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PRESENTATION

Nothing has contributed more to the well-being of humanity than medicines. Even at the simplest level, we find it difficult to imagine the agony of toothache before the invention of painkillers.

In Europe at the start of the 21st century, we take it for granted that everyone should have more or less immediate access to the latest advances in medicine. Only rarely do we think about the economic resources required to deliver this service. However, the continuous introduction of new and increasingly expensive medicines, together with an ageing population which consumes more and more health resources for a longer period of time means that we are forced to consider the best way of distributing resources which are inevitably limited. This must address not only medical, economic, legislative and administrative issues, but also ethical ones, such as those related to the equity of resource distribution and the role played by the patient in the decision-making process.

Not only do medicines account for a significant portion of health expenditure, but they are the element of health spending which has grown most rapidly in recent years, a trend which seems unlikely to change significantly in the near future.

It seems reasonable, then, that any consideration of how to allocate health resources appropriately should pay close attention to that element of health expenditure which has risen most.

The concept of the "rational use of medicines" has been defined precisely by the WHO. However, it has been used as an umbrella term for a range of measures designed to ensure that the financial resources to fund medicines are allocated in such a way as to deliver the greatest possibles gains in health and well-being for the population.

Although the term may seem slightly unfortunate (appearing to suggest an irrational use of medicines, without establishing what this might be) it encourages us to use the best knowledge available to us at the moment of

taking decisions related to the authorization, prescription and dispensing of medicines. Taking what is arguably an overly reductionist approach, the tendency has been to consider the rational use of medicines primarily within the framework of evidence-based medicine.

By exploring the ethical issues, we hope to broaden the focus of a discussion which has tended to be extremely technical, making it the exclusive preserve of experts. This can obscure the fact that we are simply analysing such basic issues as the allocation of resources or, more specifically, withholding a health product or service from a part of the population when resources are limited, breaking down the various factors which must be taken into account when reaching such decisions.

Contributions from members of the discussion panel provide a range of complementary viewpoints, offering the reader a multidisciplinary perspective from which to draw his or her own conclusions.

Josep Lluis Segú
Chairman of Ediciones Doyma, S.L.

The rational use of medicines: ethical aspects

Juan Bigorra

Introduction

The expression "the rational use of medicines" is open to a wide range of interpretations. The World Health Organization (WHO) defines the rational use of medicines as requiring that patients receive medications which are appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and their community[1]. Interpretation depends on the individual point of view; for some, it means using the very latest (and potentially the most effective) medicines to treat any complaint or discomfort, while for others it means using those medicines with the lowest cost and for which the most extensive meta-analysis data is available, effectively excluding recently introduced medicines. An extreme interpretation, although unfortunately not an uncommon one, is that rational use of a medicine is use which complies with a fixed annual budget.

The perspective changes according to the expectations and needs of the people who research, market, distribute, prescribe, dispense, fund and consume the medicines. The decision as to which is the correct perspective is not an easy one, entailing the need to balance a range of interests: those of a sector which generates 520,000 jobs in Europe and which is largely responsible for funding biomedical research and the development of new treatments; the expectations of an ageing population which wants both increased life expectancy and a better quality of life; the desire of health professionals to retain the capacity to take decisions regarding the use of medicines; and the pressure of working within a health system which operates within a political framework and strives to satisfy growing demands on the basis of limited budgets.

In countries such as Spain, the use of medicines takes place in the context of an imperfect and highly regulated market where supply and demand are not directly linked. One might expect that the rational use of medicines would depend in large part on the existence of rational supply and demand, and on rational decision-making by the authorities, although this of course leaves open the question of exactly what we mean by the term "rational".

Supply of medicines: the pharmaceutical industry

Supply is conditioned primarily by the pharmaceutical industry, which researches, develops, manufactures and markets medicines, subject to strict requirements of efficacy, safety and quality. Approximately 90% of drug R&D is funded by the pharmaceutical industry, with the most developed countries – the United States, western Europe and Japan – accounting for around 88% of the global pharmaceutical market, as a result of which the tendency is for private sector pharmaceutical research to satisfy needs and expectations in these countries. In developed countries, conditions such as cardiovascular risk factors, psychiatric disorders, diabetes, asthma, bone and joint conditions, and cancer are the most lucrative in terms of return on investment. This is reflected in the R&D effort. While there are 361 projects researching lipids, and 195 projects looking at obesity, there are only 6 projects focusing on Chagas disease, and 24 projects dedicated to leishmaniasis, the majority of which are conducted in the academic sector or by small companies[2].

At present, according to the calculations of international health consultants IMS, the average R&D cost of bringing a new medicine to market is almost 600 million dollars. At the same time, average sales for a new drug are 200 million dollars after 11 years. In other words, many new medicines will never be profitable[3]. It is no surprise, then, that market forces play a major role in conditioning pharmaceutical R&D.

The number of new drugs brought to market has declined markedly over recent years as a result of rising costs and the increased complexity of pharmaceutical R&D. The United States' Food and Drug Administration (FDA) reviewed 60 drug approval applications in 1998, but only 30 in 2000. In Europe, the European Medicines Evaluation Agency (EMEA) received 58 applications during 2001 compared to only 31 in 2002[4]. This, together with the growing exposure of the industry's leading companies to generics, which will account for 69% of sales within the next 5 years, means that the pharmaceutical industry is at a crossroads which demands a radical change in a sec-

tor which must find a way of improving productivity in R&D and becoming more transparent not just in financial terms, something which it already does quite well, but in terms of its contribution to improving the health and well-being of society in general[5], if it wishes to gain the social backing which at present it lacks.

Interventions to regulate supply, particularly in Europe, have tended to focus on the introduction of further criteria, in addition to those of efficacy and safety, such as clinical effectiveness or comparative efficacy, economic effectiveness or budgetary impact. Other unwritten criteria which in practice operate to regulate the supply of medicines include budgetary compartmentalization, due to the separation of pharmaceutical expenditure from other areas of the health budget, with the result that the impact of medicines on other areas of the health budget (for example, by reducing hospital expenditure) is ignored[6]. While the time factor, where the fact that benefits of drugs often occur 10 or 15 years down the line (for example, in the treatment of risk factors) means that financial decisions may be taken on the basis of the immediate budgetary impact but without taking proper consideration of long-term health benefits.

Demand for medicines: health and market influences

From a health perspective, demand can be seen as the total global amount of illness expressed as millions of years of life lost, adjusted for incapacity. The scale is breathtaking. Illnesses such as respiratory infections, AIDS, diarrhoea, malaria and tuberculosis each account for more than 30 million years of life lost per year[7]. In some cases, this is demand which cannot be met under existing market conditions, although access to patented medicines for the poorest countries is under review as a result of the growing awareness of many, including the pharmaceutical industry, of the need to show greater solidarity with the most disadvantaged. In other cases, the problem has its roots in the problems which beset developing countries, such as the absence of physical infrastructure, military, social and political problems, and the lack of an adequate health and pharmaceutical policy. Many of the principal causes of mortality in the Third World could be eradicated by a policy of providing access to low cost generic drugs.

If we consider health demand in the developed world, this is conditioned not only by the impact of illness, but also by rising expectations both of life expectancy and of quality of life within the framework of a political system which promotes this aspiration. Evidence of this can be seen in any election campaign.

The clash between the efforts of the pharmaceutical industry to generate as much demand as possible, the introduction of new and increasingly expensive technologies, the expectations of patients, the massive expansion of the health system, as a corollary of which health professionals are able to dedicate less time to each individual patient, and the growing pressure on health system administrators, who are subject to budgetary restrictions which do not reflect demographic changes and rising demand, all mean that the use of medicines finds itself at the heart of a conflict involving health outcomes, iatrogenic effects and economic considerations.

In the face of this, some authors have proposed that the solution is to be found in the strict application of the criteria of evidence-based medicine, understood as the systematic and almost exclusive use of information derived from accessible random trials and the corresponding meta-analyses, when reaching decisions about clinical practice. However, the most extreme proponents of such an approach ignore four key issues: a) most of the information which enables us to reach the correct decision about any individual drug's role in the medical arsenal is obtained several years after it is brought to market; b) clinical trials and meta-analysis relate to a type of patient and conditions of use which generally differ from those found in normal clinical practice; c) the results of clinical trials are expressed in statistical terms and are not directly applicable to individual patients, as is empirically demonstrated by everyday clinical experience (something which we expect to be confirmed scientifically as we increase our knowledge of the genotypes and phenotypes which predict individual responses to drugs), and: d) Sackett's

original definition of evidence-based medicine has little in common with the dogmatic fixation with "clinical trials" and "meta-analysis", but rather means integrating the best available evidence with clinical experience, knowledge of physiology and disease and the patient's preferences when reaching decisions about individual patients[8].

Generating demand in industrialized countries

The main generators of demand are: political systems in Europe, which make the population aware of their right to unlimited access, free of charge, to almost the entire range of health services, without any real health education policy to accompany it and without any clear guidelines regarding the use of health resources by the population; demographic trends – an ageing population and a growing number of immigrants; and a health industry which pursues its own interest in expanding the "market".

Information and promotion activities may provide real value by increasing knowledge of illnesses and how to treat them[9]. However, the capacity of the promotional activities of pharmaceutical companies to modify prescription habits[10] and their tendency to distort the focus of scientific information for their own benefit[11] mean that we need to strengthen compliance with codes of good practice in drug promotion. A controversial issue concerns information and marketing aimed at patients. Although critics argue that this raises the threat of the medicalization of society, rising costs and a greater risk of negative impact of medical intervention, there is an increasing demand for patients to be provided with the information they need in order to participate actively in the prescription process[12]. The time has come when we need to take a more mature approach to patient participation, as part of a genuine debate concerning the hidden rationing of health resources. Claire Rayner, President of the Patients' Association in the United Kingdom, has argued that what really hurts is that this rationing is being conducted with so much secretiveness and with such a focus on elderly patients[13]. Some go further and argue that age based rationing should be illegal[14]. It is worrying to consider what could happen in Spain if there is not a constructive debate about the future of health provision in the context of an ageing population, and medicines clearly need to be included in this debate. Having accepted the need for measures such as better information and education about medicines, and promoting the use of generics, there would appear to be three options: slowing the speed with which new therapeutic advances are adopted; introducing higher levels of co-payment by users; or increasing the percentage of public resources allocated to health in general and to the provision of medicines in particular.

Some proposals to make supply more rational

1. *Redesign pharmaceutical R&D.* Pharmacogenetics, genome studies and proteomics open up new prospects for far more precise research in the design of drugs which are more accurately targeted to meet the needs of individual patients. At the same time, the traditional focus on clinical development to demonstrate efficacy and safety should be complemented by more pragmatic studies designed to assess clinical effectiveness, impact on patients' quality of life and economic effectiveness, as far as possible prior to marketing, to facilitate more informed decision-making with regard to the evaluation and adoption of new technologies[15].
2. *Improving post-marketing evaluation.* Public interest is best served when there is a wide range of options, together with the information which makes it possible to determine which option is best for each specific situation. As a result, rather than concentrating on measures which restrict the range of therapeutic options, regulatory agencies and the industry should focus on developing programmes to promote the most effective possible use of available options, taking into account not just criteria of efficacy, effectiveness and safety, but also compliance and pharmacological interactions[16].
3. *Rationalizing public funding criteria.* This should be done in a transparent manner, which is consistent with the values, principles and laws of each

society, allowing opportunities for new technologies in order to evaluate their effectiveness during the post-marketing stage. We need to provide sufficient resources to fund innovation through a firm policy on generics.

4. *Define a framework for collaboration between civil society and the pharmaceutical industry*, including cooperation projects with developing countries, research into orphan diseases, investigation of health outcomes, and studies of the efficiency of health systems.

Some proposals to make demand more rational

1. *Objective analysis of the development of health demand.* This requires detailed study of epidemiology, demographic trends and the impact of the adoption of new technologies.
2. *Return to Sackett's original definition of evidence-based medicine (avoiding dogmatism)*: managing evidence but also drawing on the knowledge arising from clinical practice, giving it objective value through the rigorous application of observational methods to evaluate the health results obtained using medicines[17-19], incorporating the preferences of patients who are informed and wish to participate in their health care through a shared decision-making model[20].
3. *Require ethical promotion*, through the rigorous application of a code of good practice in the promotion of medicines, and by encouraging research and continuing medical training.
4. *Undergraduate and postgraduate education, and continuing professional development*. Improving the training of those working both in clinical pharmacology and in health care, and raising the standards of materials used by the industry to promote their products.

Finally, it is important to stress the need to make progress in this area, because the choice is clear: rational use or rationing. And the risk is that "rationing" will be applied at the expense of those groups with little or no social influence, and will restrict innovation, weakening the capacity of the industry to continue investing 17 to 20% of its sales income in R&D, something which would do no favours to the millions of patients suffering from diseases which are currently untreatable.

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The rational use of medicines: ethical aspects

Xavier Carné

Treatment as an art

The art of treatment is indissolubly linked to the medical act, and is as old as humanity itself. Although the first therapeutic remedies may have been stumbled upon by chance, in primitive medicine there are at least three ways of understanding and practising treatment: spontaneous help, magical cures and empiricism. In many ancient cultures, treatment is a magical-religious activity which also contains some empirical elements. From a very early stage, then, the magical (or irrational) element has coexisted alongside the experience-based (or rational) one.

In the mid-20th century, with the explicit formulation of the controlled clinical trial method by Sir Austin Bradford Hill, there was a major advance from medicine based on uncritical empiricism to one based on scientific evaluation. This important step had a major impact on pharmacology. The method described by Bradford Hill has three key features: a) the existence of a group with which to compare the effect being studied; b) the random allocation of the population to the different study options, so that study groups are comparable; and c) the use of masking techniques to prevent bias in the evaluation of study variables.

Since the Second World War, the number of new drugs available has risen steadily. Together with a range of other scientific-technical, economic and social factors, they have made a massive contribution to improving the quality of life and increasing life expectancy in the west.

Clinical pharmacology as a specialist discipline has its origin in the 1960s, as a response to the thalidomide disaster and with the explicit support of the World Health Organization (WHO). During this period, thanks to progress in chemical synthesis, the pharmaceutical industry produced a huge range of new drugs, whose effects on humans (both beneficial and adverse) had to be evaluated scientifically. One of the fundamental operating objectives of the disciple is, precisely, to promote the rational use of medicines at every stage of the treatment process.

The shift towards rationalism in health care culminated during the 1990s with the popularization of meta-analysis as a method upon which to base therapeutic decisions, and with the triumph of the approach originally formulated by David Sackett and known as "evidence-based medicine" (EBM)[1]. This movement advocates that all therapeutic decisions should be based on "evidence" or "scientific proof", clinical trials and other methods which quantify the risk-benefit balance of pharmacological interventions.

EBM represents the culmination of the rationalist creed in which we find ourselves immersed. However, the importance ascribed to the results of a clinical trial and the decision as to the quality of these results are not intrinsic to the data but rather a consequence of how we understand and evaluate them. This is why EBM should be seen as a necessary but not a sufficient condition of establishing a specific course of treatment for any given patient. The vast range of clinical options, together with the fragmented nature and uneven quality of the information available with regard to many conditions, is a basis for caution before recommending, far less imposing, the application of a specific set of clinical guidelines[2].

In some contexts, EBM resembles a sect, with its own priests and liturgy, in response to which its first organized opponents have appeared. These included the self-titled Clinicians for the Restoration of Autonomous Practice (CRAP). This group, which has remained underground so far to protect itself from "retaliation from grand inquisitors in the new religion of EBM", recently announced itself in an article laced with English humour published in the *British Medical Journal*[3]. In it, the 'crappies' challenge the gurus of EBM with their own weapons: they demand proof, based on clinical trials and meta-analysis, that the EBM movement has done more good than harm to the cause.

Today's pharmaceutical market

Faced with a pharmaceutical market which is flooded with molecules, the vast majority of which are mere repetitions of others, the WHO has argued that the selection of essential medicines (325, in its twelfth version) is one of the most cost-effective ways of improving health access across the globe, both

in the developed world and in developing countries. The 2002 version of the model formulary proposed by the WHO starts with a chapter titled "Rational approach to therapeutics"[4]. In it, the authors argue that, "medicines should only be prescribed when necessary and, in all cases, the benefits of administration are considered in relation to the risks involved"[4].

At the start of the 21st century, we are still a very long way from the globalization of human rights. The "nutrition-medicines-vaccines-health" axis, together with the pairings of "education-culture" and "housing-infrastructure" (drinking water, sewage system, transport or energy) constitute the three fundamental axes on which the rights of human beings should be based. In all three areas, the differences between the northern and southern hemispheres are vast and continue to grow.

At least on paper, medicines, together with vaccines, are one of the most widely available and easily accessible health interventions. In developing countries, pharmaceutical expenditure accounts for no less than 40% of the health budget[3]. However, over half of the population of Africa, for example, has no access at all to medicines or any other health service.

The responsibility of the pharmaceutical industry

Meanwhile, in Europe we live in an advanced capitalist society which sees medicines both as one of the key tools for achieving health and, at the same time, as a consumer good. European social security systems have put medicines within the reach of all citizens.

The pharmaceutical industry is a very powerful one which should be considered both as "high risk" and as "high benefit". Bringing a new drug to market may require 10 to 15 years of R&D, together with investments of 500 to 600 million euros, in order to obtain patent rights which have a limited lifetime[5]. This is, then, an economic area which is in constant flux, and where the laws of the market are combined with high levels of state intervention.

The market for medicines is, without doubt, an unusual one. The State defines the rules governing the authorization, registration and pricing of medicines, together with the general conditions of use by users. At the same time, the State, through its social security and public health systems, is responsible for a very significant proportion of expenditure on medicines by citizens. To a large extent, with the significant exception of over-the-counter medicines, it is not the patient or service user but rather the prescribing doctor who decides upon consumption, sometimes in collaboration with the dispensing pharmacist. The pharmaceutical industry expends far more time and resources in generating and disseminating medical information relating to its interests than on producing medicines[6]. It is not, then, a context in which the rules of the market operate freely and without interference.

This is the model which currently exists in Europe. In the United States, however, it is much closer to the classic supply and demand model. Health in the USA is, above all, the concern of the individual citizen, who has the task of arranging affairs so that he or she has suitable health cover.

While subtle, the differences between the USA and Europe can be seen in the operation of the registration authorities. Both in the United States and in Europe, a new medicine is authorized so long as it satisfies the three basic requirements of quality, safety and efficacy. However, while for the Food and Drug Administration (FDA) "efficacy" means "superiority compared to placebo", for the European Medicines Evaluation Agency (EMEA), the efficacy of a new product in a specific indication must always be evaluated in comparison to one of its competitors. Study of the efficiency or cost effectiveness of new drugs is left for post-marketing phases and, in the first instance, these are not considered by the regulators.

The liberal philosophy underlying the North American model implies that, once the criteria of quality and safety have been met, it is the market which will determine the utility of any given product and the role it will ultimately play in the treatment of any specific condition. And, as we know all too well, the market does not always obey the laws of logic.

Although the European Union system was designed to ensure that decisions about the registration of a medicine should be independent of decisions

about funding its use, in practice the small differences in the behaviour of the registration authorities on either side of the Atlantic are a reflection of the dual role assigned to the state in Europe: that of guaranteeing the properties of the new medicine, on the one hand, and that of financing its use, on the other, in contrast to the US model of the "minimal state". However, and despite these differences, it can be argued that neither in the United States nor in Europe are the regulatory agencies strong enough to successfully resist the commercial interests of the powerful pharmaceutical industry[7].

Improving rationality in the consumption of medicines

Silvio Garattini has demonstrated that, of the antineoplastic chemotherapies introduced in the European market between 1995 and 2000, the advantages of the new products when compared to the older alternatives are at best slight, and at worst non-existent. The costs, however, are far, far higher[8]. This finding is probably valid in any other area of therapeutics. Nor is it generally possible, in terms of cost-effectiveness, to justify the fashion for developing and marketing enantiomers after the patent for the original form of the drug has expired.

With the development of products based on biotechnology, pharmaceutical expenditure has risen to levels which not even the most optimistic believe to be sustainable for the welfare state in the medium term. If we wish the health care system to remain viable, we will have to reform it dramatically, starting by making it more rational.

However, making our use of medicines more rational is not something we can achieve without also achieving significant change to habits relating to the use and consumption of many other goods. It is the consumer society we have all constructed which is profoundly irrational. The waste of energy or water in large cities in the industrialized world, the dominance of private transport (manufacturing ever faster cars for ever more crowded roads), or the consumerist binge of the Christmas season in large shopping centres are just some of the many examples one could cite. It seems that, as human beings who are not just rational but also emotional and driven by passions, we are unable to limit ourselves and put an end to so much waste.

Throughout the western world (both in the United States and in Europe) there has been a significant rise in so-called "alternative or complementary medicines", natural medicines, homeopathy, Bach flowers and a whole range of other options based on an uncritical empiricism[9]. Although the rational bases for these different systems are intrinsically contradictory, they are often presented as if, taken together, they constituted a valid homogeneous alternative to the failures of the all-powerful technology of conventional medicine.

Ignoring what happens in the south, for those of us in the north it is difficult to accept that the technology at our disposal cannot provide us with immortality, that there are some ailments which are beyond the reach even of modern therapeutics. In response, just like people did in times long past, we turn to magic and irrationality.

In a world divided between a north obsessed by consumption, and a south whose main purpose is simply to survive, we return to our starting point: that therapeutics continues to be an art which seeks to maintain a precarious balance between magic and rationality. In the meantime, some of us, whether operating within the discipline of clinical pharmacology or elsewhere, continue to strive for a more rational therapeutics.

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Discussion session

Following the papers by Dr Bigorra and Dr Carné, there was a discussion session chaired by Dr Josep Lluís Segú, Managing Director of *Ediciones Doyma* and Chairman of *Medimedia Ibérica*.

At the suggestion of the chair, the contributions to the debate were structured as follows:

1. Definition of the concept of rational use of medicines.
2. Analysis of supply.
   - Current supply of medicines.
   - Introduction of new products.
   - Funding supply.
3. Analysis of demand.
   - Demographic variables.
   - Access to information (information, training, advertising).
   - Expectations of the population.
   - Development of new technologies.
4. Political aspects of the rational use of medicines.
5. Evidence-based medicine as a paradigm for evaluating the use of medicines.
6. Proposals for improvement.
7. Outlook for the future.
   - Influence of genetics on the development of medicines.
   - Impact of patient empowerment on the rational use of medicines.
   - Effect of new data collection and processing technologies on daily decision-making.

After the individual contributions, each of the participants summed up the proposals and conclusions shown below.

Proposals and conclusions

Josep Eladi Baños

"Rational use necessarily involves improving the training of health professionals with respect to the scientific aspects of medicines."

Analysis of supply

A key issue when considering rational use relates to how medicines are funded. This is essential when deciding what definition of rational use to apply. In other words, above and beyond any statement of good intentions, is the health administration concerned about the cost of medicines if these are ultimately funded by private health companies or individual patients?

The problem of funding is a major issue for one of the key players in the system, the health administration, which is involved both in authorization and funding. In addition, the administration is responsible for supervising the correct use of medicines by health professionals, but its interventions in the past have usually been motivated more by the desire to reduce pharmaceutical expenditure than by the wish to improve the range of medicines on offer. However, in Spain it is also important to note the efforts made during the late 1970s and early 1980s, as part of the transition from the Franco period to democracy, to remove from the pharmaceutical market a vast number of products which contained amphetamines, combinations of antibiotics or products with an unacceptable risk:benefit ratio. In addition to this 'clean-up' operation, recent years have seen an overriding concern with the cost of expenditure, with far less emphasis on the quality of prescription, a somewhat paradoxical situation. It is hard not to see the funny side when those who are responsible for authorizing the price of a medicine and whether to include it in the National Health System subsequently complain of the resulting cost.

Another, more logical second consequence of how medicines are paid for relates to their direct use by patients. If patients pay for medicines out of their own pocket, the problem of rational use appears to become less central; in fact,

quite the opposite is true. Self-medication involves the use of medicines without medical supervision (despite the warning to "consult your doctor or pharmacist"). This recommendation almost always falls on deaf ears, due to the fact that patients generally use drugs with which they are already familiar, and whose properties they believe they understand. This is an important point to take into account when designing educational policies to promote rational use.

Proposals for improvement

Rational use necessarily involves improving the training of health professionals with respect to the scientific aspects of medicines. This seems to me to be beyond question: a decision can only be taken freely when it is also an informed one. Another question is who should be responsible for providing this information, and I would like to discuss this matter in a little more detail.

Traditionally, the health administration is held to be responsible for providing information about medicines to health professionals. In favour of this position, it has been argued that we need to counteract the flow of information which reaches health professionals from the pharmaceutical industry, generally biased in favour of the medicines it produces. This line of argument is disingenuous because it confuses two quite separate problems, and ignores a range of situations which need to be addressed individually.

It is legitimate for the pharmaceutical industry to inform about the products it wishes to sell, and it is understandable that it should wish to do so in a way which coincides with its own interests. This recognition does not mean that information can be provided in any way whatsoever, and even less that it should be allowed to contain inaccurate claims about the benefits of products or hiding the problems deriving from their use. Where this happens, there is sufficient legislation to prevent it; if, in addition, promotional activities are conducted in an appropriate manner, the industry also has an ethical code to regulate this. None of this, of course, means that the information provided by the pharmaceutical industry should be treated as the sole basis upon which to take decisions when prescribing medicines.

Frequent references to the responsibility of the health administration to provide the information needed to ensure that health professionals use drugs in a rational manner take no account of the responsibility that such professionals have for their own training, and of their duty to exercise this responsibility in an independent manner. In other words, doctors cannot and should not forget the importance of the act of prescribing, and should seek for themselves all the information to help them to do so in the way which is most beneficial for their patients. There are plenty of ways of obtaining information without receiving it from the administration, and insisting on the role of the administration is therefore a paternalistic way of denying the capacity of health professionals to exercise both their right and their duty to be familiar with the medicines they are using. This sort of "pharmacological centralism" should be deemed totally unacceptable among those who are fully responsible for their decisions and who cannot claim they were "simply following orders" if they prescribe the wrong treatment.

Ramón Bayés

"Is it acceptable, rational and ethical that half of the research, manufacturing and commercial efforts of the pharmaceutical sector go to waste?"

Proposals for improvement

During the discussion, the question of "poor compliance with treatment" was raised on several occasions; where patients not enrolled in a clinical trial are concerned, this rate often ranges from 25 to 50%.

However good a medicine is, and however appropriate the decision to prescribe it, if the medicine is not used then it is no use at all. For practical purposes, it as as if it did not exist.

And, if a medicine is misused, as in the case of antibiotics or anti-retrovirals, the result can be to cause harm not just to the individual patient but to public health in general.

I therefore pose the following question. Is it acceptable, rational and ethical that half of the research, manufacturing and commercial efforts of the pharmaceutical sector go to waste?

Personally, it has always struck me as surprising that the pharmaceutical industry, which spends millions of euros researching and marketing new drugs, and the administration, which (at least in Spain) pays a large part of the health bill, have to date displayed so little interest, in terms of euros, in researching strategies for improving the currently unsatisfactory levels of compliance with treatment.

There are methods of administering and monitoring prescriptions which have demonstrated their efficacy in controlled studies in illnesses such as human immunodeficiency virus[1], in which complexity of treatment is combined with recommendation of a compliance rate of over 95% for an unlimited period of time. Why are such studies not extended to other illnesses and their results not applied to clinical practice?

Of course, interventions designed to improve compliance with treatment would have a cost in terms of training doctors in counselling skills, something which is not new in Spain[2], and we would have to spend more time talking to patients, or allocate more resources to hospital and primary care services, so that the care team would include a psychologist or a pharmacologist with a good knowledge of counselling strategies who, after diagnosis and the identification of treatment by the doctor, would analyse and resolve with the patient on a one-to-one basis the problems raised by adhering to the treatment.

By acting in this way, not only will we achieve better compliance, but we will also raise the satisfaction of service users[3] by increasing their participation in and understanding of the logic of treatment, and in all likelihood reducing people's need to search for alternative medicines of dubious efficacy. Creating an individual relationship between patients and health professionals generates Hawthorne and placebo effects in patients, and these could strengthen the perception of positive subjective effects, which are essential to quality of life.

It is true that this proposal, at least apparently, would make care more expensive but, emotional and ethical gains aside, it would also give rise to a genuine communication process which, even in purely financial terms, might well outweigh any additional expense by delivering improved compliance, less wasted medicines, less reduction of the therapeutic effect of the drugs used, higher user satisfaction, and an improved image for both pharmaceutical companies and the public health service.

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Margarita Boladeras

"In our country, we have a health system which provides universal service of high quality, but with major imbalances and contradictions."

As both Xavier Carné and Juan Bigorra explained very clearly in their presentations, the production and use of medicines are influenced by a wide range of factors, some of which are far from rational. It would be good to use this cross-disciplinary, multi-sector forum to debate the problems of planning research and cooperation between public institutions and private companies in R&D programmes and other activities which are controlled by the authorities.

A better understanding between the administration and the industry could be beneficial for everyone if they reached agreements which helped to harness the potential of the sector (while respecting the freedom of the different actors within it) and preventing the proliferation of products of the same type, the duplication of investments designed to achieve the same ends, etc. Is it possible to overcome the problems which habitually hinder dialogue between the pharmaceutical sector and the administration?

In our country, we have a health system which provides universal service of high quality, but with major imbalances and contradictions. The increase in health expenditure year after year is creating a situation which is unsustain-

able. Expenditure on medicines is one of the causes of this unsustainability and, as Dr Carné has explained, the development of new biotechnological products will only increase this further. Despite this, there is considerable dissatisfaction among health service users, as is shown by the growing popularity of alternative medicines.

With respect to demand, it has been argued that this is determined by the existence of need, coupled with the ability to pay. However, it should be noted that need may be subjective, and that information and advertising have a significant influence on the perception of need and the creation of expectations. Information may be designed to help people and improve their quality of life, but it may also be an instrument of propaganda which distorts reality. Users are very sensitive to health-related messages and are easily influenced by them. This is particularly important, and it should be remembered that manipulating human feelings in this way can have irreparable consequences. It is therefore essential to ensure that the supply of information is governed by ethical principles.

Abusing people's trust creates a lack of confidence which is very difficult to rebuild. Good information should be designed to achieve just the opposite: increasing knowledge, clarifying what can and can't be expected, limiting expectations, promoting appropriate use.

Of course, it is not only service users who need information and training; health professionals and dispensing pharmacists also need them. The continuing professional development of professionals has become increasingly important in a context where the rate of change continues to increase. Here, again, I wonder whether it might be possible to make better and more coordinated use of the resources deployed in creating and disseminating information.

We often talk of freedom of choice, but it is easy to forget that one can only ask for something if one is aware of its existence, and that it is impossible to prevent unknown risks. Freedom of action can only occur in a context where the individual has the capacity to take decisions, is capable of distinguishing between different options, and is aware of their consequences. Providing information about different treatment options and the benefits and risks associated with specific medicines is one of the fundamental duties which doctors have to their patients, but it often does not occur (many of the problems arising from the failure to take medicines correctly could be prevented by better information).

Good communication, whether between doctor and patients, between drug companies and the users of their products, or between the health authorities and their staff, is one of the most basic ethical obligations.

Joaquim Bonal

"The rational use of medicines is not the same thing as reducing financial expenditure on medicines."

Definition of the concept of rational use of medicines

I agree with the definition of the World Health Organization.

Analysis of supply

When registering new medicines, in addition to efficacy and safety, the concept of comparative efficacy should be included. For new drugs, it should be required to show that these are superior to those which already exist.

The funding of medicines should be dependent on the comparative efficacy of new drugs, and society should be tougher on the pharmaceutical industry. Drug research should not be the exclusive responsibility of the industry, the state and supranational bodies such as the European Union. Public bodies should establish research programmes in collaboration with universities and not-for-profit organizations, and also with the industry in fields of particular interest for public health.

Analysis of demand

Demand should be defined in terms of ability to pay, not in terms of 'need', a concept which is very subjective. The pharmaceutical industry is not an

appropriate source of information for the public; this responsibility should be met by health professionals – doctors, pharmacists, nurses etc.

There are studies which show that 20% of visits to hospital emergency services are due to problems relating to medicines, and that over 60% of these problems are preventable.

In Spain there are over 20,000 pharmacies which are not used by the health system as agents to improve the use of medicines and to provide counselling to users. The recent "pharmaceutical care" movement among pharmacists is indicative of the desire among this group to assume greater responsibility within the health system, working more closely with other professionals and with doctors in particular.

Political aspects of the rational use of medicines

We need to be clear that the rational use of medicines is not the same thing as reducing financial expenditure on medicines. These concepts are frequently conflated in the political sphere.

The use of medicines is far from rational; prescription decisions are heavily influenced by the marketing activities of the industry and, at times, by pressure from patients and the health authorities. In the case of medicines available without prescription, use is influenced by advertising, and little weight is given to the advice of dispensing pharmacists.

The pharmaceutical industry is driven by the need to generate financial profit; we cannot, therefore, expect the industry to promote rational use.

Another serious problem derives from the fact that over half of the world population has no access to medicines, a major political problem which must be addressed at an international scale. We urgently need to search for imaginative solutions which enable us to "share" scientific progress across the world. The developed countries must take responsibility for this and show solidarity with the developing world.

Xavier Bonfill

"Evidence-based medicine has a key role to play in the information process."

Pharmacological provision offered by the health service should be based on the best scientific evidence, within the relevant social framework. This requires the necessary information to have been generated through well-designed and relevant studies; this information, once analysed, synthesized and protocolized, must be readily available; health professionals must be familiar with it or able to consult and interpret it correctly; the patient's preferences must be known and incorporated into the decision-making process; whatever clinical decision is finally taken must be viable and applied correctly; and there must be final evaluation to provide feedback.

The methodology required to underpin this has been called evidence-based medicine. If it is applied rigorously, sensibly, flexibly and under the right conditions, it can be very useful for health professionals and patients alike. If it is distorted, either by being understood in a dogmatic way or as the result of very subjective or partial criticisms, then its impact will be negligible.

Victòria Camps

"Rationality in the research and manufacture of medicines should be measured in terms of benefits which are not purely economic."

Definition and concept

The concept of rationality can be understood in a number of ways. It is not clear exactly what "rational use" means. It depends on who is doing the using. If the user is the patient, then rationality will be prescribed, in principle, by his or her doctor. If the user is the doctor, then the rationality of the use of the medicines prescribed to the patient will be measured in terms of efficacy and safety, values which in principle are vouchsafed for by the fact that the medicine has been validated. We know, however, that the research and manufacture of medicines are also designed to achieve another objective, to generate economic profit. The question might be, then, whether it is

rational to seek this objective. The pharmaceutical industry must pursue the objective of maximizing its benefits, just like any other industry. However, a medicine is not just any product. Rationality in the research and manufacture of medicines should be measured in terms of benefits which are not purely economic. Economists have accustomed us to the notion that demand always stimulates supply. However, the opposite is also true: supply always generates demand. In a consumer society, people's needs grow in response to the supply the market offers. And medicines are not immune to this process. Supply, even if it is superfluous, generates demand, particularly if it is accompanied by effective advertising campaigns. Use, then, depends on supply. And if this, or the production which creates it, is not rational then the use itself cannot be rational either.

Philosophers have drawn a distinction between two meanings of rationality: means rationality and end rationality. The first consists of a search for the means of achieving a set of pre-established goals which, in principle, are not questioned. If the aim of the industry is to make money, then means rationality consists of providing the best means of doing so. Ends rationality, by contrast, evaluates the end goals. I do not believe it makes sense to talk of a "rational use" of a medicine if we do not also consider the end goal and the entire process, not just the act of medical prescription or of consumption by the patient. Put another way, it is impossible to avoid the most fundamental question. Is the production of medicines rational? Is this production performed for a rational end, that of ensuring the fundamental right to healthcare?

When we are speaking of a basic right, like the right to health, it is impossible to separate rationality from need. The World Health Organization states that, "medicines should only be prescribed when necessary and, in all cases, the benefits of administration are considered in relation to the risks involved." But necessary for whom? It is impossible to satisfy all human needs. And we have already noted that these grow as market supply expands. When evaluating needs, we have no option but to make comparisons. I am not talking of Africa, where needs are unquestionably much more pressing than our own. Instead, I will limit myself to discussing Europe, and the "welfare state" model. Is this model sustainable in the context of dramatically expanding and potentially unlimited needs?

The concept of need is not one which can be studied empirically. We create our needs according to our values, and these are the same values which underpin our basic rights and the welfare state which was created to safeguard them. Basic needs, then, cannot be determined by the market dynamic of supply and demand or by corporate interests, but rather by the common interest which, in this case, should define: a) which sectors of the population, or conditions, are most in need of research and financial investment, and b) which pharmaceutical expenditure should be covered by the health budget. These definitions inevitably entail imposing limitations both on the pharmaceutical industry and on the wishes of consumers, bearing in mind that consumer demand reflects both market influences and the influences of the health system which prescribes drugs.

Joan Costa i Pagès

"The patient, as an active participant in the health process, receives disproportionate and at times misleading information which generates false hopes and increases demands on the prescriber."

Definition of the concept of rational use of medicines

The term "rational use of medicines" generates serious doubts when it is used in a partisan or one-sided manner from one side or other of the medical scenario. Regulators sometimes abuse the term, as does the pharmaceutical industry from a promotional perspective. The prescriber may be pulled in one or the other direction depending on the more or less scientifically well-founded arguments put forward.

Analysis of supply

Supply is conditioned both by scientific factors and also by political and economic ones. Only financial interests can explain the withdrawal and substitution of effective and relatively safe drugs and their replacement by

others with similar levels of efficacy and safety but which are far more expensive.

We must strike a balance between the need to introduce new products, fair profits for the pharmaceutical industry, and the sustainability of the health system. If the health system were to move towards sharing the costs of drugs with users, then users would need to have reasonable access to the drugs they need to maintain a level of health which is in accordance with the moral and ethical standards of our society.

The basis for the funding of supply should be separate from decisions about registration.

And we also need to build links so that the health needs of the population can generate demand for research which, with the support of the state, would enable pharmaceutical companies to generate products which directly reflect health needs.

Analysis of demand

Demand may be conditioned by the prescriber (doctor who has participated in trials which, while contributing to scientific knowledge, also encourage prescription and on occasions generate false hopes). In this regard, post-authorization studies (despite the legislation which accompanies them) run the risk of facilitating the dissemination of drugs.

The patient, as an increasingly active participant in the health process, receives disproportionate and at times misleading information which generates false hopes and increases demands on the prescriber. And the prescriber, on occasions, gives way to ill-founded requests from patients.

There is a culture of prescribing new drugs promoted by the commercial networks of the pharmaceutical industry, which, while contributing indirectly to professional development (an area where there is a lack of objective, independent information), also encourages the prescription of new products in preference to other more cost-effective options. It is, of course, logical that sales networks operate to promote those products with the highest profit margins for pharmaceutical companies.

We must distinguish between demand and need. We have to agree on how to define needs, and who is to define them. We have to resolve the political conflicts which mean that politicians are more responsive to demands than to needs. And we also have to resolve the contraction which arises from the fact that health systems focus not on health itself but rather on health services. As a result, the emphasis is on curative rather than preventive medicine.

Evidence-based medicine as a paradigm for evaluating the use of medicines

There are many doubts about whether evidence-based medicine provides a basis for taking genuinely scientific decisions. There is a danger that these decisions are open to manipulation or bias by other interests.

Proposals for improvement

- Searching for and promoting stable, independent, objective information sources, without underlying economic or political interests, something which is not easily done.
- Possibility of establishing codes of good practice with objective controls.
- Need to adapt the academic world to the real requirements of the outside world.
- Detailed study of the reasons behind the trend away from traditional medicine and its replacement by alternative therapies. Is it because these therapies offer better scientific guarantees than traditional medicine, or has traditional medicine forgotten the relational aspects which today's patients want to be addressed? Does scientific medicine take the wrong approach?
- We need to ensure that the need for sustainability does not mean that policies are based on financial considerations alone, and that there is space for the development of the qualitative aspects of health care.
- Rational use should involved the commitment of everyone involved in the use of medicines. We should be aware of potential conflicts of interests at every stage of the process of developing and using medicines.

Sergi Erill

"Perhaps it would be better to talk of the reasoned use of medicines."

Definition

It is important not to confuse rational use with use which follows the recommendations of the authorities, even if these recommendations are based (or are meant to be based) strictly on scientific data: in this case, clinical trials, meta-analysis etc.).

Perhaps it would be better to talk of the "reasoned" use of medicines. Many years ago, Louis Lasagna complained of "knee-jerk prescription", referring to prescription which had its origins in advertising material. It does not seem desirable to promote any type of "knee-jerk prescription", whatever the quality of the stimulus.

We should not ignore the "cost" element when seeking to define what we mean by rational use of medicines. Indeed, we should insist that the notion of "cost" goes beyond the strictly financial. For example, we should consider the cost to the patient, in terms of quality of life (something which has to be analysed in each individual case).

Analysis of supply

Perhaps we need to insist on the fact that actions provoke reactions, and that even behaviour which may seem reasonable and fair can bring unwanted consequences. For example, the price setting arrangement which exists in Spain would be seen by many to be an important and necessary measure, but we should also remember that as a result useful medicines such as sedating antihistamines, which are indicated as a nocturnal treatment for persistent pruritus, have virtually disappeared from the market (or the public health system).

Analysis of demand

The distinction between demand and need seems entirely correct, but we must be aware that there are many cases in which the limits between the two are not clear. What might be seen simply as a demand in the case of ordinary acne, can constitute a genuine need in the case of the disfiguring acne suffered by some young people.

Evidence-based medicine as a paradigm

While I am in absolute agreement with the principles which inspire evidence-based medicine, I think it is important to stress that this should be a philosophy, not a religion, and I am concerned at its potential use as an instrument of power.

Jordi Faus

"Today's patients demand more information about their condition, the medical and pharmacological treatment options available, and the treatment which is finally chosen."

Definition and concept

Unfortunately, when defining a term in a legal document (regulations, contracts etc.) the intention is to regulate rather than to define.

In defining the meaning of rational use, I propose remaining within the original limits of the term, in accordance with which rational use means effective and safe use. This meaning retains significant ethical content, quite separately from the economic considerations linked to the sustainability of the social protection system in Europe. As I will explain below, the sustainability of the system with respect to expenditure on medicines necessarily involves the efficient management of public resources and, in this regard, a rational approach to funding.

Analysis of supply

Medicines cannot be marketed without marketing authorization granted by a public body responsible for evaluating their quality, safety and efficacy. These three parameters are often talked of as the three barriers the drug must

overcome before accessing the market. Finally, there is the concept of a "fourth barrier", a term which has two meanings. Sometimes it is understood to mean that a medicine will not be authorized unless it demonstrates a qualitative comparative advantage, in terms of safety or efficacy, over existing products. But the term the "fourth barrier" is also used to refer to the notion that in order to be authorized the new product should present an advantage in terms of economic cost with respect to existing products.

In my opinion, the administrative process of evaluating drugs should be limited to the first three barriers. Requiring a fourth barrier (therapeutic advantage) strikes me as dangerous and contrary to the basic principles of our market economy (whoever was first to market would benefit from an unacceptable monopoly which would go further than the protection offered by the patent system). With respect to the notion of the fourth barrier as an instrument of budgetary control, I would argue that decisions regarding the technical evaluation of a product should be separated from purchase or funding decisions.

As respects the funding of the supply of medicines, I believe that the administration has sufficient regulatory instruments to perform its functions under the best conditions. Once a clear separation has been established between regulatory activity and funding, I am inclined to introduce into the discussion other elements related to the market dynamic, such as the effective evaluation of the advantages offered by a new product, so that purchasers can determine how much they are prepared to pay.

Analysis of demand

Today's patients demand more information about their condition, the medical and pharmacological treatment options available, and the treatment which is finally chosen. In this context, the current regulatory framework sets a series of limits on the communication of information to patients by drugs manufacturers. The manufacturers, however, are in the best position to provide information and to assume any legal responsibilities which would result if they disseminated misleading or inadequate information. We also need to recognize that new technologies enable patients to access uncontrolled information sources.

When considering which actions to take in order to satisfy the needs of society, we should not forget the patient who does not wish to be informed or the citizen who does not wish to become a patient.

With respect to the promotional activities of drug manufacturers aimed at health professionals with prescribing or dispensing responsibilities, there are already a number of laws which are designed to ensure the accuracy of the messages addressed to health professionals and a separation between prescription decisions and manufacturers' contacts with health professionals. We need to promote policies to ensure compliance with these laws, and we should also recognize the efforts made by the industry in adopting a new code of good practice and creating effective instruments to monitor and enforce it. The existence of effective standards and controls is, without doubt, a necessary condition of the rational promotion of medicines, but it is not a sufficient one. It is also necessary for everyone involved on the supply side of this market (the manufacturers) to accept the challenge of competing with one another on the basis of absolute respect for this legality, in the understanding that the medium and long term of the industry depend upon it. On the supply side (health professionals) it is important to stress that they also have an important role to play.

Proposals for improvement

- Insist on the separation between decisions about the technical evaluation of a medicine and economic decisions relating to funding.
- Improve the administrative environment in both regards: a) speed up procedures for the evaluation of medicines, and b) more efficient management of the public resources allocated to the funding of medicines. With respect to point b), I think it would be important to consider ways of making the prescription process more rational, combating illegal practices and fraud, and implementing co-payment mechanisms which transfer to consumers part of their responsibility in this area.
- Establish mechanisms enabling pharmaceutical companies to provide information about their products to those patients who wish to receive it.

- Monitor the Code of Good Practice for the Promotion of Medicines, and involve professionals with prescribing or dispensing responsibilities in its management.

Paloma Fernández Cano

"Health education and education about medicines are neglected subjects. Everyone talks about them, but to judge by initiatives in these areas, few people really believe in them."

Definition

Medicines are almost the only health technology whose rational use we discuss. Generally, we talk of the appropriate use of technologies, and I believe that this is a better approach, above all if we wish to emphasize the care quality aspect, in this case, pharmacotherapeutic quality.

In my opinion, the classical definition of rational use should incorporate two increasingly important aspects: a) it should make explicit that, when talking of clinical needs, we include the prevention aspect (primary care), the value of which is more and more clearly established and widely accepted; and b) it should include the role of the patient, which is decisive for successful pharmacotherapy. Under the current definition, the patient "receives the appropriate medication". One of the principal causes of therapeutic failure is, precisely, non-compliance, which is closely linked to a concept of treatment in which the patient "receives". It would be preferable for the definition to include something along the following lines: "… the patient, in consultation with his or her doctor and on the basis of sufficient information, decides to take the appropriate medication …".

Analysis of supply

When determining supply, the pharmaceutical industry, which is the supplier of the vast majority of medicines, behaves in a perfectly rational manner, in accordance with the incentives which exist in the market. If the rules about authorization and reimbursement established by the health authorities or by the funding bodies of different countries permit or facilitate the marketing of, for example, enantiomers of existing products, then some companies will develop enantiomers. By contrast, if there is no money available to pay for medicines to treat diseases in the Third World, then the industry will only develop such products on an occasional basis.

Even if we accept this logic, it does not appear to satisfy the medical needs of humanity, and therefore has to be complemented by measures which correct how the market operates.

I believe that, as citizens, we should pressurize governments into supporting research into medicines for the most prevalent diseases in developing countries, and for orphan and rare diseases, something they can do by modifying demand through measures to encourage the pharmaceutical industry to invest in these areas. An interesting recent initiative is the creation of global funds supplied by developed countries and administered by international bodies with the aim of researching diseases in the Third World.

From a health, economic and social perspective, it is desirable to have a wide range of medicines, making it possible to adjust medication to different patient populations, individual therapeutic responses and patient preferences. However, if the supply of medicines is to be truly sustainable then we also need to promote genuine price competition, encouraging funding on the basis of the therapeutic value of the medicine: that is, according to its effectiveness, safety, convenience for the patient or usefulness in specific populations.

Analysis of demand

Health education and education about medicines are neglected subjects. Everyone talks about them but, to judge by initiatives in these areas, few people really believe in them. Their scope means that they involve not just the doctor, who has very little time available for this task, but also a huge range of agents, starting with the education system as part of education for citizenship, and including health professionals, manufacturers and health authorities.

Recently, there has been intense debate as to whether it is desirable for the pharmaceutical industry to address patients directly by providing informa-

tion and through advertising, something which is perfectly legal in the United States. We cannot ignore the cultural gulf or differences between health systems when transferring the debate to Europe. However, we have to consider, first of all, the right of the patient to be informed and, secondly, patients' preferences, clearly expressed in surveys, that information should be pluralistic and should come from a range of sources. Logically, this includes the manufacturer, who is a very important source of information about its product, so long as the relevant codes are respected.

In a world in which there is a proliferation of junk information about health from obscure sources whose interests are difficult to identify, it seems paradoxical that the pharmaceutical industry should be denied this possibility, subject to the relevant controls. Many general information and awareness-raising campaigns promoted by the pharmaceutical industry have performed a very useful health role, and this effect could be repeated with individual patients. The key is in the quality of the information, its accuracy and balance, not the source.

A separate although related issue concerns the advertising of prescription drugs to the general population. In my opinion, this issue should be approached with great caution. Recently, the G10 Medicines group – a high-level group consisting of representatives of the European Commission, the member states, the pharmaceutical industry, patients associations and representatives of health insurers – has set out the need to make a practical distinction between information and advertising which reflects the European cultural and health environment.

Political and management aspects of the rational use of medicines

A surprising issue concerns the use of pharmaceutical expenditure figures in public debate. As Professor Ortún has pointed out, month after month the growth in pharmaceutical expenditure is linked with other macroeconomic figures, such as GDP growth or the unemployment rate. The emphasis on expenditure, which has increased since January 2002 when the process of transferring competency for health to regional government was completed, has unleashed competition between regions which threatens to swamp the genuine debate about whether expenditure has been deployed well, and whether the amount spent is enough or not.

Another surprising feature is the superficial analysis, at least in public debate, of pharmaceutical expenditure. Despite the powerful information management tools available to us, we only know the average expenditure per prescription and the number of prescriptions. There is no detailed analysis of the reasons behind these figures or of whether they represent an appropriate use of medicines or not. This situation becomes more surprising if we compare it, for example, with the information available about care activities in hospitals or primary care centres.

The process of setting drug budgets, which are based on past experience, with rises dictated by the availability of funds rather than by predictable variations in supply and demand, do not exactly contribute to better management. Again, it recalls old-fashioned hospital budgeting, which gave rise to continuous deficits which had to be paid off at regular intervals. From a management perspective, it is disheartening that the increases in preventive care activities envisaged in management contracts (for example, increased detection of high blood pressure) are not reflected by a corresponding increase in the pharmaceutical budget. And, in a similar tone, one could talk of the increase in the population being cared for or changes in supply (generics, patent expiries, new drugs).

Finally, and in contrast with the emphasis on expenditure, there is little interest anywhere, including among the pharmaceutical industry, in conducting studies into the quality of medicine use: there are few serious, rigorous studies of the appropriateness of prescriptions to indications, despite the fact that these would shed important light on whether the medicines used, and therefore the money spent, are correct. Nor are there sufficient studies of drug-related problems to identify both the magnitude and the causes of such problems, with the aim of taking measures to reduce them.

Proposals for improvement

In addition to addressing the points mentioned above, reducing the political tension which surrounds expenditure on drugs, without relinquishing con-

trol over it, would help to make progress towards more realistic budgeting. Some initiatives worth exploring include:

- Developing pilot plans for integrated disease management. There is extensive experience to show that the integrated management of a disease without interrupting the levels of care influences use of medicines, increasing the quality of care and reducing total health expenditure, even if pharmaceutical expenditure increases. It is worth exploring these ways of organizing care more enthusiastically.
- Developing more flexible approaches to budgeting and breaking down the barriers between different budget headings to promote the efficiency of the whole care process, instead of simply maximizing the efficiency of each individual part of the process.

Outlook for the future

An important way of improving the use of medicines is by using information and communication technologies, and tools to support clinical decision-making in particular. Shared, online use of the patient's electronic medical records, clinical practice guidelines and pharmacotherapeutic protocols by the doctor during consultation, together with databases of information about the dosage, interactions and incompatibilities of medicines will revolutionize care practice.

This connectivity may be one of the most far-reaching changes in terms of enabling the correct use of medicines. Several studies have shown that electronic tools to support clinical decision-making are the most effective means of achieving substantial, sustained changes in clinical practice, including the use of medicines. If to this we add electronic prescriptions, which should help to improve the dispensing process, in a few years we will have substantial improvements in the rational use of medicines.

Joan Gené Badia

"Evidence-based medicine and knowledge management techniques have been enormously useful in creating a methodology and language which is shared between managers, patients and clinicians."

In my role as someone who is responsible for the public provision of primary care services, my aim is to ensure that pharmaceutical prescription offers the best possible response to the health needs of the population being cared for. We understand that prescription is a component of the overall care process. At the Institut Català de la Salut (ICS) improving prescription occurs within the framework of a clinical management project which seeks to promote greater professional involvement in the management of care resources, the continuous improvement of processes, and the incorporation of scientific evidence to clinical practice.

With regard to prescription, we have developed three major initiatives: the Clinical Practice Guidelines, the Prescription Quality Standard and the New Medicines Evaluation Committee.

In 2001 we published the first two Clinical Practice Guidelines for the Primary Care Division: Hypercholesterolemia and Dyspepsia-H. pylori. These were followed by guidelines on high blood pressure, pressure sores, recommendations for the use of urinary incontinence pads and glycaemic control reagent strips.

In addition to the full-length version, all of these guidelines are also produced in a pocket format containing the key concepts, tables and decision-making algorithms to facilitate rapid consultation. We also publish an A4 version of advice for patients addressed to citizens, who can also access the other material via the ICS website (www.gencat.net/ics). Centres receive disks containing teaching material for use in sessions with primary care teams. We want to promote the dissemination and implementation of the content of these guidelines, using them to add value to the primary care process.

The Prescription Quality Standard is a series of indicators which establish the ideal prescription profile of a primary care doctor, on the basis of the inci-

dence and prevalence of the most common pathologies and the best scientific evidence about how to treat them. The standard is used both as a basis for establishing individual targets and for evaluating the quality of prescription of professionals, teams, services and areas. Achievement of standard recommendations rose by 9% in 2001 and by 10.2% in 2002.

The New Medicines Evaluation Committee reviews all the new drugs which appear on the market and issues an opinion on whether or not the new drug should replace the one being used for this indication. The report is distributed to all health professionals, and can also be accessed by members of the public via the internet (www.gencat.net/ics).

Managing the clinical performance of professionals in a large public organization is a complex task. One must always consider the scope of the impact of interventions not only on public health but also on public opinion. Such initiatives can only be successful if they employ a rigorous methodology and are conducted with complete transparency. Evidence-based medicine and knowledge management techniques have been enormously useful in creating a methodology and language which is shared between managers, patients and clinicians.

Javier López Iglesias

"A better informed patient, who understands the messages he or she receives, will be better placed to deal with and manage his or her illness."

Definition

Throughout the presentations, we have mentioned the name of Professor David Sackett, based at the University of Oxford, who is one of the leading developers of the concept of evidence-based medicine. In a talk he gave in Madrid, Professor Sackett, in an attempt to clarify the definition of the rational use of medicines, noted that the term was subject to different interpretations.

Perhaps it would be no bad idea if all definitions of the rational use of medicines were to include a note pointing out the potential for interpretation from at least three different perspectives: the political, the perspective of daily clinical practice and, last but by no means least, that of the patient. By representing different forms of demand and different interests, each of these three perspectives would undoubtedly enrich any final definition.

Proposals for improvement

As the only journalist taking part in this discussion, I have been asked to consider the relationship between the media and today's topics.

Education and information

Which comes first: education or information? This question has already been raised by some of the participants with reference to the relationship between education, information and patients. This is something of a "chicken or egg" question. That having been said, it is worth noting that, as regards a patient's competence with respect to his or her illness, information is an essential component of the education process.

Clarity of the message

With respect to the rational use of medicines, one issue to be raised has been the value and capacity of messages. We need to start from the simple notion that the importance of communication and information lies not in what the message says but in how it is understood. This concept is often forgotten by the health system, despite innumerable studies showing that a better informed patient, who understands the messages he or she receives, will be better placed to deal with and manage his or her illness.

It is not difficult to detect the lack of acceptance, by the system as a whole and by many of the professionals working within it, of the necessity and value of ensuring that its message is understood. Practically all professionals use a metalanguage which sets them apart from lay people, but this is very detrimental to the daily practice of medicine and pharmacy.

It results in poorly informed service users or patients who complain that health professionals are not interested in explaining things and wish, instead,

to retain a position of authority with respect to individuals who lack information and are therefore unable to participate actively in the decision-making process.

Responsibility of the communicator

It is clear that the responsibility for communication does not only involve health professionals. People working in the media also have a vital role to play. There are few areas of information, and few fields of journalism and the media, where specialization is more necessary. In order to achieve this specialization, communication professionals must be committed to continuing professional development. Information about medicines and their rational use is a clear case where such specialization is necessary, involving as it does complex information which demands extensive knowledge of those handling it. There is a direct and clear relationship between better training of those providing information and the quality of the information itself.

Two medicine-related examples should suffice to illustrate the harmful effects of ill-considered information. There are very clear examples, in recent history, of both extremes: social panic and the creation of false hopes.

Health information professionals need to accept that the audience for our information (readers, viewers, listeners, internet users etc.) need very clear and intelligible information, which steers away from conjecture and speculation, in order to avoid the problems noted above.

A final proposal or suggestion

Medicine, pharmacy and health science courses should include the topics of information and communication. It makes no sense for the education of professionals whose duties include communicating with and informing people not to cover the subjects and techniques which form the basis of successful communication and information.

Maria Antònia Mangues

"I agree with drawing a distinction between the rational use of medicines and rationing the use of medicines, with the risk which the second of these options inevitably entails."

Throughout the debate we have noted how the demand for health services in general and the demand for medicines in particular are growing relentlessly. We have also noted the challenge of ensuring the sustainability of European health systems, and the need to find formulas for creating sustainable models without sacrificing quality and justice.

In this context, I would like to focus on the action of prescribing. I will consider some of what I consider to be the most important aspects, while recognizing in advance that I can only offer a partial vision of the problems involved.

The prescriber's decisions are designed to ensure that the medicines chosen produce the best results in each of the patients treated.

However, there is solid evidence of a high degree of variability in prescription habits. The same pathology may be treated quite differently depending on the patient's point of entry to the health system, and some of these prescription habits are not backed by the best scientific evidence available. This is also applicable to other medical and surgical procedures, and it has been estimated that up to 25% of them are arrived at in a poorly reasoned manner.

Different pharmacotherapeutic approaches lead to different clinical outcomes, and in some cases do not deliver real health benefits, but instead compromise the quality of care while adding to health expenditure. Decisions regarding the prescription of medicines should be based on the best available information about the effectiveness, safety and cost of different therapeutic options. If authorities and prescribers accepted and adopted these cost-effective practices, we would improve the health benefits of medicines and use the available resources in the best possible way. It would also be useful if there were procedures for preventing the inappropriate use of medicines. The resources this would free up could be employed effectively, helping to improve both the efficiency and the fairness of the system.

A very positive experience in this regard has been the Pharmacy and Therapeutics Committees established in Spanish hospitals during the 1970s. Since their creation, they have focused on selecting medicines for inclusion in each centre's pharmacotherapeutic guide, with the selection process being based primarily on the best available scientific evidence. They have also been involved with protocolizing treatment, producing clinical practice guides, and monitoring the use of medicines. All of these activities have made a clear contribution to a more rational use of medicines. In the primary care context, where far larger volumes of medicines are prescribed and consumed, there have been a number of interesting initiatives designed to make the use of medicines more rational. However, they are far less widely implemented than in the hospital setting.

In my opinion, two actions which would help to improve the current situation would be, firstly, to promote the training of health professionals, and secondly, to "invest" in the health education of the general population.

Health professionals often find themselves overwhelmed by an avalanche of information, and it becomes increasingly difficult to ensure that the information from research is transferred to the professional knowledge base, a process which is indispensable if it is to play a role in decisions about care.

Updating scientific knowledge and making it available through continuing professional development programmes provides a scientific basis for prescription decisions, and other care decisions.

The lack of such training programmes is currently covered, at least in part, by the pharmaceutical industry, which uses them to its own benefit, using marketing practices which have been shown to have a direct influence on prescription habits. In this respect, rigorous compliance with good practice codes for the promotion of medicines would constitute a major improvement to the current situation. However, as health professionals we should not delegate to the pharmaceutical industry something so fundamental to our professional practice as the training programmes designed to ensure that our knowledge remains up to date.

Finally, the patient has had very little say in decision-making. Instead, somebody else has assessed his or her state of health and decided upon treatment.

In general, patients are not sufficiently informed while, at the same time, they consider that they are entitled to unlimited access, more or less free of charge to all health services. These two factors do not exactly help the public make sensible use of health resources based on shared decision-making.

I agree with the distinction drawn by Dr Bigorra between the rational use of medicines and rationing the use of medicines, with the risk which the second of these options inevitably entails.

Vicente Ortún Rubio

"The concept of need is difficult to define. We can talk of technical need (clinical, epidemiological etc.), felt need, expressed need, comparative need, etc."

I heartily agree with the presentations by Dr Xavier Carné and Dr Juan Bigorra, and would like to offer the following observations using the headings suggested by the chair of today's seminar, Dr Josep Lluís Segú.

Definition of the concept of rational use of medicines

The definition put forward by the World Health Organization does not strike me as perfect, but it is widely accepted and incorporates the concepts of efficacy, safety, appropriateness and social opportunity cost, and it is therefore acceptable. The common meaning of instrumental rationality (means/ends) implies that the most rational action is that which achieves the same health outcomes as another for a lower social cost.

Current supply of medicines

In a context of private production and research funded privately by companies driven by the profit motive, supply is aimed at the population who can express effective demand and, preferably, suffer from chronic problems. There are various ways of directing supply towards the health needs of the global population:

- Economic and social development to escape from poverty and the biological hardship which causes disease.

- The current World Trade Organization negotiations in Doha to solve the conflict between the incentive for innovation represented by the patent system and the problem of limited access, particularly by the poor, which results from this system.
- Transfer of public and private resources from rich countries (and from the wealthier of the poor countries) to stimulate effective demand for medicines designed to meet the needs of poor countries.
- We have to appeal to the social responsibility of companies, but we cannot depend on their "good-heartedness". Corporate "good-heartedness" will only be sustainable when it is listed on the Stock Exchange. Meanwhile, it is the job of the state to ensure the achievement of a range of social objectives.

Supply of innovation

Between 15 and 20% of the cost of a drug corresponds to variable costs, and 80 to 85% represents the recovery of fixed costs (research, promotion, launch etc.). It seems sensible, then, to propose Ramsey pricing, where each country pays the variable costs and shares the fixed costs in inverse proportion to the price elasticity of the demand for medicines. Those countries which significantly reduce consumption of a medicine in response to a small price rise (high elasticity) and which are normally the poorest countries, would pay a lower share of fixed costs than rich countries.

For this to work, arbitrage or resale from low price markets to high price markets, would have to be prevented. There are services where arbitrage is not possible (dentistry, for example); where it is possible, companies resort to adulteration of the product (methyl alcohol, rapeseed oil etc.), the loss of guarantees with resales, increasing resale costs (labelling, packaging) or, the method most applicable to health, vertical integration towards the consumer. This involves integrating the care process of which the medication for which there is downward price discrimination forms a part.

We need to promote the transfer of public and private resources from rich countries (and from the wealthier of the poor countries) to stimulate effective demand for medicines designed to meet the needs of poor countries.

Analysis of demand

Perhaps it is helpful to distinguish between demand – an observable behaviour which depends on individuals' willingness to pay for a good or service – and the everyday use of the word to refer to an expressed need.

Distinction between need and demand

The concept of need is difficult to define. We can talk of technical need (clinical, epidemiological etc.), felt need, expressed need, comparative need, etc.

It is worth noting that the health systems of the developed countries, with the exception of the United States, establish the obligatory health insurance of their populations with the aim of ensuring that access to health services depends on criteria of need rather than of demand (willingness to pay).

Socially, the establishment of which needs are deemed most important is achieved by setting priorities, more or less explicitly, in a more or less centralized or participative manner, etc. – a process which is on the rise across the globe. Explicit priorities satisfy criteria of democracy and efficiency, and priorities which relate services with conditions or illnesses do so more effectively than categoric portfolios of services (in which some services are always included, and others are always excluded).

A country can decide to publicly finance its needs using cost-effective technology. The limits on what is publicly financed depend on a range of factors: the country's resources, majority wishes and cultural preferences, among others.

Another part of the demand (for services which have no effect – but which may be convenient, pleasant, entertaining etc.) must be funded privately. This is one of the methods which enables European welfare states to be sustainable.

Authorizing a drug and funding a drug

These are two very different decisions which should be kept separate: authorization according to fixed criteria (open to discussion, Food and Drug

Administration, European Medicines Evaluation Agency, etc.), and funding on the basis of cost-effectiveness for public bodies and using whatever criteria are deemed appropriate for private funders (insurance companies, for example). Both public and private funders must ensure their sustainability and combine health inputs (drugs, among others) in an efficient manner.

User orientation

We suffer from a serious shared decision-making deficit (benign prostatic hyperplasia, hormone replacement therapy, etc.). Much remains to be done.

We would do well not to make matters worse and guide ourselves by the problems of the "wealthy, well and worried", bearing in mind, instead, the health paradox that those who complain of the greatest morbidity are people and regions which objectively are best off. For as long as there is still room for major improvements to both life expectancy and quality of life, there is no place for trivial interventions designed to make a minuscule and ridiculous improvement to yet another health-related quality of life index.

Information

This, in particular prognosis, should be standardized and "industrialized". Information about medicines cannot come from an interested party (just as I cannot be the source of information about the quality of classes I deliver). Dr Bigorra mentioned the "real value of the information provided by the industry ... to modify prescription habits ... and their tendency to distort the focus of information for the benefit of the industry ... we need to strengthen compliance with codes of good practice in drug promotion." I agree, but would also add "... and the public production of information".

Information about effectiveness, quality, suitability, health variations, etc. constitutes a public good: its consumption by one person does not prevent its consumption by another, and it is almost impossible to exclude anyone from consuming it. When produced by an independent agency (a big assumption) it can be more accurate and useful than when it is produced by manufacturers.

Direct-to-consumer advertising

The empowerment of patients deserves something more useful and less controversial than this, particular in the case of patients with chronic illnesses. Empowering the patient (through information, monitoring etc.) to better manage his or her illness is a fundamental part of illness management programmes (acting at every stage of the illness, on a populational basis). This is far more useful, for patients with type 2 diabetes, chronic obstructive pulmonary disease, asthma, heart failure etc., than direct-to-consumer advertising of oral hypoglycemics.

Eduard Rius

"Rational use obviously goes beyond the economic or financial aspects of health."

Although it seems unnecessary to clarify in a forum such as this what we mean by the "rational use of medicines", and in this respect I share the definition used by the World Health Organization, I do think it is important to bear in mind, when talking about the Spanish public health system, that in general "rational use" has been associated exclusively with the need to "rationalize" pharmaceutical expenditure.

"Rational use" obviously goes beyond the economic or financial aspects of health. In the past, the focus of managers and politicians on spending devalued the concept of "rational use". Fortunately, this situation has changed in recent years, and today there are active policies for the rational use of medicines which are yielding fruit. The involvement of health professionals in these areas has been very significant, and this has been a very positive development, as has the involvement of the industry.

At the same time, there is a range of other issues which need to be taken into account when considering policies for rational use. Firstly, we cannot separate policies for rational use from what constitutes "pharmaceutical provision" in our country, by which I mean existing supply, medicines funded by the public health service, aspects relating to the registration of a medicine

and whether or not it is covered by public funding, or the level of co-payment in Spain (which is among the lowest in the European Union).

Something similar occurs when we analyse the "pharmaceutical market" and the different participants in it, and if we compare what happens in the United States with what happens in Europe. In Europe the customer of the pharmaceutical industry is the state, who in the final analysis pays the pharmaceutical bill, while in the United States the customer is the patient. As a result, both doctor and patient play a very different role. However, regardless of the differences, in both systems patients need more information and the capacity to decide about treatment.

In this respect, the impact of information and communication technologies is very important. Patients are increasingly well informed and no longer comply with the classic "agency relationship" which characterized doctor-patient relations in the past. As a result, we need to ensure reliable, high quality information for the general public. When dealing with such increasingly well-informed patients, health professionals must act as a "knowledge manager" or "information manager".

At the same time, we must also remember that the "classical" definition of health has changed. Today, talking about health means talking about quality of life, a far wider and more subjective concept, which has major implications for citizens' expectations of health systems.

Many of the issues relating to rational use entail a dialogue between the industry and the health administration. A dialogue which should make it possible to set out a framework to enable both the growth of expenditure and the coordination of expenditure with overall health budgets. And a dialogue which is necessary when we consider research and the need to increase the resources allocated to R&D. The industry should investigate those health problems which are most prevalent in our society, in cooperation with research centres and universities.

Ultimately, what is at stake here is the sustainability of the system over the medium and long term. Of course, sustainability involves the rational use of medicines, but it also has many other implications which are not addressed with sufficient courage and objectivity by those responsible for taking decisions. And I am not referring only to politicians. I refer to society as a whole. And this is why the organization of this seminar by the Foundation is such a positive development.

Josep Vergés

"It is sometimes surprising, even paradoxical, that the same society which demands absolute rigour with regard to drugs, 'forgets' about the fraud which exists with respect to other products."

It is impossible to ignore the role played by evidence-based medicine in shaping rational demand for medicines. Those of us who have been trained in the methodology of clinical trials, meta-analysis and scientific evidence in general are totally in favour of it. However, this does not mean that we should neglect the knowledge acquired during normal clinical practice, what one might term the doctor's "clinical eye". As Dr Bigorra noted in his presentation, evidence-based medicine, together with the rigorous application of observational methods, the preferences of the well-informed patient, etc. can also be useful. At a theoretical level, one sometimes wonders what would happen today if we had to evaluate medicines such as furosemide, digoxin, theophylline and many more which, in their day (over 30 years ago) were approved on the basis of trials with numbers of patients which today would be deemed quite insufficient to reach valid conclusions and which, however, we continue to deem to be of recognized therapeutic value. No doubt the same will be said in 20 years time when people look back on today's evaluation criteria.

Another important issue to consider in the rational use of medicines concerns the continuous development of all the professionals involved in taking decisions about the prescription of medicines. This continuous development in therapeutic matters should be provided by medicine or pharmacy faculties, as part of their doctor training programmes; however, some medicine faculties in Spain still do not offer a course in clinical pharmacology. I believe that continuous therapeutic training should be delivered on an intensive

basis in a clinical/university setting, and that this training should be led by the professional associations of doctors and pharmacists, scientific societies etc., as it is in other countries. We should note that, at present, the professional training, attendance at conferences, grants etc. received by doctors and pharmacists in the workplace is provided in the main by the pharmaceutical industry. I believe in the need to establish clear criteria to make sure that this occurs within an ethical framework; the Spanish Code of Practice in the Promotion of Medicines, proposed by the pharmaceutical industry, could be a major step forward in this regard.

In my opinion, just as there is rigorous control of medicines by the pharmaceutical companies, the industry association, the Department of Health etc., so there should be strict control over so-called miracle medicines, magical objects, clairvoyants, healers etc. It is sometimes surprising, even paradoxical, that the same society which demands absolute rigour with regard to drugs, 'forgets' about the fraud which exists with respect to other products.

Another important role is that played by the patient. I agree that patients should have extensive information which is rigorous, well documented and accessible. The question is, how much information should the patient receive? All of it, or just some of it? Information has to be sufficient to enable the patient to know clearly what he or she is taking. The information leaflet should be clear and precise. Some health professionals argue that the current content is correct, while others argue that it contains too much information (adverse effects etc.) which often limits the use of medicines by the patient due to the fear generated by so much information.

The different stakeholders – the pharmaceutical industry, the health administration, patients, health professionals, scientific societies, patients etc. – must work together to improve the health of our patients, on the basis of clear objectives and shared responsibility.

I would like to end by thanking the Víctor i Grífols Foundation for organizing events of this sort, which provide a valuable opportunity for reflecting upon these issues which affect us all.

Contributors to the discussion in alphabetic order

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- Ramon Bayés, Professor of Basic Psychology at the Autonomous University of Barcelona and Member of the Board of Trustees of the Víctor Grífols i Lucas Foundation
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- Margarita Boladeras, Professor of Moral Philosophy at the University of Barcelona
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- Josep Lluís Segú, Managing Director of Ediciones Doyma, S.A.
- Josep Vergés, Medical and Scientific Director of BioIbérica, S.A.

Publications

Bioethics monographs:

26. *The three ages of medicine and the doctor-patient relationship*
25. *Ethics: an essential element of scientific and medical communication*
24. *Maleficence in prevention programmes*
23. *Ethics and clinical research*
22. *Consentimiento por representación (Consent by representation)*
21. *Ethics in care services for people with severe mental disability*
20. *Ethical challenges of e-health*
19. *The person as the subject of medicine*
18. *Waiting lists: can we improve them?*
17. *Individual Good and Common Good in Bioethics*
16. *Autonomy and Dependency in Old Age*
15. *Informed consent and cultural diversity*
14. *Addressing the problem of patient competency*
13. *Health information and the active participation of users*
12. *The management of nursing care*
11. *Los fines de la medicina* (Spanish translation of *The goals of medicine)*
10. *Corresponsabilidad empresarial en el desarrollo sostenible (Corporate responsibility in sustainable development)*
9. *Ethics and sedation at the close of life*
8. *The rational use of medication. Ethical aspects*
7. *The management of medical errors*
6. *The ethics of medical communication*
5. *Practical problems of informed consent*
4. *Predictive medicine and discrimination*
3. *The pharmaceutical industry and medical progress*
2. *Ethical and scientific standards in research*
1. *Freedom and Health*

Reports:

4. *Las prestaciones privadas en las organizaciones sanitarias públicas (Private services in public health organizations)*
3. *Therapeutic Cloning: scientific, legal and ethical perspectives*
2. *An ethical framework for cooperation between companies and research centres*
1. *The Social Perception of Biotechnology*

Ethical questions:

3. *Surrogate pregnancy: an analysis of the current situation*
2. *Sexuality and the emotions: can they be taught?*
1. *What should we do with persistent sexual offenders?*

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