



**Position statement
on the Dutch EU Presidency initiative**

“Priority Medicines for the Citizens of Europe”

Summary

The initiative by the Dutch Presidency of the European Union is welcomed by the Medicines in Europe Forum, given the enormous gap between the drug market and public health requirements in Europe and the rest of the world, especially poor countries.

The Medicines in Europe Forum points out, however, that development of new drugs is not the chief priority among possible measures designed to tangibly improve the health of European citizens. The leading priorities are the following:

- large-scale primary prevention, notably based on nutritional and environmental measures, as recommended by the World Health Organization at the 57th World Health Assembly in 2004;
- better prevention of errors linked to the use of existing drugs, notably through better packaging;
- better prevention of adverse effects of existing drugs, through more effective and transparent pharmacovigilance.

Regarding new drug development, the Medicines in Europe Forum identifies the following priorities:

- relevant comparative pre-marketing evaluation, in

The Medicines in Europe Forum, a group associating 60 organisations of patients, consumers, health professionals and health insurers in 12 European Union Member States, welcomes the initiative taken by the Dutch Presidency of the European Union in the field of medicinal products. All member states are now confronted with a growing financial crisis as they struggle to provide their citizens with access to increasingly expensive new drugs, whose added

therapeutic value relative to existing preventive or curative treatments is rarely known. A re-assessment of research priorities can only be beneficial, and the Dutch Presidency should be praised for launching a public debate.

The Medicines in Europe Forum nevertheless considers that, in its present form, the “Priority Medicines” initiative will only contribute to improving the health of EU citizens if it takes into account other key determinants.

order to avoid the release of drugs with unknown added therapeutic value, which may prove to be more harmful than existing products;

- research aimed at palliating for current inadequacies in the following areas: useful older drugs that are considered no longer profitable by drug companies; drug utilization by patients; comparisons with non drug treatments; drugs for health disorders whose severity sometimes serves as a pretext for inadequate pre-marketing assessment (cancer, multiple sclerosis, Alzheimer’s disease, viral infections, some rheumatic diseases and related pain); drugs for groups of patients at special risk, particularly the elderly ;
- decisions on research priorities and funding must be made transparently *vis-à-vis* European citizens.

Increasingly numerous pharmacovigilance scandals are shaking the foundations of the drug market and revealing the failings of drug companies and medicines agencies; decisive action by Member States and national health authorities is urgently needed.

The Medicines in Europe Forum would particularly welcome an initiative by the EU Presidency aimed at tightening rules on drug evaluation, focusing research on the most needy patients (including patients outside the EU), and making primary prevention a leading priority.

The reforms most urgently needed in Europe concern primary prevention, based on non drug measures, and better use of existing drugs in order to avoid medication errors and adverse effects.

The development of new “priority” drugs is important, but with two provisos : new drugs must be rigorously evaluated prior to their market release; and research priorities must correspond to concrete needs identified by epidemiological studies.

These needs concern a number of patient groups in Europe, and far larger population groups in poor countries, that Europe must undertake to assist.

Making primary prevention a true priority

Many of the health problems affecting European citizens require first and fore-

► most preventing measures. Large-scale primary preventive measures targeting nutrition, the environment, infections, accidents and behaviors are therefore crucial. Funds devoted to these measures would have a bigger impact on public health than would the same funds used for curative treatment. This is the notion underlying the WHO Global Strategy on Diet, Physical Activity and Health defined at the 57th World Health Assembly in 2004.

For example, obesity, cardiovascular diseases and diabetes are mainly linked to dietary and lifestyle habits. What is needed is not yet another new cholesterol lowering or antidiabetic drug, but better education of children and health professionals, and measures to resist the lobbying of the food industry.

The fight against smoking, which is a leading cause of cardiovascular diseases and cancer, is currently far too inadequate. Here again, what we need most is not new smoking withdrawal drugs but large-scale public health campaigns and more effective constraints on the tobacco industry.

The toxicity of new chemical substances used in agriculture and industry is barely assessed prior to marketing, and even less so once the product is in use. The number of new chemicals continues to rise, and studies of their impact on the environment, animals and humans are inadequate. We encourage the Dutch Presidency of the EU to take the measures necessary to ensure that the risks associated with new chemical substances, and especially the risk of cancer, are properly assessed.

Preventing errors linked to the use of medicines: don't forget drugs already on the market

The European Union has consistently failed to take the measures necessary to prevent medication errors, the high human and financial costs of which have been documented in the United States and in some European Union Member States. These errors are partly due to failures in professional practices, but also to inadequate packaging and poor quality information for patients (labeling, patient information leaflet, etc.). For example, ambiguous expression of a drug concentration or poor design of a dosing device can lead to the administration of a toxic dose, or an inadequate warning on the labeling of a teratogenic drug can lead to its use by a pregnant woman.

In addition to the need for a stronger and more transparent adverse drug reactions monitoring (pharmacovigilance), we also need a program for reporting medication errors, analyzing the causes, and proposing strong measures to prevent them. When Directive 2004/27/EC is transposed into national law, it should lead to slight improvements in some packaging items for new drugs such as more legible international non proprietary name (including in Braille), and user-tested patient information leaflets. But many medication errors will continue to occur if nothing is done to improve the packaging of existing drugs.

The Medicines in Europe Forum welcomes the Council of Europe's initiative aimed at preventing medication errors. We note that the European Commission and the European Medicines Agency also express the wish to improve patient information on medicines, but currently pay little attention to the information provided by companies on

their product packaging and patient leaflets, and fail to ensure that all unit doses permanently bear identifiers.

The Medicines in Europe Forum would also welcome an initiative by the Presidency that targets drugs that are already on the market.

Preventing adverse effects of existing drugs

The European Union has long had a regulatory framework on pharmacovigilance, and each Member State has its national pharmacovigilance system. In practice, however, the monitoring and prevention of adverse effects are both highly inadequate: scant attention is paid to adverse effects in pre-marketing clinical trials (trials tend to focus on efficacy, not on risk); the adverse effects reporting system is inadequate (little involvement of health professionals and patients); the processes of data collection and analysis are unacceptably secretive; and little reliable information trickles down to health care professionals or patients.

One major priority is to reinforce pharmacovigilance through a transparent information policy for health professionals and patients, which is a crucial first step in their effective participation in adverse effect prevention.

Member State medicines agencies and health authorities must start to oblige companies to complete the pharmacovigilance studies on which marketing authorization is often conditional. Too often these demands are simply ignored, and any results are rarely made public. Medicines agencies must also reassess the risk-benefit balance at the time of the five-yearly renewal of marketing authorization, notably by examining whether safer drugs have arrived on the market in the meantime.

The Medicines in Europe Forum would also welcome an initiative by the Presidency in favor of more active and more transparent pharmacovigilance.

Making thorough, reliable assessment of new drugs a priority

After an improvement in drug evaluation in the early 1980s, following application of the first European directive on marketing authorization and on pharmacovigilance, the regulatory process has gradually fallen into disarray. Pharmaceutical majors drew medicines agencies (including the European Medicines Agency) into an international compromise on drug assessment (the International Conference on Harmonisation or ICH process), which permits new drugs to be marketed on the basis of a not too exacting evaluation dossier. As a result, most new drugs are authorized without proper knowledge of their added therapeutic value or their optimal conditions of use.

The priority for drug development in Europe is to stop authorizing inadequately assessed drugs in the name of free trade, and to re-evaluate drugs that are already on the market, in order to improve the rational use of existing treatments.

The Medicines in Europe Forum proposes the following measures:

– when a new drug has not been compared with a reference treatment available for the same disease or the same symptom, medicines agencies must demand a relevant comparative assessment before granting marketing authorization. More and more new drugs offer patients no tangible advantages, while exposing them to greater risks; some drugs have to be withdrawn after years on the market at exorbitant prices. It is



irresponsible to authorize drugs with poorly documented benefits and risks simply in the name of free trade.

–when comparative trials of a new drug are flawed (inadequate or excessive dose of the reference treatment, inappropriate trial populations, etc.), medicines agencies must demand new comparisons at optimal doses in patients for whom the product is actually intended. Irrelevant trials are a waste of resources, and it is the taxpayer who eventually foots the bill.

–companies must be obliged to determine how long their drugs take to be effective, and when efficacy starts to wane. Likewise, the optimal treatment duration must be properly determined in order to avoid unnecessary drug expenditure and adverse effects.

–regarding the optimal dose regimen, dose-finding studies are often the weakest element of clinical evaluation dossiers on new drugs (or old drugs proposed for new indications), meaning that the therapeutic margin between effective doses and doses inducing adverse effects is poorly defined.

–identification of adverse effects is not a sufficient priority in clinical trials: the main focus for companies and their investigators is simply to show that a product is effective. Safety information is therefore lacking.

–drugs are often authorized for second-line use because they are not more effective than existing options in first-line treatment. Such authorizations should only be granted if the new drug has a different adverse effects profile from that of the reference drug, or if it is effective when the reference drug fails. These questions must be addressed in pre-marketing trials. The same applies to drugs authorized for third- or fourth-line use, in cancer therapy for example.

–data are often lacking on

patients at special risk, not only patients with renal or hepatic failure, but also elderly patients, in whom the risk of drug-related complications is particularly high.

Currently, most clinical and pre-clinical studies in Europe are funded by pharmaceutical companies, who have a fairly free hand. Many drugs are authorized (even though they are inadequately evaluated) on condition that the company conducts further trials, but this obligation is often ignored.

Before clinical trials begin, drug development projects should be examined by medicines agencies, or by independent bodies if agencies, being financially dependent on drug companies, fail to deliver, in order to determine: –the adverse effects that are most likely to occur in clinical trials, based on prior animal experiments, and that should be particularly looked at ;

–what treatments already exist in the therapeutic indication at hand; what patients and health professionals really want; and the types of comparative trials required.

Research priorities targeting current inadequacies

The Dutch Presidency's initiative aimed at redefining research priorities is welcome because it highlights discrepancies between drug development and patients' real needs: most drugs are currently developed for a small number of "profitable" health diseases, to the detriment of other important but not profitable diseases, according to industry.

In recent years the European Union has developed certain measures intended to meet the needs of patients with rare diseases, one example being Regulation 141/2000/EC on orphan drugs. The Medicines in Europe

Forum wishes to see this regulation properly implemented: in particular, orphan drug status must be attributed (and maintained along the years) only to products intended for very small patient groups, and progress in the treatment of these diseases should be regularly evaluated.

The European Union is currently drawing up a Regulation on pediatric drugs. Some groups of children need specific formulations and dose strengths, and certain drugs need to be evaluated in specific child populations. This useful project should not delude us into believing that so far medicines for children were totally lacking: for some conditions there are actually many of them and they are often excessively consumed (e.g. antibiotics in some countries, psychotropics in others). The Medicines in Europe Forum recommends that populations of children lacking appropriate drugs be precisely identified, and not defined simply on the basis of current practices, which are often irrational, sometimes irrelevant, and occasionally dangerous.

In many other areas the problem is not a lack of drugs *per se*, but rather inadequate assessment of existing options: how best to use them, how to avoid their adverse effects, and especially how to choose the best treatment. In the view of the Medicines in Europe Forum, research priorities should aim to fill gaps in our current knowledge. For example:

–useful old drugs, which are generally cheap, are no longer studied in comparative trials (dose-finding studies, comparative class trials, etc.). Worse, companies sometimes withdraw these products from the market simply because they are no longer profitable. Support for research on these drugs, and perhaps assistance with their marketing, should be treated as a priority in particular cases. One outstanding

example is that of diuretics used as antihypertensive drugs ;

–few reliable data, and especially observational studies, are available on the optimal conditions of drug use, especially during long-term treatments and for drugs used in multiple combinations. Such studies could improve the use of existing drugs, limiting both medication errors and adverse effects ;

–too few comparisons between drug and non drug treatments are available, owing to the separation between research teams and divergent financial interests. Yet non-drug treatments (surgery, physiotherapy, behavior psychotherapy, etc.) are potentially beneficial in many areas ;

–in the field of cancer therapy, many drug combinations are used without having been properly evaluated. Even in recommended treatment protocols, dose regimens differ from one side of the Atlantic to the other, or from one "school" to another. As cytotoxic drugs often have major adverse effects, the different protocols used for a given indication should be identified and evaluated.

–in serious illnesses such as multiple sclerosis and Alzheimer's disease, drugs should only be authorized when they have been compared with the reference treatment, especially when placebo-controlled trials show only a marginal benefit and serious adverse effects. The severity of a given disease and the limited efficacy of a reference treatment in no way justify taking short-cuts in the pre-marketing evaluation: on the contrary, strict assessment is needed to offer patients a realistic hope of relief ;

–regarding pain relief, new drugs are often tested in conditions for which they are not actually intended; this is particularly the case of WHO step II analgesics.

–in rheumatoid arthritis ►►

► and other rheumatic diseases, almost all newly marketed drugs are immunosuppressants. The long-term risks of such treatments call for research on alternative approaches.

–in viral diseases such as hepatitis, treatment efficacy is based on viral load. This is an acceptable provisional endpoint, for want of anything better, but what really matters is the impact of treatment on mortality and morbidity.

Restoring confidence and credibility of authorities through transparency

Patients, health care professionals and citizens of the European Union are ready to support effective health initiatives. But experience shows that most research in Europe, and especially drug development, is done by private companies, and that regulatory agencies are not sufficiently demanding. As a result, companies have a free hand in their search for short-term

profitability, regardless of patients' interests. This situation has generated a plethora of drugs that offer no therapeutic advance whatsoever, and many of which target a limited number of profitable health problems.

If public funds are to be invested, the choice of research priorities, and the monitoring of this research, must be fully independent. Transparency is the best way of guaranteeing this independence. The Medicines in Europe Forum proposes the following measures:

–once priorities have been identified, a schedule of research work to be funded by the European Union should be made public;

–continued public funding should be conditional on due respect of the research schedule;

–public funding should be conditional on transparent research costs;

–health professionals and patients should be involved in defining research priorities, and also in controlling public funding;

–a public register of clinical

research priorities receiving partial or total public funding must be created.

–when a new drug hits the market the results of all clinical research should be made public, including trials with negative results, prematurely terminated trials, and any protocol modifications.

Supporting drug development for neglected diseases in poor countries

During the co-decision procedure preceding the adoption of Directive 2004/27/EC on medicinal products, the Medicines in Europe Forum noted a regrettable lack of interest on the part of the

European Commission, health ministers, and some European Members of Parliament in access to drugs for the poorest countries.

The Medicines in Europe Forum welcomes the fact that the WHO report on drug priorities commissioned by the Dutch Presidency mentions the needs of poor countries.

The Forum hopes that this will translate into a decisive financial and intellectual commitment by the European Union to research into the most serious diseases affecting these countries (malaria, tuberculosis, HIV/AIDS, sleeping sickness, etc.), and the adaptation of existing drugs to use in tropical countries.

The annex on neglected diseases in the WHO report entitled "Priority Drugs for Europe and the World" commissioned by the Dutch Presidency of the European Union describes the scale of the problem and suggests a number of steps designed to start to rectify it.

**The Medicines in Europe Forum
November 2004**