siados» productos, pero la diversidad tiene muchos aspectos favorables: en tanto que la imposición de restricciones de diversos tipos puede afectar la terapia e impedir el progreso. La contención de los costos, por su parte, puede implicar falsas economías: el ahorro actual puede, a largo plazo, acrecentar los costos de la salud. El mundo requiere constantemente nuevos y mejores medicamentos y la industria multinacional de medicamentos es la única entidad que cuenta con un historial acreditado para proporcionárselos. Se la acusa de comercializar preparados «irracionales» y de «dumping», pero un medicamento que sea inapropiado en el «Norte» no lo es necesariamente en el «Sur». Por las actitudes que asumen ante los países en desarrollo los grupos de presión interesados en estas cuestiones parecen propensos al paternalismo, pero los enfermos del mundo merecen algo más que polemicas.

Making the most of Medicines

1. Introduction

Rupee for rupee, peso for peso, shilling for shilling, pharmaceuticals represent the most cost-effective component of health care in developing countries. The products needed to immunise all children under five – the most vulnerable group in a society – against major infectious diseases, to treat them for diarrhoea and to prevent and treat their malaria, intestinal parasites and acute respiratory infections, need cost no more than US$ 1 or so per head. But it is of crucial importance not to take the pharmaceutical industry's remarkable contributions to improving health for granted. We must constantly examine and re-examine the use of medicines, as well as any proposed changes in their use, in case a system that has made available to mankind a remarkable flow of life-saving medicines is irreparably damaged by attempts to eliminate actual or perceived abuses, failings or shortcomings. Kicking the pharmaceutical industry may give satisfaction to those who dislike successful multinational companies but it is not those companies who are responsible for the health problems of the third world nor, by the same token, able to solve them, and it is a disservice to developing countries to delude them with solutions that do not exist and with fairy tale scenarios.

2. The main aims

Put yourself in the shoes of the chief executive officer of an innovative multinational pharmaceutical firm. Your main objectives are, clearly, to deliver useful medicines to the sick and to run a profitable business.

It is a reality of the competitive, consumer-orientated, demand-led system that investment capital will put up with delays in return on investment – and in the pharmaceutical business the research and development of any one medicine can take a decade and involve an investment of up to $100 million – but eventually goods of all kinds, medicines included, have to be sold and a profit made or the

company will fail. Employers and suppliers expect to be paid promptly, medicine distribution is not achieved without cost, and medicine promotion is indispensable if prescribing health professionals are to be informed about products. All this costs money.

In particular, research is expensive. The road to a successful product is both long and treacherous. Pharmaceutical innovation is a risky business. When the research programme is blessed with success, the financial rewards can be satisfying – and can fund further research and new developments. But lean years can and will occur. That must be taken into account.

Furthermore, it is taking longer and longer to progress from the first germ of an idea or the synthesis of a new molecule to getting a product on the market. This means that "me-too" research is less and less attractive and true breakthroughs, while more difficult to achieve, are more and more important in the scheme of things. It means, too, that this lengthier pre-marketing phase has eroded effective patent life. That can be combatted in two ways – restoring patent life by legislation and with innovations that make it more difficult for competitors to develop rival products.

3. Bonus discoveries

Of course, research and development are not confined to the pre-marketing stage of a medicine's history. Many important attributes of medicines first come to the surface after it has been registered. Lidocaine was used for years as a local anaesthetic before its qualities as a life-saving anti-arrhytmic were appreciated. Diazepam was long in use as a tranquilliser before its value as a treatment in epilepsy was discovered. Amantadine was worked up and marketed as a preventive against influenza: its utility in Parkinsonism was a happy chance find. Medicines introduced as anti-cancer agents have turned out to be useful for diseases as different as psoriasis and arthritis. The list goes on and on.

Post-registration research, therefore, is extremely important. It permits follow-up on new therapeutic leads or on any concern about toxicity and it increases our knowledge of pharmacokinetics or pharmacodynamics in special population groups. Such research is expensive and hard to justify in purely financial terms if the patent on a medicine is about to run out, because if the research is successful, generic competitors can benefit from the innovator's research without having to pay for it.

So, profits are not only important – they are essential. The pharmaceutical industry can survive only if it is profitable. Multinational pharmaceutical companies have no need to apologise for making profits. Of course the company that spends some of its energies on "good works," such as an "orphan drug" for a very limited population, can survive, and every country has an "orphan drug" and "orphan disease" problem, that is, drugs or diseases that are not pursued because such remedies would be economically unprofitable. But a company that spends too much of its resources on "orphan drugs" cannot survive. So it is silly to expect the industry to play Lady Bountiful, as if philanthropy were its business. The market place cannot take care of all social problems, which is why we also need government and private charity.

Some have suggested that medicine patents should be abolished because they increase prices and impede the flow of medicines to poor countries or poor people. But almost without exception, important pharmaceutical inventions have come about through the expenditure of money and effort in capitalist countries. It is naive to expect that without patent protection, innovative companies would be willing to risk millions, and years of effort. There is a similar problem in supplying medicines below cost to third world countries. While industry has helped to meet the needs of these countries by special pricing arrangements, inevitably the question arises – if medicines are going to be sold below cost, who foots the bill?

Nor are profits necessarily bad for society. Making and selling medicines is not what the Americans call a "zero-sum game," where winners imply losers. For when patients buy needed and effective medicines, the manufacturer may make money but the patients gain in health. Everyone gains. Only when medicines are unnecessary or valueless does the consumer lose while the seller – in the short term, anyway – gains.

To avoid a situation in which there are losers and to maximise public and private benefit, doctors must not overprescribe, underprescribe or misprescribe and patients must not overuse, underuse or misuse.

A patient who does not receive a needed medicine (or enough of it) is decreasing the total social benefit it makes available. A patient who receives a medicine he does not need, or which is not effective for his condition, is putting money in the manufacturer's pockets but not helping himself. The same is true for a medicine which is appropriate but is prescribed in too high a dose or for too long.

4. Working together

To achieve an optimal state of affairs needs the cooperation of all involved – patients, health professionals, academic teachers and the pharmaceutical industry. An ignorant public demanding treatment where none is needed or available will engage in wasteful and potentially harmful usage of medicines. The same is true for doctors with eccentric or mistaken ideas about drug indications, or who are inept diagnosticians. Doctors and patients may differ in their value judgments or attitudes towards risk-benefit, but what we must aim for is an appreciation – as accurate and precise as possible – by patients and doctors alike of the hazards of untreated disease as well as potential benefits and risks of treatment.

We also need special education for different populations both in different countries and within individual countries (for no one national population is homogeneous). Therapeutic practices differ among the European nations, for example, and it is not easy to explain such differences or to make value judgments about whether one contry's approach is better than another's. An illiterate patient in any country cannot possibly be educated by written material. To acknowledge these differences is not to invoke a pejorative "double standard" but to face reality. Much has been said about differences in labelling from one country to another. Many of these differences can be explained by local custom, law or need, and again, it is foolish to insist on a uniformity that cannot be achieved or is not desirable. A country that lacks a modern health professional infrastructure and resources, for example, needs a different approach from one that does.

Mainstream economists might argue that pharmaceutical companies have every incentive to strive for the widest possible use of their products. Why, the argument could go, should manufacturers fret if

doctors and patients overuse medicines – should they be their brother's keeper and protect people from their own weaknesses? And doesn't the system work best when each competing company seeks to dominate the market?

But if such cynicism is not in the best interests of the consumer, it is certainly not in the best interests of the manufacturer either, as everyone in the industry fully recognises. Any short-term benefits for companies that such an approach might produce could easily do long-term harm, as history teaches. When the pharmaceutical revolution began, some 40 years ago, industry was under few constraints. Advertising was flamboyant and aggressive; excessive claims were common. In the long run, this did a wholly disproportionate amount of damage to the credibility, reputation and esteem of the industry, far more than its accomplishments deserved.

5. Limitations' limitations

In more recent years, the pharmaceutical industry has increasingly come under fire. It has been charged with making excessive profits and criticisms have helped the introduction of various constraints, among them limited lists.

But how large a range of products is best for society? The number of chemical entities on the market in different European countries, for example, varies greatly, from 750 in Sweden to 2,500 in West Germany. In terms of the formulations of those chemicals, the range is even greater, from 2,500 in Sweden to 12,000 in West Germany.

While Norway has nine beta-blockers, Britain has 17. Surveys indicate that doctors in the Netherlands do not use all 22 of the non-steroidal anti-inflammatory prescription medicines that are on the market, but when they are questioned in detail it turns out that although one doctor may use only seven such medicines, his seven are different from another's favourite seven. In Norway, which demands that medicines have their entry on the market justified before they are registered, doctors prescribe only four to six of the available medicines in this class, but 40 per cent of doctors there prescribe medicines for their patients that have not been approved for sale in Norway (but are available by special request).

Many doctors take care of most of their patients with a fairly small range of medicines. But if one considers all patients who are therapeutic problems, the need for a broader range is obvious. That does not mean that a poor country should not consider for its public sector programmes something like the World Health Organization's model list of essential drugs, since it is a reasonable approach to a "bare bones" formulary which can serve as the starting point for a list of necessary medicines for a developing country. It must be noted, though, that the essential drugs concept, which may be appropriate for a country's public health sector, should not be used to deny other medication therapies to patients in the private sector.

There is a further point. Third world doctors and patients alike may understandably resent being told what "luxury" medicines they should do without, because that implies that the poor are not entitled to the same medical options as the privileged.

6. The realities of "need"

At first blush, it would seem hard to dispute that in order to be approved for registration a medicine should be shown to be better than those already on the market. But in practice, this is far from easy. It is extremely unlikely that two chemicals, even if very closely related and seemingly all but identical, are completely interchangeable in all patients. Differences between chemicals can always be expected, even if they seem trivial.

But what judgment should one make about registration when dealing with an antiepileptic medicine which is more toxic than others already on the market, and not more effective than standard medicines for treating most patients with this disease, but which, nevertheless, is vital in controlling the convulsions of a small number of patients? For the individual patients for whom such a medicine is critically important, that drug is indeed "needed" and "better" than any other.

That is not to deny that work is needed before registration to delineate differences and identify population sub-groups that are uniquely helped by the new medicine. Before any medicine is put into any human being, the argument should be clearly developed as to why it is expected (from animal work) that it will deserve to be on the market, and what gap in the therapeutic cupboard it will fill.

It has also been argued that having too many similar medicines on the market produces clutter which harms attempts to educate the profession in their proper use. While this may be an unintentional side effect of companies' efforts to promote and diversify their product lines, the effect of making similar medicines available is stiffer competition between manufacturers, which tends to push prices down. Moreover, when a free market exists, fraud and coercion are less likely than when it does not – it is indeed paradoxical that many who favour generic competition are opting for what would in fact be a monopoly approach, for it would mean that only one medicine would be available for treating each given disease, even if made by different manufacturers.

Furthermore, there are many ways for a medicine to become "better." A medicine – a syrup for children, say – which is given a new, more pleasant taste may remain chemically just what it was but can mark as important a step forward medically as an entirely new chemical entity, as can the extra convenience of a medicine that need be taken only once a day instead of four times, because both improvements will increase patient compliance, a vital factor always, just as important as doctors' understanding of medicines. Combination medicines, too, can help make treatment both easier and cheaper.

7. True and false economies

The buzz word of the day is "cost-containment." Third party payers and governments are increasingly concerned to keep health spending down. But no matter how popular medicines may be, they represent only a small fraction of any nation's budget, so even if they were eliminated entirely, the impact on a nation's economy would be slight.

Nevertheless, governments and individuals will, rightly, try to save money if they can. The point, however, is to avoid false economies. Short term "savings," especially in health can (and in fact almost invariably will) increase costs in the longer run. Of course it costs money to take a medicine to prevent the recurrence of peptic ulcer. But it will cost still more if someone comes down with a recurrence of the condition and loses time from work, or needs

surgery. Antibiotics cost money, but if they save a patient from going into hospital, they will more than pay for themselves. Discharging a psychotic patient is both more humane and more cost-effective than continued institutionalisation.

Attempts to save money by enforcing generic competition or weakening patents can be counterproductive in the long term too. Pharmaceutical firms that are not innovative do not help to solve the problems of patients who are not now as well treated by the available medicines as they might be. It is shortsighted to act as if the only health problem in the world is how to distribute to patients the medicines that are already available. The world continues to need new and better medicines. There is hardly any major disease for which medicines that are either safer or more effective would not be desirable. And there are many diseases for which no cure has yet been found. Hobbling the multinational pharmaceutical companies would be utterly foolish, for it is they which have consistently "delivered the goods," whose track record in inventing and making available outstanding new medicines is not only unequalled but not even remotely approached by anyone else.

8. Marketing of medicines

Innovative multinational firms have been accused of marketing useless or even dangerous medicines to the third world. Some preparations marketed in developing countries may, certainly, seem "irrational." But not only are some of these marketed in their home countries for equally "irrational" purposes but much of the best and most effective health care, and medical practice itself, is irrational – the placebo effect, for example. Traditional remedies and homeopathic medicines are sold in some of the most scientifically advanced lands. The pharmaceutical industry needs to keep working toward the replacement of the more toxic and less safe medicines in developed countries and poorer ones, and specific accusations of bad practices by the pharmaceutical industry need to be investigated and discussed, as they are under the IFPMA code, with proper steps being taken to correct deficiencies when they exist, but it does not follow that because a medicine is not marketed in the western world, it is inappropriate for a developing country. For example, western countries do not any longer suffer from indigenous malaria but many third world countries do. The same is true for certain kinds of infectious diarrhoeas. For a poor country with a very limited health budget and many different kinds of bacterial disease, it might well be cost-effective to treat most infected patients with chloramphenicol, a medicine whose usage is greatly restricted in the United States because of a rare but serious side effect, aplastic anaemia. Chloramphenicol is cheap, easy to procure, does not disturb the gastrointestinal tract, does not produce skin rashes or allergic reactions, and can be taken by mouth. For every patient who might die from chloramphenicol-related aplastic anaemia, thousands will be saved from dying of infections treatable with this antibiotic. To take yet another example – a product like medroxyprogesterone acetate, better known by its brand name Depo-Provera, is not approved for parenteral contraception in the United States, but in many other countries it is. Multinational pharmaceutical companies have been accused of "dumping" such products, which they do not or cannot sell at home, on developing countries, but there is a difference between "dumping" and the sale of a product that represents a different national value judgment. It is not "dumping" for the American manufacturer of this contraceptive to promote it abroad for the purpose of contraception and in no way reprehensible for it to be marketed abroad even if it cannot be in the United States. And as a United Nations General Assembly resolution in 1982 reflected the desire of third world countries to have the right to the final say about whether unapproved products from other countries should be exported to them, it is important for the developed countries of the 'North', and pressure groups within them for that matter, not to indulge in galloping paternalism in their attitudes towards the nations of the developing 'South'.

9. Reason and ethics

No industry deserves to be shackled by regulatory requirements that are unreasonable or unethical. For the pharmaceutical industry, an approval process that is slower than it needs to be, or which makes requests for duplication of evidence that cannot be justified by genetic or other scientific requirements, is unreasonable. And when products are arbitrarily or capriciously removed from the market, that is un-

ethical, indeed indefensible, for it is denying ill people the best available treatment. There is too much of a tendency to deal with a problem like the abuse of a medicine by a few by removing it from the market for the many.

It is vital that the pharmaceutical industry, governments, regulatory agencies, health professionals and the public should look on the problems of drug discovery, production, distribution and use as challenges to the various components of society working together rather than as adversaries. And to be anti-business is not synonymous with being pro-society. The pharmaceutical industry on its own cannot possibly solve all the health problems of the third world but sometimes its critics seem to consider that they have a right to be disappointed with it, angry with it or even entitled to penalise or punish it, for not having done so. There has been too much harpoon-throwing like this, too many insults. The sick of the world deserve better.

What is the clinical picture in cases of massive overdose? Are there any important uses not predicted by earlier studies? It is essential, therefore, to study drugs after they are marketed, as well as before. But we must not equate this need with the need for formal monitoring of a given group of patients intended only to discover new ADRs, or even intended to check out premarketing estimates of observed toxicity. To do so is to fly in the face of all we know.

Rossi et al state that spontaneous reporting is usually viewed "as the least sophisticated and scientifically rigorous . . . method of detecting new adverse drug reactions." This may be true in Webster's dictionary sense of sophisticated meaning "adulterated," "devoid of the obvious traditional or popular appeal," or "complex," but I submit that spontaneous reporting is more "worldly-wise, knowing, subtle, and intellectually appealing" than grandiose, expensive Phase IV schemes that divert funds and manpower away from more useful pursuits and increase the price of drugs to consumers.

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1. Wardell WM, Tsianco MC, Anavekar SN, et al: Postmarketing surveillance of new drugs: II. Case Studies. *J Clin Pharmacol* 1979;19:169-184.
2. Wardell WM, Tsianco MC, Anavekar SN, et al: Postmarketing surveillance of new drugs: I. Review of objectives and methodology. *J Clin Pharmacol* 1979;19:85-94.

Letters to the Editor should be typed double-spaced (including references) with conventional margins. The length of the text is limited to [illegible] manuscript pages.

CONSUMER REPRESENTATION ON FDA PANELS

To the Editor: In Louis Lasagna's Sounding Board article in the April 20 issue of the *Journal* he makes some statements about the consumer representatives who have been appointed to advisory committees by the FDA that I hope are due to his ignorance rather than to his bias.

I have been a consumer representative on an OTC panel of the FDA for the last six years, and I have met with many of the consumer representatives on other FDA panels. Most of us were recommended to FDA by the Consumer Federation of America, a federation of over 200 organizations representing a wide range of interests, including farm groups, senior citizens, labor unions, cooperatives, veterans, credit unions and women's groups.

The consumer representatives themselves come from varied backgrounds, and are certainly from the drug-consuming public. We are "concerned about chemical hazards," but we seek to diminish the use of medicines only when they are ineffective, or when their use creates risks not warranted by their benefits. We are not "invariably pejorative" in our attitude toward the pharmaceutical industry and the medical profession. Nor do we consider the industry "at best incompetent and at worst deceitful or evil," although we have noticed examples of both. We have indeed learned a great deal about the relevant issues and the process of regulation. We have also learned which manufacturers have provided meaningful data about the safety and efficacy of their products, and to what extent such data either have not been presented or are not available. We have also discovered how much money is being spent for drugs that have not proved effective and safe and have, in some cases, aggravated the conditions for which they were bought, or have delayed the search for more appropriate remedies.