# Patient access to innovation: Biopharmaceuticals, 4th hurdles and socioeconomic issues

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**Abstract** Biopharmaceuticals and innovative therapeutic solutions offer treatments that are increasingly tailored to patient needs. Although biotechnology has produced health benefits, biopharmaceutical products require resources that governments had not planned or budgeted for in the appropriate time frame. As a result, economics has entered the healthcare arena without taking a number of important societal concerns into account. More specifically, several governments have introduced procedures to evaluate the cost-effectiveness of newly approved medicines. Unfortunately, patient access is not an equation of public budget figures, but an equation of government priorities.

Therefore, this paper describes the limits of traditional pharmacoeconomic evaluations particularly when applied to innovative biopharmaceuticals and offers solutions to the questions they pose.

**Keywords:** innovation, orphan drugs, rare diseases, patient access

## Introduction

This paper describes the link between biotechnology and innovation and the evolution of this relationship. Today, thanks to genomics, medicines are increasingly tailored to the genetic makeup of individual patients.

The important avenues opened by these technologies lead healthcare research to the discovery of innovative solutions for diseases that were previously untreated. An example of this is the large contribution that biotechnology has brought to the area of rare diseases. The increasing availability of innovative therapies asks the question as to their affordability. Therefore, governments are confronted with a fundamental dilemma, namely: how to ensure patient access to innovative therapies and control limited resources available in their healthcare budgets.

In Europe, where healthcare systems are essentially managed by public health authorities, the above-mentioned dilemma leads to contradictory behaviour in terms of requiring high standards of healthcare services while at the same time reducing

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funding. This is where pharmacoeconomics enters into the equation. Although it is understandable that governments need to measure the impact of a new therapy on national budgets and plan future investment in healthcare, this impact cannot be assessed in terms of traditional cost-effectiveness criteria.

When innovation meets the social and policy aspects of the right to receive treatment as in the case of rare diseases, the limits of traditional pharmacoeconomic evaluations are even more evident. New opportunities require new perspectives. It would be unethical to refuse patient access only because the use of old parameters does not give the right answer.

Conditional approval, early access and conditional marketing are legislative instruments that can offer a way for policy decision makers to reconcile effective use of financial resources with enhanced patient access.

## Biotechnology and innovation

Innovation can be defined in many ways. In healthcare, the improvement of patient quality of life and the introduction of new therapies for as-yet untreated diseases are widely accepted parameters of innovation.

Scientists have dated the first medical record to approximately 2100 BC. The document describes the extraction of an active ingredient from a herb using a process of pulverisation and maceration in oil or water, followed by boiling, filtering and then adding the extract to a beer solution for oral administration. Undoubtedly, there is a similarity with technologies that were used for centuries to produce traditional medicines.

Since the turn of the 20th century, biological research has been identifying biomolecules with therapeutic potential. Many of these molecules were extracted from their native source and produced for widespread medical use. However, the complexity of the extraction and purification processes made production extremely difficult. In the mid-1970s, two key discoveries not only overcame these difficulties, but opened a big avenue for several biotechnology companies dedicated to producing therapeutic proteins by hybridoma technology and genetic engineering.

Today, everybody talks about the 'promise' of biotechnology. In biopharmaceuticals, this is already a reality: 84 biotechnology products are currently available worldwide, which means that 60 million patients are benefiting from these drugs. On a global basis, more than 500 biopharmaceutical products are in clinical trials. Of these 500 products, the USA is leading with 369 medicines in development.[1]

Whereas early recombinant products approved were invariably replacement proteins, today, major target indications of biopharmaceuticals in clinical trials include cancer, infectious diseases, heart disease, neurological disorders and respiratory conditions. Essentially, biopharmaceuticals have already started to target the major causes of mortality in the developed world.

Thanks to human genomics – the study of genes for the development of new treatments – and pharmacogenetics – the study of how genes determine patient response to a given a medicinal treatment – biotechnology is leading to new generations of drugs that avoid adverse drug reactions and are tailored in part to an individual's metabolism.

## Biotechnology and uncharted territories: The case of rare diseases

Nowhere is the interdependence of biotechnology and innovation better demonstrated than in exploring the uncharted territories of rare diseases.

The Orphan Drug Act, enacted in the USA in 1983, grants limited market exclusivity for companies that invest in developing drugs to treat rare diseases (less than 200,000 patients). The rationale is that some conditions occur so infrequently that the cost of developing and bringing to market a medicinal product to diagnose,

prevent or treat that condition would not be recovered by the expected sales of the medicinal product. The pharmaceutical industry would be unwilling to develop the medicinal product under normal market conditions; these medicinal products are called 'orphan'.

A key principle underpinning this legislation is the notion of the rights of people affected by diseases treatable by orphan drugs: a concept that is supported by the notion of social justice and equity and the fact that individuals with rare disorders share the same desire for effective treatments to relieve or remove their conditions as those with common disorders. Orphan drug legislation is the result of an unwritten contract between society (or at least governments, as the expression of society's will) and the pharmaceutical industry to undertake R&D 'without return on investment' in exchange for a period of market exclusivity.

Up to the end of September 2000, 204 orphan drugs have been approved by the US Food and Drug Administration (FDA) which means that over 10 million patients receive the right treatment. Between 1991 and 1997, Singapore, Japan and Australia adopted their own orphan drug legislation. In 2000, the European Union enacted Regulation 141/2000 on Orphan Medicinal Products.[2] In places where orphan drug legislation has been implemented, a substantial portion of medicines that have been awarded this status are biopharmaceuticals.

## Patient access to therapeutic innovation: The case of the European Union

Every healthcare system has as an underlying principle, the notion of social justice and equity that patients have the right to equal access to treatment. The case of the European Union is particularly interesting because it reflects the major efforts realised after the Second World War to coordinate and integrate different economic and social systems overcoming the cultural barriers.

The premise of the creation of the EU, as stated in the Treaty of Amsterdam, is 'the creation of an area without internal frontiers', in order to 'promote . . . economic and social progress'. Health is a fundamental factor in economic progress, a fact highlighted by Dr Gro Brundtland, Director General of WHO, in her speech to the 51st World Health Assembly: 'Health is not only a moral obligation and a basic human right. Health is pure and sound economics'.

The EU also has a clear mandate to promote human health. Article 152 of the Treaty explicitly requires the EU to ensure a high level of human health protection and, in particular, to carry out activities that prevent human illness and disease. The new Charter of Fundamental Rights in the European Union also states that 'Everyone has the right of access to preventive health care and the right to benefit from medical treatment under the conditions established by national laws and practices'.

Patients suffering from a similar condition should be entitled to effective and appropriate treatment, wherever they live in the EU. The concept of equal access is included in the EU Regulation on orphan drugs, which states that 'action at Community level is preferable to uncoordinated measures by the Member States'.

While access to care, and the structure of national health services, is jealously guarded by member states, their influence is in fact not unchallenged *de jure* and *de facto*. European citizens are increasingly aware of their rights, increasingly educated in health matters, and increasingly demanding improvements in treatment. The recent decisions by the European Court of Justice on the Kohll and Decker cases[3] recognise citizens' rights to seek appropriate treatment as and when required within the territory of the EU.

*Therefore, do patients in the EU have access to innovative medicines?*

A recent study presented in March 2000 by Europe Economics, an independent

research centre,[4] shows that for many EU patients, access to innovative medicines has been extremely slow. In the study, a sample of 22 major breakthrough products that came onto the market in the late 1980s and early 1990s, the patients in the last EU member state to receive access typically had to wait four years more for access than those in the first. Patient access to important new medicines lies at the heart of modern medical care.

EU patients had to wait, on average, over two years after a medicine was first licensed by at least one EU member state before it was first consumed in their country. There are major differences among member states in the delays and other restrictions that patients are confronted with in obtaining access to important new drugs.

Delays in first consumption were, on average, lower for medicines launched during the later years of the survey, but increased in France, Belgium and Denmark. For major medicines authorised in the EU, patients in France, Greece and Portugal had to wait, on average, 10 quarters or longer for medicines to become available.

Analysis of a sample of 24 drugs awarded Community marketing authorisations between 1995 and 1997 through centralised approval, a mandatory procedure for biotechnology products, shows that average delays in consumption through pharmacies were longest in Portugal, Italy and Spain and were also relatively long in Greece, Belgium, France and Ireland.

To understand the importance of patient access to innovative treatments upon receiving marketing authorisation, we have to consider that the creation of new medicines is a long and costly process, and new drugs are available to patients only after a development period of between eight to ten years on average. During this time, research and clinical development departments of pharmaceutical companies, in close conjunction with academic clinicians, establish the exact profile of the new substance, its indications, the benefit–risk ratio, the best ways of using it in given clinical conditions.

After that, in the case of an EU centralised procedure, another $1\frac{1}{2}$ years is required to comply with a series of administrative procedures to obtain a marketing authorisation. Only then can the manufacturer start the pricing and reimbursement negotiation procedure in the EU member states to make the product available for patients. In the meantime, patients are not able to access the drug, unless under compassionate use programmes if applicable.

The delays for price fixing and/or reimbursement approval reveal that ill people are discriminated against, depending on their country of residence, since they do not have the same access to medicines that prevent or treat their illnesses.

## The role of economic evaluations for biopharmaceuticals and innovative medicines

New pharmaceuticals and other technological advances mean that health services are now able to do more for people than was ever possible before. Continuing development means that the potential for people to benefit from these treatments increases every year. These important achievements have produced health benefits and at the same time required resources that governments had not planned for or budgeted in due time. The budget time horizon of innovation is not the same as that for a national budget. As a result, investment in healthcare has become a cost and in the world of finite resources, economics has entered the healthcare arena.

Today, we talk about health economics as the application of the discipline of economics to the topic of health. Recently, several governments around the world, and especially in the EU, have introduced pharmacoeconomic procedures or evaluation processes in order to admit to reimbursement newly approved medicines, granting (or not) the patient access to new treatments.

In some cases, as in the UK, a specific government body was created in order to

ensure that the following criteria are fulfilled:

- A significant health benefit to all patients for whom the drug is indicated.
- A significant impact on other health-related government policies.
- A significant impact on NHS resources if the drug is given to all patients for whom it is indicated.

This is NICE, the National Institute for Clinical Excellence, which was established under the National Institute for Clinical Excellence Regulations 1999 (1999 No. 260).

In order to conduct its appraisals and reach health economic decisions, NICE applies a methodology known as pharmacoeconomics, a discipline whose objective is to evaluate medical strategies according to at least one economic criterion (eg number of consultations, number of days hospitalised, cost of medication, quality of life). The current types of pharmacoeconomic studies are as follows:

- *Burden of disease:* expresses the direct and indirect consequences of an illness on a population in pecuniary units.
- *Cost-consequences:* compares the cost of a therapeutic regimen with its consequences.
- *Cost-minimisation:* the consequences of two strategies are equivalent and a simple cost analysis is sufficient.
- *Cost–benefit:* compares the cost of a therapeutic regimen with its consequences, expressed in pecuniary units.
- *Cost-effectiveness:* compares the cost of a therapeutic regimen with its consequences, expressed in physical units of effectiveness.
- *Cost–utility:* compares the cost of a therapeutic regimen with its consequences, expressed in qualitative variables, quality of life.

It is important to remember that health economics is not a science, but a craft. At best, it is a useful, rational and analytical tool among several that help decision makers in healthcare to make better decisions. But this tool is unsuitable for decisions on whether or how doctors should treat individual patients. Its function is to provide data for decisions on whether healthcare is receiving value for money. A good tool maybe, but still a tool.

To create the right conditions and ensure patient access to innovative treatments is not an equation of public budget figures, but an equation of government priorities. If we look at the recent past, we can easily see that the general drivers for patient access in the EU were: equal access to medicines in the 1950s and 1960s; quality of treatment in the 1970s and 1980s and cost-containment in the 1990s to date. Which driver to apply is a typical policy maker's decision.

Choice, priorities and resource limitations are indeed governments' responsibilities and remain in the hands of legislators and regulators. 'Society', in health affairs, will reflect the interplay between public opinion and opinion leaders. Therefore, governments should establish the ethical and financial climate in which medicine can operate; decide where healthcare stands in relation to other claimants for resources, and encourage a more effective mode of operation, including a more cost-effective use of the available resources.

## Assessing innovation: The limits of traditional cost-effectiveness analyses and the case of orphan drugs

Innovation in general and particularly in healthcare, is part of the heritage of humankind. Innovation is the fruit of research and research is the fruit of culture. In one word, innovation is an expression of the cultural value of a society at a given time. The recent advances in research in healthcare have produced not only a new generation of drugs, but introduced technologies that are intrinsically connected with the right of individuals, especially in the field of life-threatening or chronic and seriously debilitating diseases. Assessing innovative medicines is not an isolated exercise that is conducted in a vacuum.

Recently, J.-M. Graf von der Schulenburg and C. Hoffmann noted[5]

> 'The societal value of a health care programme is a function not simply of the total number of life years or QALYs [quality adjusted life years] produced, but also of the degree to which concerns for equity are respected. Such concerns may include a preference for treating the severely ill before the less severely ill (all else equal), a preference for equity in health and a preference for not discriminating too strongly against those with a lesser capacity to benefit, be it in terms of lesser increases in their level of functioning or fewer years that their improved functioning may be enjoyed. Because of such concerns, the priority rating that the general public would assign to different health programmes may not be reflected in conventional cost-effectiveness and cost–utility ratios'.

The need to incorporate societal concerns for fairness in numerical valuation of health programmes represents very significant deviations from value measurement in conventional cost–utility analyses, which focuses on efficiency only. The difficulties of economic evaluation in healthcare raise a dramatic concern when applied to orphan drugs.

The orphan drug legislation is the answer to the economic dilemma of rare disorders: under predefined conditions, society at large decides to take on the cost of research and cost of treatment where the mechanism of the market-place, owing to the limited number of patients, has clearly failed.

The questions that traditional pharmacoeconomic evaluations (eg NICE appraisal) leave open when related to orphan drugs are as follows:

- Are the traditional *cost effectiveness* analyses applicable to an orphan drug that is by definition a cost for society?
- Are the traditional *quality of life* analyses applicable to an orphan drug that by definition is designated for the prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition?
- Are the traditional *clinical effectiveness* analyses applicable to an orphan medicinal product that should only demonstrate significant benefit for patients affected by rare conditions? The implementing regulation states that 'significant benefit means a clinically-relevant advantage or a major contribution to patient care, such as improving quality of life'.
- In cost and clinical effectiveness analyses, one is asked to compare existing treatments: how can one compare a product that has been designated 'orphan' based on the rationale that there exists no other satisfactory method of prevention or treatment of the condition in question?

The risk we face today is the dramatic limitation, if not exclusion, of patients from access to orphan drugs especially in Europe if, to this specific group of medicines, standard pharmacoeconomic appraisals are applied.

The 'multi-level Europe' based on the Treaty of Rome, as recently revised by the Treaty of Amsterdam, can easily undermine the positive impact of the new orphan drug regulation for patients affected by rare diseases. In fact, after EU marketing authorisation is awarded by the EU Commission, an orphan drug will undergo the traditional pricing and reimbursement processes as applied in the 15 EU member states. This means there will be 15 different procedures, which instead of creating equity in patient access, lead to unequal treatments based on the country of residence and national budget priorities at any given time.

In 1994, Professor Henry Grabowski noted:[6]

> Price controls on innovative new drugs have extremely negative consequences for smaller firms exploring new technologies, such as those in the emerging biotech sector. Biotech firms concentrate their R&D activities on long-term discovery research and are highly dependent on venture capital and external investment sources. It is not an accident that biopharmaceutical firms are primarily a U.S. phenomenon, where the market for pharmaceutical products has not been subject to extensive government price controls...

The basis of traditional meta-analysis

reviews is a restrospective evaluation of the published clinical trials. The limits of this methodology are strictly linked to the aim of clinical trials:

- They are designed to give an answer to predefined clinical end-points related to safety, efficacy and quality of the product.
- The patient population is well defined based on rigorous inclusion and exclusion criteria that are approved by independent ethical review boards. This population is not a mirror of the real population.
- Clinical trials by definition do not take into consideration factors required for budget impact analyses such as prescription habits, self-perception of the disease, local or national healthcare services structures.

Using meta-analysis evaluations to model the impact on budget resources is similar to extrapolating the economic fundamentals of Venice in the 16th century from Shakespeare's *Othello*.

Modelling a subgroup patient population on the national health services population has meaning for certain types of conditions (eg infectious diseases), but has little relevance for diseases where the cause determines the number of patients (eg genetic disorders) or where the origin and means of propagation of the disease are still unknown (eg multiple sclerosis or Parkinson's disease). In particular, with well-defined patient subgroups, a government can easily plan the needed resources, thereby ensuring the availability of innovative therapies for the patients.

Whether or not a government is willing to pay for these therapies is a different question. This is a matter of health policy priority setting, an area that governments cannot delegate to technical bodies. Otherwise, health technology assessment agencies will be perceived as a means for governments to ration drugs without having to take the blame for it. As a result, pharmacoeconomic evaluations, conducted in some European member states as a condition for drug reimbursement and hence, patient access, are an additional hurdle that create inequity and delay the availability of innovative treatments. This is known as the '4th hurdle'. Patient access to innovative treatments should be the outcome of the marketing approval process based solely on considerations of safety, efficacy and quality. The introduction of the 4th hurdle as a mandatory step restricts access to needed medicines for all.

In addition, the 4th hurdle has brought about a divide between the EU and the USA; namely EU patients are treated with older medicines than their US counterparts despite recent healthcare budget increases in many EU member states.

So, why do patients in the USA often have quicker access to innovative medicinal products than in the EU?

## Conditional approval and expanded access: Possible solutions for the availability of innovative biopharmaceuticals

Since 1987, the US FDA has adopted several regulatory procedures to speed up the availability of new therapies for serious or life-threatening conditions, thus demonstrating the potential to address unmet medical needs for these conditions.

In the USA, expanded access programmes (emergency use, individual patient use or compassionate use treatment of investigational new drugs, IND) and accelerated development programmes (fast-track drug approval) were created to expedite the regulatory approval process of drugs for the treatment of serious or life-threatening illnesses, enhancing patient access to the right treatments. As examples, expanded access renders experimental drugs available on a wide basis to patients who do not meet the enrolment criteria of clinical trials. In most cases, a drug with an expanded access programme is already in the final stages of the approval process.

Compassionate use is a classification of an experimental drug that is made available to seriously ill patients before the drug is approved for general use. Few drugs receive this classification. Compassionate use drugs are generally free of charge to the patient.

These procedures recognise that physicians and patients suffering from life-threatening diseases are more likely to accept greater risks from products that treat such conditions. In addition, they reflect the fact that the benefits of the medicinal product need to be evaluated taking into account the severity of the disease being treated.

In essence, the US provisions state that for a life-threatening and seriously debilitating condition and according to strict requirements (e.g. hospital distribution only, specialised centres only), patients can access the therapy after Phase II studies while the sponsor commits itself to developing a Phase III/confirmatory study. In this context, 'life-threatening' means:

- diseases or conditions where the likelihood of death is high unless the course of disease is interrupted; and
- diseases or conditions with potentially fatal outcomes, where the end-point of clinical trial analysis is survival.

Given that 'seriously debilitating' refers to diseases or conditions that cause major irreversible morbidity, introducing such a system in the EU today would allow patient access to the 'right' treatment. In addition, this system would ensure quality and safety controls through strict distribution requirements.

If from a regulatory perspective, as stated before, it is possible to facilitate and deliver innovation to patients in a timely way, it is undoubtedly more problematic to ensure availability. Despite the general consensus that it is inappropriate to consider cost and pricing of a drug in its marketing approval process, these factors are still a significant barrier to patient access.

In 1999, the World Health Organisation Regional Office for Europe (WHO/EURO) held an explorative meeting with Ministries of Health and social health insurance authorities from member states to discuss the emerging use of pharmacoeconomics in decision-making procedures in reimbursement systems. Several European countries were in the process of developing pharmacoeconomic guidelines, and new national bodies were being planned to fulfil this purpose. In other countries, the development of pharmacoeconomic guidelines was assigned to existing agencies. The Australian experience, since the early 1990s, of applying pharmacoeconomic guidance in its reimbursement system was used as a reference point. The 1999 meeting concluded on the usefulness of applying pharmaco- and health economic guidance as one of the criteria in reimbursement decisions, but also recognised the considerable methodological difficulties in developing the guidelines and interpreting the results of the studies. The WHO document recognises that 'Public policies apply a variety of cost-containment measures, while at the same time striving to maintain equitable access to optimal drug treatment for all patients in need.'[7]

The main objectives of national-level policies in the pharmaceutical pricing and reimbursement area are to maintain and enhance equity and quality of drug treatment while at the same time getting the best value for the money. There are many methodological issues with measuring quality of drug treatment and, in turn, cost-effectiveness. Making judgments of clinical benefits in relation to cost-effectiveness is a sensitive and challenging area.

These challenges are heightened by a dynamic policy arena where national-level policy makers face:

- Rising drug expenditures along with greater limits on drug budgets.
- Pressures from doctors, pharmacists and consumers on the demand side.
- Large variations in clinical practice coupled with instances of irrational prescribing.
- Under-use of new effective treatments in favour of continued use of more well-known but less effective or ineffective treatments.
- Pressures from the drug industry on the supply side to recoup R&D investments.
- Rapidly changing healthcare environments.

If access is a priority, and cost an element

among others in the affordability decision-making process, the focus of cost-effectiveness analysis should not necessarily be on demonstrating cost-saving, but on identifying direct and indirect intangible benefits. Healthcare is an investment, not just a cost. The role of pharmacoeconomic evaluations is to demonstrate value in its broadest sense.

## Conclusion: Conditional marketing to avoid a 'Utopia syndrome'

The answer to the needs of governments to evaluate the impact of innovative treatments on the national healthcare budget lies in measuring the impact of these treatments under 'real-life' conditions. Granting immediate patient access upon marketing authorisation will aid government understanding of how resources should be allocated because the value of a new health technology can only be demonstrated once the technology has been placed on the market. This is the moment when analyses can be developed based on the technology's performance relative to other healthcare interventions and through the collective experience of patients, payers and healthcare providers.

Pretending at any cost that only early evaluation of innovative medicines will allow decision makers to set the right priorities, thereby enabling or not patient access to these treatments, only leads to a 'Utopia syndrome'.

As Robert Ardrey[8] states 'While we pursue the unattainable, we make impossible the realizable.'

As early as 1947, in his essay 'Utopia and Violence',[9] the philosopher Karl Popper warned that Utopian schemes must perforce lead to new crises. It is unfortunately much easier, he points out, to propose ideal and abstract goals and to find enthusiastic followers than to solve concrete problems. But, warns Popper,

> 'our fellow men have a claim to our help. No generation must be sacrificed for the sake of future generations, for the sake of an ideal of happiness that may never be realized. In brief, it is my thesis that human misery is the most urgent problem of a rational public policy and that happiness is not such a problem. The attainment of happiness should be left to our private endeavours.'

And long before Popper, the poet Hölderlin remarked: 'What has made the State into hell is that man wanted to make it his heaven.'[10]

Today, innovation and biotechnology offer solutions to patients that were unforeseeable only a few years ago. Pharmacogenetics will lead us to a new environment in which words such as prevention, treatment and healthcare will have different meanings. To ensure greater patient access to medicines, different perspectives should be taken into consideration. The author suggests compassionate use, expanded access and conditional marketing as possible solutions.

As highlighted in the section on 'Assessing innovation: the limits of traditional cost-effectiveness analyses and the case of orphan drugs', it is meaningless to apply cost-effectiveness analyses before the therapy has its place in the market. A theoretical model should always be tested against reality. The concept of 'conditional marketing' offers an innovative approach and ensures immediate patient access to a new treatment in a 'real-life' setting.

Collaborative studies conducted by industry and sponsored by health authorities, with full involvement of patient associations as well as the scientific and clinical communities, reveal the right assessment, after a period of between 24 and 36 months, on the impact of an innovative treatment not only on the healthcare budget, but on society at large.

Conditional marketing would allow all involved parties, health authorities, patients, clinicians and industry to consider the long- and short-term horizons and total impact on health. Conditional marketing is an answer to this need.

Understanding the cost-effectiveness of a particular treatment is a dynamic process involving incremental demonstration of value, which changes during a medicine's

life cycle. Therefore, continuing appraisals and dynamic applications are essential to document the eventual true value of a drug in the market-place.

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