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Meeting Report

Drugs after 1992; an equation with many remaining unknowns

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Editorial Note: The weekly medical journal of The Netherlands – the *Nederlands Tijdschrift voor Geneeskunde* – has for many years periodically sponsored expert meetings to consider medical topics of current importance. On June 15th 1990, the Journal held a conference on the situation created by the promised common market for pharmaceutical products which is to be created by the European Community. The views expressed there represented professional reactions in one member state to a development which has been motivated by international economic interests rather than considerations of health or medical care. The report which follows appears simultaneously in Dutch in The Netherlands (Ned Tijdschr Geneesk 1990; 134, Nr. 38).

The common market for pharmaceuticals within the European Community (EC), which is expected to be implemented by the end of 1992, is looked forward to by many with mixed feelings and by some with misgivings. The rules and regulations, in the works since 1965, presumably will be ready in time, although no one yet knows what they will ultimately look like. More uncertainty exists with respect to the effects of the harmonization, in the short and in the long run. Numerous scenarios are going around in articles and commentaries, mostly based on speculations coloured by the writer's angle, since all kinds of interests are involved. Not just national, political and commercial interests: the "quality of health care" – a complex concept on which every nation has its own notions – has to be considered as well. The questions which prompted this Journal Conference were: will Dutch principles concerning quality of health care become hard pressed once the harmonization is a fact? Will patients' interests prove to be adequately guaranteed once the pharmaceutical industry, the wholesaler, the pharmacist, the insurer and the government have had their say? What will be the position of the physician? Will he be allowed to keep the large measure of freedom to prescribe what he considers

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necessary? And will the drugs to be allowed in(to) our country in the future still meet the criteria we currently apply? To none of these questions can a firm answer at present be given. Admittedly, expectations are being expressed, no less interesting if the speakers are insiders. *Conclusion*: for the time being it is an equation with many unknowns that will determine the future, and these unknowns will have to be filled in by those interested in their own ways.

Registration policy

The focal issue in the discussion is the future registration policy. With respect to the conditions to be fulfilled by new drugs in our country there is hardly any discord: scientifically as well as clinically, they will have to meet very strict requirements concerning composition, safety and efficacy. Such criteria are observed seriously in our country, as well as in such countries as the United Kingdom and Denmark. In practice, this means that from the metres-high piles of reports submitted by the industry with any application for registration, reports are made very conscientiously, which then are studied by the board members. The decision is usually based on these reports. Most central and southern European countries have other systems, generated by historical evolutions and probably not to be changed easily.

The question is now whether the administrative practice as used in The Netherlands for admission of new drugs, with assessment of their composition, efficacy and safety will also find its way to the other member nations, via EC guidelines. In official circles it is expected that the central registration requirements within the EC will certainly not be less strict than those currently in force in our country, and that other countries will go through a slow growth process in that direction. In particular, a stricter supervision of the application of the criteria is expected. If this is indeed to be the case, there appears to be little ground for pessimism.

However, we are being warned even now, a clear distinction should be made between the registration for the 12 member countries that is now being aimed for and that may even be accomplished at some future date, and the current situation. That situation is that at present in some member countries tens of thousands of different drugs are available, while in other countries, such as Denmark, Norway and The Netherlands, the supply is limited to only a few thousands (ranging from 2000–3000).

It is especially Germany, France and Italy where such large numbers of drugs are admitted. The procedure followed by The Netherlands Drugs Evaluation Board is definitely not generally accepted in the other EC nations: in a number of cases the procedures are less thorough and limited to checking the safety of the drugs.

Another warning beforehand: even when legal requirements in all countries will be identical, adjusted to European guidelines, they will always remain open to individual interpretation, to say nothing about the lengths of time that may be needed for guidelines to be incorporated into legislation. Equality in law is not yet equality in practice. The interpretation will doubtless also be influenced by cultural

differences, not just in medical but also in general culture. Some put it like this: the southerner is inclined to think that things will sort themselves out, the northerner thinks from the start that they may go wrong. The exactitude with which legal regulations will be implemented will undoubtedly be influenced by this aspect.

The question arises whether all this does not constitute one more argument in favour of one central registration of all drugs, one system replacing or surpassing the various national registrations. This may sound plausible but official circles are sceptical: it proves to be an old issue. For some time the Benelux had a central drugs registration service, with centralized evaluation, an experiment that failed mostly because of political influences and which would not appear to have a chance in the EC setting, either.

The objections at the time were of a practical and of a juridical nature. The practical objection is easily guessed: the excessive numbers of drugs already available in certain member states. A single central, comprehensive registration system would generate a gigantic flood of product applications from some 1200 manufacturers or registration holders in the EC territory, which would lead to unmanageable situations as known of the Food and Drug Administration. This in itself ought to be a sufficient argument for the maintenance of, at least, a decentralized procedure applicable first of all to drugs of only national or regional importance. After all, among those 1200 manufacturers, there are only a few dozen that occupy a truly international position.

Three procedures

The European Commission in an "orientation note" describes three procedures for new drugs that may exist side by side:

- a national registration, intended for drugs that are only of local importance and accordingly are only registered in the country in question;
- a European procedure for new drugs, with a central board that evaluates the files and may decide to register. This system is already in operation for so-called high-tech and biotechnology products. In the future, decisions of this board will be binding for all member states;
- a multiple-state procedure, based on the principle of reciprocal recognition by two or more member states. A drug will be registered in a member state on the basis of its admission by another EC member state, the file of the latter member state being regarded as sufficient guarantee. The Brussels Committee on Proprietary Medicinal Products (CPMP), established as early as 1976, will when necessary act as a committee of arbitration, which will probably not be superfluous considering the possible differences in requirements in member states.

The industry has a vital interest in a central registration of new products because this will free it from the necessity of applying for registration in 12 separate member states, each time with submission of fat files that have to meet requirements varying from state to state. The European pharmaceutical industry, joined in the European Federation of Pharmaceutical Industrial Associations (EFPIA), is on the whole in

favour of such a central procedure as stated by The Netherlands Pharmaceutical Industries Association (Nefarma) in its 1989 annual report, "provided", quoth the EFPIA, "the European registration committee can guarantee a certain expeditiousness of the procedures that is not lost when at some time a few more applications than usual come in, as might occur in times of new developments".

Indeed, central registration appears practicable if the number of new drugs to be registered does not exceed a few dozen annually. Meanwhile, some experience with this system has been gained through the special "concertation procedure", a joint consultation on biotechnology and high-tech products in Brussels. A number of applications for registration have passed through this procedure, and it was found to work. Several products have meanwhile reached the market by this route. For instance, the firm of Centocor of Leiden in 1988 submitted an application for (central) registration for a monoclonal antibody and gained admission via this procedure. It took some 11 months for the board in question to issue a (positive) recommendation which included the approved industrial package insert text.

Subsequently, the separate member states still had to decide on what to do with this recommendation. For this The Netherlands, Denmark and the Federal Republic of Germany needed 1.5, 1.5 and 2.5 months, respectively, while the United Kingdom took 10 months. On the whole, the experience with this special procedure has to be assessed positively, as Centocor's R.A. Drost recently stated at a symposium: the recommendation has indeed resulted in registration in a number of member states on identical conditions, which in those member states in all took a little over a year. Improvements of the procedure and shortening of the lengths of time required in certain member states are possibilities. For purposes of comparison: a new active drug substance now submitted to The Netherlands Drugs Evaluation Board will be dealt with in about 7 months, a reasonable period which in the recent past used to be considerably longer, in part because a reorganization of the Board took a great deal of time. One drawback of the central procedure that has meanwhile emerged is that it is sometimes started too hurriedly, which may result in the CPMP issuing a negative recommendation. Such a recommendation is practically irrevocable.

Apart from this central procedure intended for new, innovative pharmaceuticals there remains the problem of the countless drugs marketed in, especially, Italy, France and Germany. Can these situations be cleaned up?

According to reports, the European Commission intends to start a procedure against the West-Germans because in the Commission's opinion the German method of coping with the old product range (drugs which, although admitted, have still not been assessed for efficacy and safety) fails to meet the requirements of guideline 65/65 (guideline of 26 January 1965 concerning adjustment of the legal and administrative regulations regarding proprietary drugs, with a series of subsequent amendments). But regardless of whether this procedure will take place, it is felt that a drugs supply of such volume and diversity is by definition not acceptable for circulation within the EC, not even in the framework of (reciprocal) recognition of permits.

This leads the discussion to a relevant juridical-political problem: how is power distributed among the member states on the one hand and the European Commis-

sion on the other? The EC treaty does not provide for an autonomous public health section. For this reason, the member states will be disinclined to grant the Commission a major say wherever public health is involved: this domain remains primarily one of the responsibilities of the member states. Following this reasoning, the view may be defended that one single community procedure for the evaluation of drugs will also be contrary to the purport of the treaty itself: the powers of the Commission and of the Board will have to be established by a decision of the Board each time a case of this nature comes up. Admittedly, this may be avoided by a compromise, by establishing a form of "shared responsibility" between the Commission and the member states themselves: the central evaluation of new innovative drugs would then in any case be the responsibility of the Commission, being the only competent authority, while the other evaluations remain a matter for the member states themselves. Under such a system it is improbable that a cleaning-up of excessive drug assortments will take place: every member state remains boss within its own borders.

The influence of The Netherlands

Conversely, the question is: to what extent will the various member states be able to influence central registration policy? It is to be expected that each will want to maintain its own "protection level" via Brussels, as well, and will certainly not be prepared to lower this level, for instance because of economic interests. Will this not be beyond the power of a small nation such as The Netherlands?

The influence of The Netherlands, we are warned, should not be rated higher than its number of votes in the European Parliament warrants. The Netherlands might try to reach agreements at Benelux level, but even between Belgium and The Netherlands differences of view can be pointed out. The Netherlands by itself will therefore not be able to accomplish much. Furthermore, if a member state lodges objections and these objections are overruled, the drug in question will at a given moment be admitted for the entire European Community, including the nation that lodged the objections. On the other hand, when objections from one member state lead to a negative decision, this decision will also be binding for all other member states, including the state from which the product originates. Thus, rejection of a drug may also have a cleaning-up effect.

Still, it is of great importance to The Netherlands to keep the protection level high: the drug must be qualitatively sound. If the threshold of the central route proves too low, might the national threshold perhaps be raised? The national possibilities are limited but they do exist, as will appear below.

"Free circulation"

Apart from all this, it can be deduced from the proposals of the Commission that a common market for drugs in the European Community will be of limited

magnitude. The "market without internal borders" in Europe will number 250 million inhabitants (compared to 190 million in the U.S.A.) but only the major multinationals will be capable of including all 12 member states in their marketing efforts.

Also, the "free-circulation supply" should be taken with a large pinch of salt: for every drug a national licence will always be required, and that was initially definitely not intended. On the contrary, the intention was that a drug, once licensed in, for instance, the German Federal Republic, would then circulate in all 12 member states without much more paper work being required. This, now, has proved not to be feasible by a long chalk with the consequence that even in the future licences will have to be granted and the mass of paper work will remain. The cynical remark is heard that in each of the 12 member states reams of paper will still have to be filled to achieve an acceptable assortment of drugs.

How can a greatly increased supply of drugs, including less desirable ones, on the Dutch market be prevented? What are the available tools? All eyes are on the medical insurers, but these mostly pay for what is licensed. Might something be arranged via inclusion in the drugs package? If the number of reimbursable drugs is kept within limits, the pressure will go down by itself. But is it possible for drugs that are officially permitted, under whatever system, to be declared non-reimbursable or to be refused registration?

Restriction of the number of registrations is not a possibility. How to justify licensing drug X of manufacturer A, and a little later refusing to license drug Y of manufacturer B, when the two preparations in fact contain the same active substances? Any government doing so would run a strong risk of being summoned before the Luxembourg Court for putting up artificial barriers. On the other hand there is a rule that has been applied successfully for a long time now: that no combination preparation of more than one licensed drug will be registered unless it is clearly shown to have an added value. This rule is not unimportant, considering the boom of such preparations, particularly in Germany; there, cocktails of different drugs are popular and insight into the assortment of preparations is accordingly greatly impaired.

Are there no other possibilities of controlling the supply? The government has introduced the "drugs reimbursement system" in an attempt to "restructure the market effect". Under this system, drugs are grouped by class. For each group, a mean price is stated which may be reimbursed for a drug belonging to that group. For more expensive drugs the patient pays the difference. Although this system caused great commotion in the industry, the patients' associations and the Consumers' Union, and although it certainly needs some improvement, it might nevertheless exert considerable influence on prescribing behaviour. The main problem is the so-called equivalence of drugs within a group – a concept difficult to substantiate. Still, the government expects that this measure together with the adjustment of the price list structure for dispensing physicians under the Health Care Expenses Act will lead to an important saving on expenditure, possibly amounting to a thousand million guilders, in which case, it is expected, the rise of the cost of the drugs assortment would be halved. An important secondary effect of this system is

that, when the economic prospects of drugs sales in our country diminish, the long-run survivors will mostly be the important drugs. In addition this might stimulate the development of truly innovative drugs.

Prescribing behaviour

But does the consuming party play no part at all? What, for instance, is the influence of the prescribing physician?

In their prescribing, physicians may on the one hand be very conservative in that they tend to persist in a particular prescribing pattern, while on the other they may be inclined quickly to follow the industry when a new drug is introduced. A typical example is that of the beta-blockers, the market of which remained for years in the hands of one manufacturer, until a second drugs company, after a great deal of effort, succeeded in penetrating it. Some ten others, however, never got very far in this sector.

In this case, the medical profession stubbornly kept to the prescribing pattern once selected. To entirely newly introduced drugs, on the contrary, they prove to be highly sensitive and they are even easily confused about them. This confusion would doubtless grow much worse if the number of drugs available in our country were to increase sharply.

May the physician be expected, in case of a spate of new drugs, to be the consumption-limiting factor by a moderate prescribing behaviour? Considering the focal part he plays in the use of drugs, this could certainly be a possibility, but at the very least training and post-graduate education would have to be improved in anticipation of such situations.

Already, however, there is a tendency in The Netherlands to develop and use limited "formularies": in the regions as well as in individual hospitals, GPs and specialists increasingly consult with pharmacists about what drug is to be preferred for what complaint. Once consensus is reached, parties agree to stick to that choice. The resulting formularies as a rule contain a selection from different groups of drugs of which the pros and cons are known from scientific literature and practical experience. In these cases there is no need to fear a proliferating drugs supply, certainly not if the price factor is taken into consideration more than formerly.

And as regards the consumer: who exactly is he? Up to now the patient had little influence on what the physician prescribed for him, in fact he could hardly be regarded as a consumer at all. This situation appears to be changing. Patients more and more prove to be aware of what is going on in public health and medicine, and increasingly they approach their GP with questions and desires which he will try to satisfy. The future patients will probably more often ask their doctors for drugs of which they have heard or of which they have had experience abroad. If the patient benefits from such a drug, and it is available, the physician will prescribe it. In this way, pressure on the drugs supply might rise again.

It is the increasing flood of information via the media that informs patients and consumers of (new) technologies, methods of treatment and drugs and so promotes

their involvement in the choice. Consumer organizations are certainly not against this, although they wonder whether too much information might not do more harm than good. Furthermore, confidence in the physician should not be impaired. Therefore, information for the consumer as well as that for physician and pharmacist should be of good quality. The structures to achieve this certainly exist in The Netherlands.

For the rest, doctors are being approached and worked on ever more intensively by the industry, to make them include new or other drugs in their prescribing pattern, perhaps take part in "trials" of preliminarily admitted drugs or engage in so-called "post-marketing surveillance". By the latter is meant recording positive and negative effects of drugs which admittedly have been tested clinically, but of which the effects and side effects have not yet been assessed sufficiently in practice. Post-marketing surveillance may be a matter of debate, and debate there has been, but it is difficult to do without it. It is the only way of finding out if a drug in the long run comes up to expectations; it is sometimes called "phase 4 research". It is noted, however, that it is an expensive and time-consuming business and only makes sense if predefined (side) effects are looked for. Without a clear-cut structure the findings are useless.

We may add that the Public Health Council (Gezondheidsraad) has set up a committee to assess post-marketing surveillance, and this will doubtless issue a recommendation soon. The European Commission in its last proposals on the future registration system will pay attention to this problem, also.

Future use of drugs

The chairman: "Can we, to conclude, answer the question whether the use of drugs will increase considerably once the European economic internal borders will be abolished?"

Although it remains crystal-gazing, there is no real need to fear that use will increase as the supply grows. At present, 80% of the costs of the entire range of proprietary drugs (4000) is accounted for by 800 preparations, which leaves 20% for the remaining 3200. It appears that actually it makes little difference to consumption whether there are 4000, 6000 or 10 000 admitted drugs.

Footnote

The conference was attended by: Dr A.W. Broekmans (internist, Drugs Evaluation Board), Prof. Dr M.N.G. Dukes (MD LL.M, World Health Organization), N. van 't Grunewold LL.D. (National Association of General Practitioners), Mrs. C. Hodgkin (coordinator Health Action International, Europe), Prof. Dr H. Lamberts (Activities Committee, Nederlands Tijdschrift voor Geneeskunde), J.F.C. van Luyn (Medical Insurance Board), Prof. Dr F.W.H.M. Merkus (pharmacist, Medicofarma), F. Moss LL.D. (Royal Dutch Pharmaceutical Association), Dr L. Offerhaus (internist, World Health Organization), Dr A.J.P.M. Overbeke (Editorial Board, Neder-

lands Tijdschrift voor Geneeskunde), Prof. Dr H.G.M. Rooijmans (Board of Governors, Nederlands Tijdschrift voor Geneeskunde), Mrs. Prof. H.D.C. Roscam Abbing LL.D. (University of Limburg), R.J. Samsom (Ministry of Welfare, Public Health and Culture, General Management Health Protection), Drs H.C.M. Tijmensen (Management, Contact Organ National Organizations of Medical Insurers); organizers: E.J. Beer and J. van der Heide. The Chair was taken by Prof. Roscam Abbing.