a deficiency of adenosine deaminase or ADA deficiency. Today, the biotechnology company Genzyme part of the the Sanofi group has commercialized orphan drugs to treat genetic metabolic disorders such as Fabry, Gaucher or Pompe disease. This legislation has allowed pharmaceutical companies to grow and conduct non-stop research over the past years. The business model in this sector therefore moved from blockbuster to nichebuster as a source of profit. We can see several consequences to this. Half of all orphan drugs on the market are antineoplastic drugs. As a general rule, drugs with an orphan status are used with very few diseases compared to how many orphan diseases there are. Seven out of the ten most-sold orphan and anti-cancer drugs in the US are true blockbusters as they bring in over a billion dollars per year. Molecules such as Gleevec, which is commercialized and protected by several orphan statuses result from a strategy known as salami slicing to cover several therapeutic indications and therefore a larger population with a greater prevalence than rare diseases. In some cases a drug soon to become generic can have its monopoly extended by acquiring orphan status for a new indication. Such was the case of Sildenafil commercialized to treat erectile dysfunction before being used to treat pulmonary arterial hypertension in newborns. Finally, treatment costs associated with orphan drugs range from a thousand to hundreds of thousands of euros annually per patient. The increased availability of these drugs along with their very high cost and their use to treat chronic conditions opens debates about the sustainability of our public health services. Is legislation an effective way to lead to new drug development? Beyond the number of orphan statuses granted we can question how efficient such legislation is for the development of new drugs. The effects might be indirect perhaps linked with the biotechnological revolution, with human genome sequencing or with policies for the transfer of technology between universities and pharmaceutical companies, etc. It remains to be seen whether market exclusivity or tax credits are the best incentives for pharmaceutical companies.

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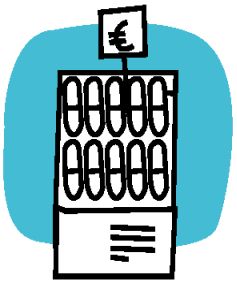

Even orphan drugs cannot avoid financial evaluations but typical methods would be inappropriate for rare diseases. Other than the numerous reports from consulting companies there is unfortunately little serious academic work on the issue which has consequences on public decision making. At the end of November 2017, US Congress decided to cut orphan drug tax credits to the dismay of patient associations.

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