Editorial
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Medications, Science and Politics: A difficult compromise

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Medicines have significantly contributed to the improvement of the health status of population over time. Moreover the use of new medicines accounted for a 40% increase in life expectancy during the 1980s and 1990s.[1,2]

From a public health perspective, the main goal in the pharmaceutical sector is that of making readily accessible efficacious, high quality and safe medicines, including the more recent and innovative ones, to all those who need them, regardless of their income or social status. Nevertheless the importance of medicines to population health has been accompanied by rising pharmaceutical expenditure, thus putting pressure on health care expenditure. The countries of the Organisation for Economic Co-operation and Development witnessed a 4,6% annual average growth in pharmaceutical expenditure per capita from 1995 to 2005.[3] Since 2000, average spending on pharmaceuticals has risen by almost 50% in real terms.[4]

The EU Member States have to consider how resources available for pharmaceutical and other means of health care can be prioritised to best effect. In this context the main objectives to be pursued include: (a) the promotion of innovative medicines with added therapeutic value (b) improving the clinical and cost effectiveness of prescription medicines (c) more extensive use, where appropriate, of low cost generic drugs.

Innovative drugs have a patent that extends protection, usually for a period of 20 years. Once the patent expires, pharmaceutical companies can manufacture a generic or biosimilar product. Generic and biosimilar drugs must be chemically equivalent to their brand-name counterparts in terms of active ingredients but may differ in peripheral features, such as excipients, color or shape, and the specific manufacturing process. Drugs prescribed generically may be dispensed as either a branded product or a lower cost nonbranded one.

Generics have existed throughout the history of the pharmaceutical industry, but modern generics firms emerged only in the mid 1960s. The 1984 US Drug Price Competition and Patent Restoration (Hatch-Waxman) Act was the decisive moment in the development of the generics industry. The Hatch-Waxman Act first authorized the FDA to approve generic drugs demonstrated to be "bioequivalent," which is defined as absence of a significant difference in the availability of the active ingredient at the site of drug action. Bioequivalency can be established on the basis of the maximum serum concentration of the drug, the time until maximum concentration is reached, or the area under the curve based on serum concentration as a function of time. Bioequivalence is usually assessed by single dose in vivo studies in 12-24-36 healthy volunteers. The reference product is usually the innovator product. The regulatory limits applied are that the 90% confidence intervals for the ratios (test: reference) of the areas under the drug concentration versus time curves (AUC ratio) and the maximum plasma drug concentrations (Cmax ratio) must fall between 80% and 125%. (The confidence limits are asymmetrical because log transformed data are used in the comparison.) The times to maximum plasma concentration (Tmax) for the test and reference product should also be similar.

It is sometimes claimed that the 80 to 125% limit means there can be a 45% variation between the new product and the reference product, but this is not really the case. The average ratio (point estimate) is usually reasonably close to 100% and this is the value of maximum likelihood for the comparison. If the average ratio is close to the 80 or 125% regulatory limits then the data would have to be very tight indeed to prevent the 90% confidence intervals falling outside the regulatory boundaries.

One valid concern in relation to generics is that individual patients could have idiosyncratic sensitivity to excipients such as colourings that are in the generic but not innovator product. This can occur, but is very rare and is not a problem limited to generics. Changes of excipients in innovator products could cause similar adverse effects.[5]

Physicians should know that brand to generic substitution is acceptable for drugs with high-medium therapeutic index. Therefore, after a clinical result was obtained using a specific generic drug, patient should be instructed about the need not to change it.

By definition, generic substitution is not applicable for drugs with narrow therapeutic index (NTI). NTI drugs present small differences between the effective and toxic doses. Small variations in concentration of these drugs can result in an insufficient therapeutic response or toxic appearance. FDA indicates over 25 NTI drugs used in various therapeutic indications: heart failure, thrombo-embolism, seizures, asthma, depression, thyroid dysfunction. Examples of drugs with NTI or critical dose drugs are: carbamazepine, lithium, digoxin, levothyroxine, phenytoin, theophylline, cyclosporine, warfarin, fentanyl, and immunosuppressants.[6–8] For many drugs, especially those with a narrow therapeutic range, therapeutic drug concentration or pharmacodynamic monitoring is necessary to assure the desired clinical response. Such monitoring is necessary irrespective of whether the drug is a brand name or generic product.

Another serious concern arises with biosimilar medicines which are alternatives to biological medicinal products (typically recombinant therapeutic proteins) whose patents have expired. Six such products have been granted market authorization in the European Union, including those for somatropin, growth hormone, erythropoietin and granulocyte colony stimulating factor. Consequently, the European Medicines Agency (EMA) has stipulated that approval or licensing of each of these products has to be based on evaluation of full sets of independent data, including a post-marketing pharmacovigilance plan to monitor safety and any immunological responses.[9,10] This requirement is stricter than the evidence on bioequivalence required for the licensing of small molecule generic drugs.

The generic medicines market in the EU amounted to approximately € 21.6 billion in 2006. The share of generic medicines varies greatly across the EU, mostly due to health care legislation differences between the individual countries. A widely-used approach to promote generics in European countries is the introduction of demand-side measures, notably generics substitution and International Non Proprietary Name (INN) prescribing. This measure exists in 22 EU Member States. In four countries (Estonia, Lithuania, Portugal and Romania) INN prescribing is mandatory. In 21 EU Member States pharmacists may substitute an equivalent generic. In six countries (Denmark, Germany, Finland, Malta, Sweden and Slovakia) pharmacists are obliged to apply generic substitution-unless the patient or doctor opposes substitution, the latter only being possible under clearly defined conditions.[11]

The regulation of generics continues to give rise to extensive legal and political wrangling in the US, Europe and elsewhere.[12] Generic substitution is standard practice in most EEC countries, however, there are cases where generic prescribing may not be appropriate, and in these cases drugs should be prescribed by brand name to avoid potential lack of effect, adverse effects due to toxicity or poor patient understanding, co-operation and adherence.

It is up to physicians to remain current with the latest information regarding medications. The doctor-patient relationship has been and remains a keystone of succesful therapy.

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