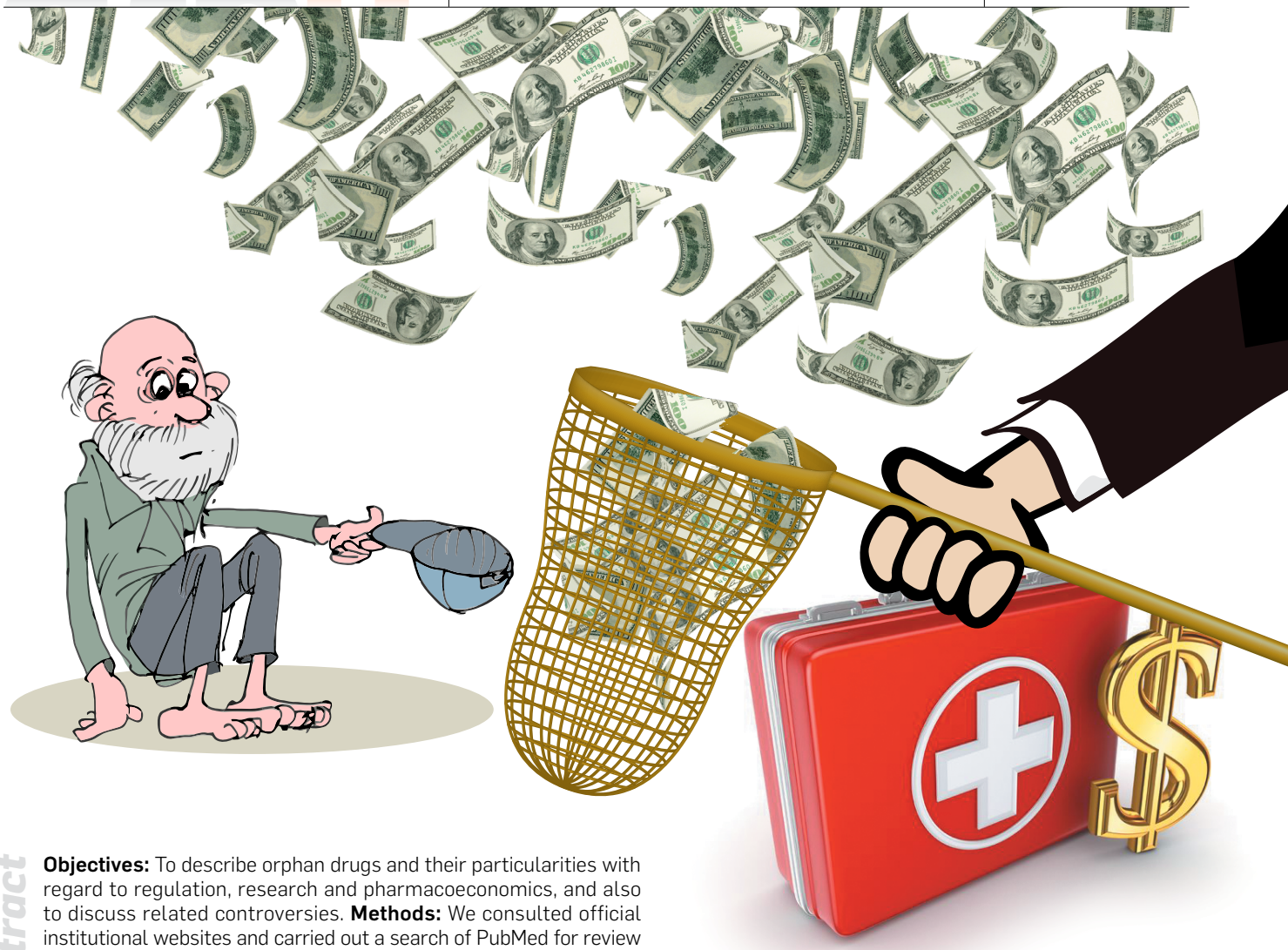
dtbn
DRUG AND THERAPEUTICS BULLETIN OF NAVARRE, SPAIN
YEAR 2015
VOL 23, No 1
www.dtb.navarra.es
@DTB_Navarre.es



abstract

Objectives: To describe orphan drugs and their particularities with regard to regulation, research and pharmacoeconomics, and also to discuss related controversies. **Methods:** We consulted official institutional websites and carried out a search of PubMed for review articles on orphan drugs (updated 13 May 2015). **Results:** Orphan drugs are drugs for rare diseases that are life-threatening or chronically debilitating, and for which it is unlikely that marketing of the medicine would generate sufficient returns to justify the investment needed for its development. They are classified as such by regulatory agencies as a previous step to clinical development and this implies incentives for manufacturers. As research on these drugs entails the problem of a scarce number of patients, alternative research designs are included. There are controversial issues regarding the quality of research, including whether pharmaceutical companies are abusing the current regulation policies to quickly launch these drugs in the market at exorbitant prices, if the definition of rare disease is distorted or if the orphan drug designation should determine the pharmacoeconomic evaluation. From a health systems perspective, an attempt to address the problem comes through the elaboration of therapeutic positioning reports, and the negotiation of pharmaceutical risk-sharing agreements. **Conclusions:** Encouragement of research and development of drugs for rare diseases is merited, but should be directed to the most relevant ones. Given the difficulty involved, research on orphan drugs should be carried out under maximum quality standards. Research funding should be reviewed in order to make it sustainable and to ensure that equitable access to drugs is guaranteed. Keywords: orphan drugs, rare diseases

Orphan drugs: regulation and controversies

JAVIER GARJÓN
Drug Prescribing Service. Navarre Health Service, Spain

Introduction

In recent years administrations, scientific societies and society in general have shown great interest in rare diseases and orphan drugs. The aim of this article is to describe the concept of orphan drugs, outline the differences compared to other medications with respect to regulation, research and pharmacoeconomics and to highlight some of the controversies regarding this issue.

To do so, various official websites (Table 1) were consulted and a PubMed search for relevant review articles on orphan drugs was carried out (last update May 13, 2015).

This article does not aim to evaluate the therapeutic contributions of specific orphan drugs.

Definition of "orphan drug"

Orphan drugs are defined as drugs that are developed as a response to the needs of public health[1]. In the European Union, a drug may be designated as an orphan drug if it complies with all of the following criteria[2]:

1 it must be intended for the treatment, prevention or diagnosis of a disease that is life-threatening or chronically debilitating;

2 the prevalence of the condition in the EU must not be more than 5 in 10,000 or it must be unlikely that marketing of the medicine would generate sufficient returns to justify the investment needed for its development;

3 no satisfactory method of diagnosis, prevention or treatment of the condition concerned can be authorized; or, if such a method exists, the medicine must be of significant benefit to those affected by the condition.

This definition includes certain points worth considering:

- The term "orphan drug" is an official label designated by the authorities.
- The differential criteria of an orphan drug are of commercial nature, that is, a drug for which the revenues are not expected to be high enough to make up for the research and development expenses.
- The designation as an "orphan drug" does not involve it has a therapeutic value.
- In many cases the criteria that the drug will provide considerable benefit to those patients with rare diseases turns out to be a desideratum, because the term orphan drug is designated before clinical development.
- It should be the indications to be considered as "orphan" rather, since drugs already marketed for common diseases can be designated as "orphan drugs" for a rare disease. For example, sildenafil for pulmonary hypertension and inhaled tobramycin for cystic fibrosis have been designated orphan drug status. An active substance can also have various designations as an orphan drug for different diseases.

Although normally the term orphan drug is associated with rare diseases, this is not always necessarily the case. In fact the designation of an orphan drug is also employed to promote the development of unattended or forgotten diseases such as malaria, frequently found in developing countries.

Regulation

The United States was the first country to regulate on this issue. In 1983 the Orphan Drugs Act was released. "Rare disease" was defined as that which affects less than 200,000 people in the USA. Today, this would represent a prevalence of 6.3/10000 inhabitants. Over time, similar legislation was enacted in Japan (1993) and Australia (1997).

The Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal product aims to establish procedures for designating orphan drugs and to establish incentives to promote research, development and marketing.[2] Henceforth this article will refer to the European regulation only, which is quite similar to that of the USA in many aspects.

The manufacturer can apply for the orphan drug designation when the above-mentioned criteria are fulfilled. The decision is taken by the European Commission upon the

Table 1. Websites of interest.

Orphanet, website offering information on rare diseases and orphan drugs http://www.orpha.net/consor/cgi-bin/Education_AboutOrphanDrugs.php?lng=ES
EMA. Orphan designation http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000029.jsp&mid=WC0b01ac05800240ce
European Comision. Orphan medicinal products http://ec.europa.eu/health/human-use/orphan-medicines/index_en.htm
EMA. Committee for Orphan Medicinal Products (COMP) http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000263.jsp&mid=WC0b01ac0580028e30
FDA. Designating an Orphan Product: Drugs and Biological Products http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/HowtoapplyforOrphanProductDesignation/default.htm

request of the European Medicines Agency (EMA).[3] In December 2014, there were 1103 orphan drug designations. Only a small percentage of these designated orphan drugs were finally granted approval.

Orphan drug designation is given by the *Committee for Orphan Medicinal Products* (COMP). The COMP is composed of: a chair, elected by serving COMP members; one member nominated by each of the 28 Member States; three members nominated by the European Commission to represent patients' organizations; three members nominated by the European Commission on the Agency's recommendation; one member nominated by Iceland and one by Norway.

Sponsors who obtain orphan designation benefit from a number of incentives, including:

- Protocol assistance.
- A type of scientific advice specific for designated orphan medicines.
- Market exclusivity. Authorized orphan medicines benefit from ten years of protection from market competition with similar medicines with similar indications once they are approved. This period of protection is extended by two years for medicines that also have complied with an agreed pediatric investigation plan which is granted at the time of review of the orphan medicinal designation.
- Fee reductions are also available depending on the status of the sponsor and the type of service required.
- Funding is available from the European Commission and other sources:
- *Horizon 2020*, the EU Framework Programme for Research and Innovation (see the theme *Personalising Health and Care* which covers *New therapies for rare diseases*);
- *E-Rare*, a transnational project for research programmes on rare diseases;
- *International Rare Diseases Consortium* (IRDIRC).

There is a common application form for orphan drug designation shared by the EMA and the FDA.

It should be made clear that the designation of a medication as an orphan drug is a preliminary phase before its actual clinical development. At the time the drug is designated as "orphan", there is no evidence about its effectiveness and thereby its risk-benefit balance is unknown.

To apply for authorization as an orphan drug a centralized European procedure should be followed.

There are three different types of approval:

- **Normal.**
- **Conditional:** when the data are still incomplete. The manufacturer is obliged to carry out additional studies and approval is renewed annually until the studies are completed and then the drug will attain normal status.

Approximately 25% of new medications in the European Union are "orphan" drugs.

- **Under exceptional circumstances:** when an applicant shows that it is not possible to provide complete data on efficacy and safety of the drug. This usually occurs when the disease is extremely rare, there is little scientific knowledge in the field, or due to ethical reasons on data collection. The information is reviewed annually to reevaluate the risk-benefit balance.

When the conditional approval is granted, it is expected that in a relatively short period enough clinical data will be obtained to attain normal approval status. In the case of approval under "exceptional circumstances" the above condition is not expected.[4] By April 22nd, 2015, of the 82 authorized orphan drugs in Europe, 9 had a conditional approval, while 15 were approved under exceptional circumstances.

Access to the markets

In Spain, once a drug is approved in the European Union, there is a process of setting prices that is negotiated between the pharmaceutical manufacturer and the Health Ministry. Orphan drugs are normally indicated for hospital diagnosed diseases and thus dispensed in the hospital setting. At present, only three orphan drugs are used for hospital-diagnosed diseases and dispensed at community pharmacies.

Access in special situations

Not all drugs are registered in all countries. Of the 82 orphan drugs authorised in Europe, only 48 of them are available on the market in Spain. Access to the rest are managed through the Foreign Medicines Service of the Ministry of Health.

In relation to those drugs that are in research and development phases, the Spanish Medicines Agency can authorize their use before marketing authorization in Spain. Access is restricted to specific patients who have no other satisfactory therapeutic alternative, to those who are not participating in a clinical trial and at a clinical stage that they cannot wait for the research to finish or drug approval. Access to these drugs can be individually based or temporally authorized by the Spanish Medicines Agency for a group of patients.

Challenges facing orphan drugs

Regulation on orphan drugs inevitably faces a conflict between early access to novel treatments that can improve the health of these patients on one hand and a rigorous evaluation of benefits and risks of the drugs on the other.

The European policy establishes that patients affected by rare diseases have the right to drugs whose quality, safety profile and efficacy are equivalent to the rest of drugs. As a result, orphan drugs should follow the standard evaluation procedures.[2]

The quality of the studies on orphan drugs can be clearly improved.

Research

Drug research for rare diseases has the inherent problem that there are few patients to include in the development process. A disease can be rare given its low incidence, and so it is difficult to carry out well-powered clinical trials. Another possibility is that the disease has a higher incidence but a short survival rate, in which case the feasibility of a clinical trial is greater. It is also true that patients with rare diseases are usually identified and belong to associations which favour recruitment and motivation to participate in clinical trials. Given the difficulties and knowing that classical randomized controlled clinical trials provide the best evidence, the EMA does not require any specific research design to authorize an orphan drug. In fact it provides guidelines on alternative designs for trials and approaches to attain the maximum amount of information from a limited number of patients.[5,6] Some of these designs include:

- **Randomization with matching controls or stratification.** If matching or stratifying individuals by prognostic factors, sample size and variability are reduced.
- **Cross-over trials:** the same patients receive both treatment and control in different sequences. Sample size is reduced as each patient represents his or her own control and variability due to subjective factors is reduced.
- **Adaptive trials:** also denominated play the winner rule. This consists of an ongoing evaluation of the results and allocation of more new patients to the group with the best results obtained in order to reach statistical significance.
- **Sequential trials.** These could be called "leave while you´re winning" and they consist of performing interim analyses and stopping the trial when statistical significance is reached according to a predetermined rule. In addition, rules to halt the trial due to futility can also be introduced.
- **Trials with historical controls.** This consists of administering treatment to all patients included and comparing the results with those patients who suffered from the disease and were followed up in a previous period.

Each of these designs has drawbacks. The "cross-over" and the "only one patient" trials only serve to evaluate responses produced in a short time period. The "adaptive" and "sequential" alternatives break researchers blinding, and in general increase the complexity of analysis and the probability of obtaining spurious conclusions.

The analysis could prove useful if Bayesian models are employed that allow for information outside the trial to be incorporated.

If it is already difficult to study the efficacy of drugs for rare diseases, it is even more so to evaluate their safety profiles. At the moment a drug is marketed, there will surely be little information to evaluate the benefit-risk balance, and hence the need for post-marketing surveillance.

Controversies

Research: Are we talking about a filter?

The challenges of orphan drug research and the pressure for quick drug marketing raise concerns as to whether there is an excessive relaxation of approval criteria.

A review of the applications submitted between 2002 and 2007 for public funding of 25 orphan drugs in Belgium showed diverse deficiencies. The duration of the majority of the studies was too short given the natural history of the disease. Thirteen reports included randomized clinical trials, of which only three presented an active control group. In the majority of the cases, other drugs showing at least partial efficacy were available for the diseases under study. For example, bosentan, sildenafil and sitaxentan, indicated for pulmonary hypertension, were not compared to epoprostenol. The ibuprofen report on ductus arteriosus in premature babies did not include trials versus indometacin, 10 times cheaper. Studies on pegvisomant in acromegalia did not include comparisons with lanreotide or octetrotide.

In some cases, controlled trials were not carried out despite having an adequate number of patients available. For example, in the case of anagrelide, there were data from 6 non-controlled studies including up to 1446 patients. There was a lack of timely dose-finding studies, especially in metabolic diseases where the data derived from small

children were extrapolated to adults with no adjustments for disease severity. Frequently there were surrogate endpoints with little evidence on any association with clinically relevant results. Some cases were surprising such as the approval of algalsidase α for Fabry disease, based on surrogate endpoints while algalsidase α was backed by results from clinical studies.[7]

A review of pivotal trials on cancer drugs registered in the USA between 2004 and 2010 comparing orphan drugs versus non-orphan drugs found that there was less double-blinding in the former case (4% vs 33%, respectively), the primary endpoint was a "surrogate" variable more frequently (68% vs 27%), and survival was evaluated less frequently (8% vs 27% respectively).[8]

Likewise, a review of 108 pivotal trials on orphan drugs submitted to the EMA found different methodological problems. The primary endpoint was a clinical outcome in only 19% of the trials. The quality of life was evaluated in 27% of the cases and only one in three showed improvement. In addition, 35% of the studies were not randomized and 41% were not blinded but no justification was given for this. Lastly, 32% were not registered in ClinicalTrials.gov or EUdraCT.[9]

In another review the use of GRADE to evaluate the quality of the evidence on orphan drugs approved in Europe concluded that it was moderate in 73% of the cases, low in 22%, and very low in 5%. In no case was quality considered high.[10]

Although orphan drugs are aimed at life-threatening or debilitating diseases, clinical trials are frequently based on surrogate endpoints. The problems associated with blinding or randomization cause concern because, given the complexity of the trials, orphan drug research is likely to be biased. The lack of trial registration makes it impossible to know whether there is any protocol violation and also makes publication bias more likely. A questionnaire to assess the evidence on orphan drugs has been developed.[11]

It could be assumed that even though orphan drugs are approved with limited evidence, this evidence (of efficacy) would increase over time. However this is not always true. For example, algalsidase for Fabry disease was approved as an orphan drug in 2000. A systematic review in 2012 did not find any robust evidence to recommend its use.[12]

Are we witnessing a flood of orphan drugs?

Given the incentives to develop orphan drugs, the exorbitant prices, and the difficulty in discovering new drugs for common diseases, orphan drugs account for a large number of applications in the regulatory agencies. In the strategy of pharmaceutical companies they are being given priority over drugs targeted at wider populations.[13,14]

The elevated costs derived are not always justified, especially when backed by important amounts of public funding.

There has been a constant increase in the number of orphan drugs designation by the EMA (figure 1). The number of applications in 2014 reached a record of 327. However, the annual number of authorized drugs has remained steady at approximately 10.

Are they always rare diseases?

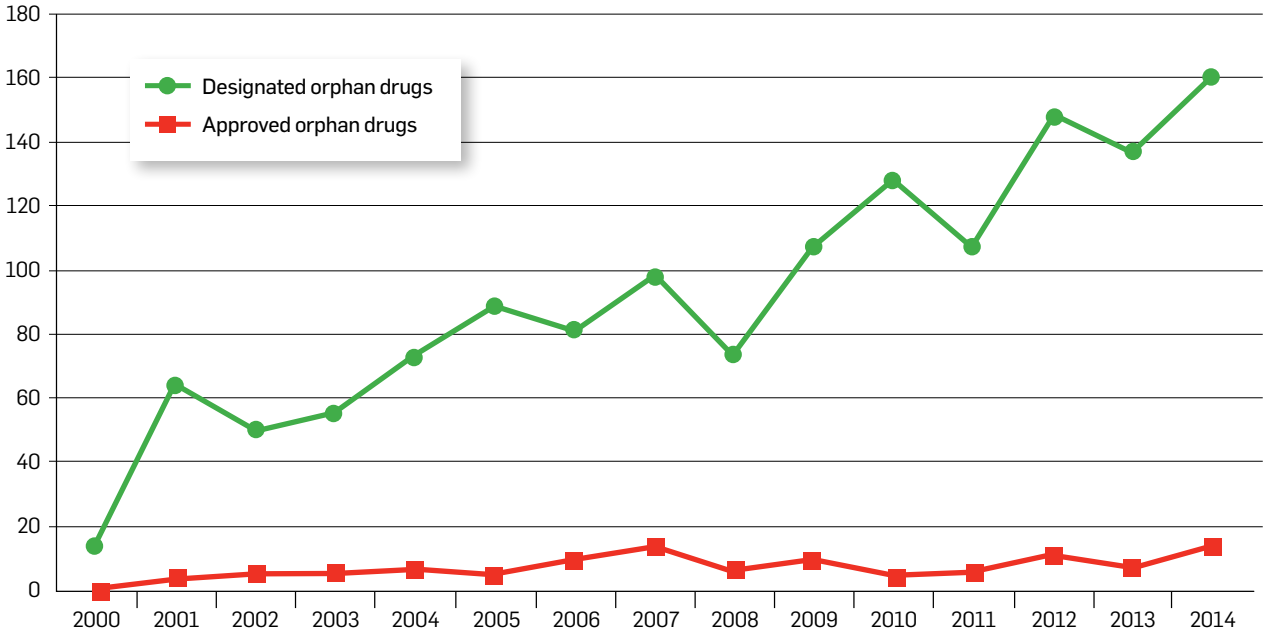
Undoubtedly, patients who suffer from some rare diseases are benefitting from the development of orphan drugs. However, as pointed out above, drug companies may be employing the "salami" strategy or excessive stratification of these diseases. A more common disease is divided into various subtypes so that each one complies with criteria as a rare disease.[15] For instance, lymphoma has been classified in dozens of subgroups in relation to the cell affected. In addition, a drug can earn a place as an orphan drug when indicated for patients who do not respond to previous treatment.[13]

More than half of the drugs approved for cancer in the US are orphan.[8] So, it is not surprising that only half of the authorized orphan drugs in Europe are designated for rare diseases of genetic origin. This does not mean that there are no other research fields to explore. Before 2012 only a quarter of very rare metabolic diseases of genetic origin (prevalence<1/100,000) had an orphan designated drug (not even approved) by either the EMA or FDA.[16] It has been shown that development of orphan drugs tends to focus on more lucrative therapeutic areas.[17]

A model for other drugs?

The conditions created for orphan drugs (public incentives, fast approval and marketing with scarce data) may have well opened a path for the development of other drugs based on innovation and early access to market rather than the search for a favorable risk-benefit balance.

Figure 1. Orphan drugs designated and approved by the EMA.



Source: EMA. COMP.

In 2014, the EMA introduced a pilot program of adaptive licensing, offering fast approval of drugs for a restricted group of patients based on small clinical studies. After the initial approval, further "normal authorization" can be granted based on additional real life studies, clinical practice and supportive studies too.[18]

The exorbitant prices of orphan drugs: are they justified?

Exorbitant prices associated with orphan drugs may cause serious problems by making it difficult for patients to gain access to them, undermining financial sustainability of the health care system and creating uneven access to treatment among patients.[17,19,20] The high price of orphan drugs is justified by the elevated research and development costs for a small market.

However, there are well-founded criticisms that the price system is working inadequately.[15,17,19,21] The cost of developing an orphan drug is usually lower than that of other drugs for more common diseases.[17,21] Orphan drugs studies may turn out to be cheaper given that they focus on rare diseases and treatment may be carried out at few reference centres. Some cases merit attention. For example, 3,4-diaminopiridine had been used for more than 20 years as a magistral formulation in patients with Lambert-Eaton myastenic syndrome, at a cost of €1,000 per patient-year. Once designated as an orphan drug, the price was raised up to €50,000 per patient-year. This led a group of neurologists and pediatricians to write an open letter addressed to the UK Prime Minister and Health Secretary requesting action to be taken on the elevated prices of orphan drugs.[22]

In other cases indication creep is produced. An orphan drug gradually expands its indications and its market is no longer small. For instance, imatinib was registered as an orphan drug for chronic myeloid leukemia and later approved for other 5 diseases with no reduction in price.[23]

Are we paying twice?

There is a confluence between public funding for orphan drugs and the exorbitant prices of these drugs paid for by health care systems. For instance, ivacaftor benefitted from funding of up to $750,000,000 USD from the Cystic Fibrosis Foundation while its market price is €244,000 per patient-year.[19]

The perfect storm?

Groups for patients affected by rare diseases demand drugs for treatment.

Agencies develop special programs that favour fast authorization of orphan drugs so that patients may have quick access to these drugs.

Once approved, the drug manufacturer attains a monopolistic status that allows it to set a high price.

Health care services have little margin for negotiation. Facing criticism that they are insensitive to patients' suffering, they cannot stop financing drugs even though the risk-benefit balance is questionable or their efficacy is unclear. Patients with rare diseases are identified, well organized and may have few alternatives.[17,24]

Even though by definition small revenues are expected from orphan drugs, some approved drugs obtained solid global sales of over 1 billion dollars (table 1), while analysts expect other orphan drugs will follow the same trend.[25]

Regulations and incentives that justifiably seek to protect and help patients with rare diseases have produced an undesirable side effect: exorbitant drug prices. Drug manufacturers have taken advantage of the current situation and ultimately of patients and health care services. It is time for correction.[26]

Pharmacoeconomic analysis

There is a debate as to whether the cost-utility assessment of orphan drugs should follow the same criteria as for other drugs. Specifically, the debate focuses on whether the same threshold on Quality Adjusted Life Years (QALYs) should be employed when considering investment,[15,27] for instance €45,000 per QALY. The problem is that orphan drugs frequently surpass these thresholds.

Those parties against the application of these thresholds resort to the "rescue rule", that is the imperative to treat identified individuals at high risk regardless of the cost. Some others argue that the rescue rule should not serve to establish priorities on general actions, and rarity per se should not be taken as a criterion, because patients with common but severe diseases also have the same rights.[15,20,27]

Whether society is willing to pay for orphan drugs is controversial. The evidence on this issue is scarce. Some studies in the UK, Canada and Norway found that the population did not consider rarity per se as relevant criterion, except in the case of very rare diseases.[21,27]

Different models are proposed to fix prices of orphan drugs. Some cases take into account the rarity of the disease (table 2).[23] Other authors propose that actual production and development costs should be considered when setting prices if orphan drugs exceed the thresholds of cost-effectiveness.[28]

Another proposal for setting the price considers the therapeutic benefit and level of evidence (table 3).[9] In real practice these criteria apply to all new drugs, orphan or not.

Currently standard criteria are not clearly used. For instance, prices in the UK do not seem to be set according to either the rarity of the disease or the efficacy of the drug.[10]

We should also admit that health care systems spend too much money on drugs for common diseases that offer little or no additional benefit.

How are the problems managed?

In 2009, Spain's Ministry of Health published a Strategy for Rare Diseases in the National Health Service, including a section on orphan drugs (table 4).[30] This document was updated in 2014. To illustrate the difficulties in analyzing these strategies, a follow-up report in 2012 revealed that none of the objectives was measurable due to a lack of responses to the indicators.[31]

The Therapeutic Positioning Report (IPT) coordinated by the Spanish Medicines Agency aims to establish the place in therapeutics of the new drugs. These should be particularly useful in the case of orphan drugs.

Other institutions that issue therapeutic positioning reports include NICE in the United Kingdom, HAS in France and IQWiG in Germany.

Risk-sharing agreements

High prices associated with orphan drugs lead some parties to propose risk-sharing agreements at the national, regional or local level. They can be defined as agreements between a payer and a pharmaceutical, device, or diagnostic manufacturer where the price level and/or nature of reimbursement is related to the actual future performance of the product in either the research or 'real world' environment rather than the expected future performance. They could be:

- **Finance-Based.** These agreements are conditioned by a set of pre-specified budget caps, discounts or restrictions that can either be based on a particular patient or on the disease population. These can include: price-volume agreements (France), expenditure caps (Australia; United States), price cuts that are attached to forecasted spending (Japan) and conditional discounts (Italy; UK).

- **Outcomes-Based.** These agreements are conditioned by a pre-specified endpoint or definition of response that dictate whether the payer will cover the treatment on an ex post facto basis. These can include outcomes guarantees (United Kingdom; United States) and form the traditional model of risk-sharing agreements, as payment is weighted entirely against the performance of the drug.

Risk-sharing agreements must not be used as an excuse to avoid performing timely research and development programs, to introduce drugs before the regulatory agencies' assessment, or as a strategy to reduce the cost per QALY. Nor should they be used when other cost-effective strategies are available.[32]

Table 2. Proposal for criteria to set prices of orphan drugs.[23]

Criteria	Price		
	€	€€	€€€
Frequency of the disease	>3/10,000	1-3/10,000	<1/10,000
Research carried out	Bibliographic review	Built upon previous knowledge	A research program is initiated
Uncertainty on effectiveness	Inconclusive data	Adequate surrogate variables	Robust clinical outcomes
Manufacturing complexity	Low	Moderate	Difficult (biological or complex formulation)
Postmarketing surveillance requirement	Little	In response to a specific issue	Studies on efficacy and safety required
Severity of the disease	Adult morbidity	Mortality, adult disability	Mortality, disability from childhood
Alternatives available	Yes	Yes, but new drug provides greater improvement	No
Impact on health	Low	Medium	High
Single indication?	No	Potential for various indications	Yes

Table 3. Orphan drugs ranked by global sales in 2014.[25]

Main substance	Brand name	Indications	Global sales (million US$)
Lenalomida	Revlimid	Multiple myeloma Myelodysplastic syndromes	4,980
Imatinib	Glivec	Chronic myeloid leukemia Malign gastrointestinal stromal tumours Dermatofibrosarcoma protuberans Acute lymphoblastic leukemia Hypereosinophilic syndrome and/or Chronic eosinophilic leukemia Myelodisplastic/myeloproliferative syndromes	4,695
Eculizumab	Soliris	Nocturnal paroxysmal hemoglobinuria Atypical hemolytic uremic síndrome	2,225
Bosentan	Tracleer	Pulmonary arterial hypertension Systemic sclerosis	1,649
Dasatinib	Sprycel	Chronic myeloid leukemia Acute lymphoblastic leukemia	1,520
Nilotinib	Tasigna	Chronic myeloid leukemia	1,511
Sunitinib	Sutent	Malign gastrointestinal stromal tumours Metastatic renal cell carcinoma Neuroendocrin pancreatic tumours	1,183
Sorafenib	Nexavar	Hepatocelular carcinoma Renal cell carcinoma Differentiated thyroid carcinoma	1,026

Table 4. Criteria of the Citizens Council of the NICE (UK).

The Citizens Council of NICE (UK) states that the National Health System should consider much higher thresholds for so called "ultra orphan" drugs (for diseases with a prevalence of 2/100,000 inhabitants or less), based on the following criteria:

1. Severity of the disease.
2. Treatment should offer health gains prior to a mere stabilization of the disease.
3. Life-threatening diseases.

Table 5. Proposal for a transparent evaluation of orphan drugs.[29]

Criterion	Low	Medium	High
Alternatives available / needs not satisfied, including non-pharmacological options.	No, the new drug does not satisfy an existing need	Yes, but important needs have yet to be satisfied	No alternative except for palliative care / the new drug satisfies an important existing need
Relative efficacy, net benefits vs alternatives including no treatment (clinical improvement, quality of life, etc. vs side effects, social impact, etc.)	Incremental	Important	Curative
Response rate (based on the best clinically relevant criteria)	<30%	30-60%	>60%
Level of certainty (documentation)	Promising but not well documented	Plausible	Unequivocal

Some proposals

An international workshop on orphan drugs held in March 2014 offered the following proposals:[33]

1. A firm diagnosis and rigorous adherence to the clinical indications of the drug are imperative for patients with a rare disease. The prescription of a new and expensive drug should be validated by a reference centre for treatment of the disease.

2. There should be a registry for each rare disease based on the diagnosis, and updated with high quality data. This facilitates the evaluation of the efficacy of the drug with a greater amount of patients than those used for drug approval. The registry allows for an evaluation of the clinical course of patients receiving the drug versus those untreated, and offers complete and unbiased data on side effects. For all this, the registry should be managed by an independent entity (table 5).

3. The cost of orphan drugs should be negotiated systematically. It is necessary to document the costs of orphan drug research, estimate the number of patients and allow for a certain profit margin. Drug costs should be based on these principles. The European Union should be prepared to negotiate orphan drugs from both an ethical and economic perspective.

Acknowledgements

We are grateful to Douglas Salzwedel of the University of British Columbia, Canada, for reviewing the text. We also thank Dr. Clint Jean Louis, of the Emergency Department of the Navarre Regional Health Service in Spain, for translating the original manuscript into English.

Conclusions

The encouragement of drug research for rare diseases is positive.

It is essential to ensure that this research impetus is directed to where it is most needed.

Drug research on rare diseases entails difficulties. For this reason the highest standards of quality should be required.

Funding and reimbursement for orphan drugs should be reviewed to ensure equitable access to drugs and long-term sustainability of the health care system.

References

1. Orphanet: una base de datos en línea de enfermedades raras y medicamentos huérfanos. Copyright, INSERM 1997. Último acceso (4 dic 2014).

2. Reglamento (CE) nº 141/2000 del Parlamento Europeo y del Consejo, de 16 de diciembre de 1999, sobre medicamentos huérfanos. DO L 18 de 22 .1.2000, p. 1 -5.

3. Register of designated Orphan Medicinal Products (alphabetical). European Commission. DG Health & Consumers. Public Health. (Accessed 5/12/2014)

4. CHMP. Guideline on procedures for the granting of a marketing authorisation under exceptional circumstances, pursuant to article 14 (8) of Regulation (EC) No 726/2004. London: European Medicines Agency; 2005 15 December. Report No.: EMEA/357981/2005.

5. Buckley BM. Clinical trials of orphan medicines. Lancet 2008;371:2051-5.

6. CHMP. Guideline on clinical trials in small populations. London: European Medicines Agency; 2006 27 July. Report No.: CHMP/EWP/83561/2005.

7. Dupont AG, Van Wilder PB. Access to orphan drugs despite poor quality of clinical evidence. Br J Clin Pharmacol 2011;71:488-96.

8. Kesselheim AS, Myers JA, Avorn J. Characteristics of clinical trials to support approval of orphan vs nonorphan drugs for cancer. JAMA 2011;305:2320-6.

9. Picavet E, Cassiman D, Hollak CE, Maertens JA, Simoens S. Clinical evidence for orphan medicinal products-a cause for concern? Orphanet J Rare Dis 2013;8:164.

10. Onakpoya IJ, Spencer EA, Thompson MJ, Heneghan CJ. Effectiveness, safety and costs of orphan drugs: an evidence-based review. BMJ Open 2015;5:e007199.

11. Picavet E, Cassiman D, Aertgeerts B, Simoens S. Development and validation of COMPASS: clinical evidence of orphan medicinal products - an assessment tool. Orphanet J Rare Dis 2013;8:157.

12. El Dib RP, Nascimento P, Pastores GM. Enzyme replacement therapy for Anderson-Fabry disease. Cochrane Database Syst Rev 2013;2:CD006663.

13. Reardon S. Regulators adopt more orphan drugs. Nature 2014;508:16-7.

14. Kumar Kakkar A, Dahiya N. The evolving drug development landscape: from blockbusters to niche busters in the orphan drug space. Drug Dev Res 2014;75:231-4.

15. Simoens S, Cassiman D, Dooms M, Picavet E. Orphan drugs for rare diseases: is it time to revisit their special market access status? Drugs 2012;72:1437-43.

16. Putzeist M, Mantel-Teeuwisse AK, Wied CC, Hoes AW, Leufkens HG, de Vrueh RL. Drug development for exceptionally rare metabolic diseases: challenging but not impossible. Orphanet J Rare Dis 2013;8:179.

17. Cote A, Keating B. What is wrong with orphan drug policies? Value Health 2012;15:1185-91.

18. Pilot project on adaptive licensing. London: European Medicines Agency; 2014 19 March. Report No.: EMA/254350/2012.

19. O'Sullivan BP, Orenstein DM, Milla CE. Pricing for orphan drugs: will the market bear what society cannot? JAMA 2013; 310:1343-4.

20. McCabe C, Claxton K, Tsuchiya A. Orphan drugs and the NHS: should we value rarity? BMJ 2005;331:1016-9.

21. Drummond M, Towse A. Orphan drugs policies: a suitable case for treatment. Eur J Health Econ 2014;15:335-40.

22. Nicholl DJ, Hilton-Jones D, Palace J, et al. Open letter to prime minister David Cameron and health secretary Andrew Lansley. BMJ 2010;341:c6466.

23. Hughes-Wilson W, Palma A, Schuurman A, Simoens S. Paying for the Orphan Drug System: break or bend? Is it time for a new evaluation system for payers in Europe to take account of new rare disease treatments? Orphanet J Rare Dis 2012;7:74.

24. Simoens S. Pricing and reimbursement of orphan drugs: the need for more transparency. Orphanet J Rare Dis 2011;6:42.

25. Knutsen RM. Rare Diseases. Med Mark Media 2015 Feb:38-40.

26. Reducing the cost of rare disease drugs. Lancet 2015; 385:746.

27. Abellan JM, Navarro JA. Utilización de AVAC en diferentes situaciones clínicas. Sevilla: Agencia de Evaluación de Tecnologías Sanitarias de Andalucía; 2011.

28. Fellows GK, Hollis A. Funding innovation for treatment for rare diseases: adopting a cost-based yardstick approach. Orphanet J Rare Dis 2013;8:180.

29. MoCA-OMP. Transparent value framework: European Commission; 2014 19 November. Report No.: Ares(2014)3857202.

30. Estrategia en Enfermedades Raras del Sistema Nacional de Salud. Madrid: Ministerio de Sanidad, Servicios Sociales e Igualdad; 2014.

31. Informe de Seguimiento de la Estrategia en Enfermedades Raras del Sistema Nacional de Salud. Madrid: Ministerio de Sanidad, Servicios Sociales e Igualdad; 2013.

32. Campillo-Artero C, del Llano J, Poveda JL. Contratos de riesgo compartido, ¿con medicamentos huérfanos? Farm Hosp 2012;36:455-63.

33. Luzzatto L, Hollak CE, Cox TM, et al. Rare diseases and effective treatments: are we delivering? Lancet 2015;385:750-2.

34. ORDEN FORAL 69/2013, de 19 de junio, de la Consejera de Salud, por la que se crea y regula el Registro Poblacional de Enfermedades Raras de Navarra.

Servicio Navarro de Salud
Osasunbidea

ISSN
1138-1043

COPYRIGHT
NA-1263/1997

INFORMATION AND SUSCRIPTION
Servicio Navarro de Salud / Osasunbidea
Plaza de la Paz, s/n
31002 Pamplona
T 848429047
F 848429010

E-mail
farmacia.atprimaria@cfnavarra.es

Web site
www.dtb.navarra.es