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DRUG INFORMATION

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Ensuring the quality of services

By 1990, all Member States should have built effective mechanisms for ensuring quality of patient care within their health care systems.

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DRUG INFORMATION

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Note

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CONTENTS

Introduction

Hosted by the Hungarian Ministry of Social Affairs and Health, the Meeting was held at the National Institute of Pharmacy, Budapest, and organized by the WHO Regional Office for Europe, with generous support from the Ministry of Welfare, Health and Cultural Affairs of the Netherlands. The participants were welcomed by the Secretary of State of the Hungarian Republic on behalf of the Minister of Welfare and by Ms Inga Lunde (Consultant, Pharmaceuticals) on behalf of the WHO Regional Director for Europe. The participants are listed in Annex 2.

Background

The Meeting was held because a number of countries in central and eastern Europe are undergoing fairly rapid transition from state-regulated economies to open-market systems. The degree of change this brings with it - and the extent to which these countries are prepared for it - naturally depends on the degree of liberalization that has occurred in the past.

In those countries where centralization has until now been most complete, the transition demands very rapid adjustment to both new opportunities and unfamiliar problems. The latter can result from acute changes in the procurement, distribution and advertising of medicines to doctors and pharmacists and also to the general public. Whereas formerly the number of medicines available was fairly limited and competition between drug manufacturers was absent or minimal, the introduction of a free-market economy will entail fundamental alterations, both quantitatively and qualitatively.

Increasingly, pharmaceutical companies will seek entry into this huge, still largely untapped market with a great number of drugs. Some of them may be based on

totally new principles, some may be very expensive, and many have similar patterns of action and therefore introduce economic competition, perhaps for the first time. The introduction of commercial marketing may in the future entail advertising of medicines to the professions and of over-the-counter (OTC) drugs to the general public with all available and acceptable methods: direct mailing, information meetings, medical representatives, clinical trials, etc. For some countries in central and eastern Europe, these processes are entirely unfamiliar.

In countries with an established market economy, proper information on the use of drugs hinges on a balance between information from commercial sources and that provided by universities and postgraduate institutions, professional organizations, the government and the medical press. Drug regulation has increasingly become internationalized in collaborative institutions like the Nordic Council on Medicines and the European Economic Community. The pharmaceutical industry has introduced the concept of self-regulation and codes of conduct. Legislation is being tightened, requiring stricter quality control and supervision of clinical trials.

However, if left unchecked, the ingress of unlimited marketing of drugs into the countries that were the subject of this Meeting might be hazardous, particularly where the rational and critical use of medicines has so far not been well developed in university teaching and in postgraduate education simply because many modern drugs were not available. The participants, therefore, addressed the following approaches:

- the role of drug regulation by national and supranational authorities;

- clinical trials and drug information;

- independent drug information services in different regions of Europe;
- the relative importance and function of all other drug information systems;
- the dangers of inappropriate or inadequate information;
- quality control of drug information; self-regulation by the pharmaceutical industry through codes of conduct.

Responsibilities and tasks in the field of drug information

Three participants described the work of authorities in their regions and summarized the work they envisaged for the next two to three years, emphasizing the desirability that policies and roles in different parts of Europe should converge and ultimately be harmonized.

The European Community and the Nordic countries have advanced furthest in formulating standards and requirements for drug information to be provided by pharmaceutical manufacturers. In the European Community, directives will cover:

- the summary of product characteristics (SPC);
- the summary basis of approval;
- the labelling of medicinal products for human use and on package leaflets; and
- the advertising of medicinal products for human use.

Developments in the Nordic countries, which go back over 20 years, are largely compatible with the proposed regulations in the European Community, though there are differences in a few matters of detail. It was also clear that the European Community could benefit from the Nordic countries' experience with:

- recommendations developed by specialist groups on drugs in their therapeutic areas;

- drug formularies which help the user to compare different drugs in the same therapeutic group; and

- local district or hospital drug committees.

Concerning information which should be given to patients, it was agreed that minimum information under various headings must be given, but that there remained many difficulties, including:

- the definition of recognized indications and the wording in which they are expressed;

- the extent and completeness of information on adverse effects;

- the ways in which the information could best be distributed, and how to ensure that patients are neither confused nor frightened by the information given.

In Czechoslovakia, Hungary and Poland, medicine control systems are in a state of transition. Old regulations and mechanisms of control have ceased to function effectively and need urgent rethinking and replacement. This may be hampered by a shortage of trained people. Attention was drawn to the basic requirements of a medicine control system which would serve as a basis for a national drug information policy.

The system of drug regulation must be adapted to cope with the great number of products which will become available in these countries. This workload, and the introduction of a completely new element of commercial drug promotion, will make new organizational and procedural demands on national authorities.

During the discussions, it was emphasized that direct and close collaboration among authorities is essential in meeting these challenges. The provision of independent information needs to be considered before marketing (at the time when the company applies for registration of a product) and during marketing. Efficient arrangements for updating information are needed. Special problems that were mentioned included televised advertisements for drugs; in Poland, for example, the existing law for controlling this is not implemented. It was also noted that doctors must be given information on prices. If they lack such information they cannot be expected to use drugs economically.

Clinical trials and drug information

Since clinical trials are an important source of drug information, especially for new drugs, the quality of the clinical trials has an important influence on the quality of the information. In the past, many clinical trials have for various reasons been unreliable or even misleading, and therefore in many countries guidelines have been developed for good practice in the design and performance of trials - the so-called good clinical practice (GCP) guidelines.

Although these differ in the United States, the European Community and the Nordic countries, they have the same aims. Their purpose is to ensure that all

parties involved in the evaluation of medicines share the responsibility of accepting and working according to such GCP standards in mutual trust and confidence. Standardized systematic written procedures are specified for the organization, conduct, documentation and verification of clinical trials. The aims are to ensure the protection of the trial subjects, to make the data as reliable as possible, and to improve the ethical, scientific and technical quality of trials. The adoption of common GCP guidelines should facilitate reciprocal recognition of trials between different countries and so reduce wasteful and inefficient duplication of trials - which could in itself be considered unethical.

The implementation of the GCP guidelines will profoundly change the relationship between clinical investigators, pharmaceutical companies sponsoring trials, and regulatory authorities. Investigators will have to get used to more critical review from ethics committees and other bodies, both local and national, with detailed checks of their work and inspection of their records. The impact of GCP guidelines will be greatest on large multicentre studies and much less on small pilot studies. Concern has been expressed that this will impede individual research workers who wish to pursue their own ideas, and perhaps this threatened species will need special help and protection.

It was pointed out that although the adoption of GCP will improve the reliability and relevance of data obtained in clinical trials, important gaps in information will remain that are not being filled by appropriate trials. Such gaps are inevitable unless regulatory authorities demand the missing data or academic studies supply them when the industry is unwilling to do so. Furthermore, the interpretation of trial data will still be largely independent of the quality of the data: good-quality data can still be misinterpreted or misrepresented. Editors of scientific

journals must continue to be on their toes to prevent marketeers from stepping on them.

Although drugs and diseases know no frontiers, medical practice is strongly culture bound. This makes it necessary to translate the clinical findings of trials into different national contexts. It may therefore be useful to conduct clinical trials of a new drug in the country where it is to be marketed, even if reliable trials have already been performed elsewhere. It should go without saying that such local trials should make some useful contribution to knowledge about the drug, and should be performed in accordance with GCP guidelines. An alternative approach might be restricted registration, allowing use only by relevant specialists. The basis for such restricted release should be close monitoring of therapeutic acceptability. This is less onerous and less expensive, and perhaps no less publishable than a mediocre trial.

Such a less ambitious approach may also use limited resources, skilled investigators and specialized clinics more effectively.

Differences between European countries in drug information systems

The core information about a drug is kept in the dossier held by the national registration authority. This contains all the relevant information about its quality and its efficacy and safety in the approved conditions of use. It also guarantees that the data have been examined by the authority - though the thoroughness with which this has been done may vary. All information about the drug issued by the manufacturer must be consistent with these data, but most registration authorities give a low priority to checking such compliance.

Information about new drugs is often disseminated in compendia for prescribers and pharmacists, and for the public in periodicals and occasionally in press statements. Often the compendia are published by the industry, but the contents must be approved by the authority. The authority also collects and assesses data obtained after a drug has been marketed - e.g. from clinical trials and adverse reaction (ADR) reports - and disseminates selected information whenever this is considered necessary. The data come from a wide variety of sources: manufacturers, spontaneous ADR reports, regulatory agencies in other countries, the scientific literature, WHO.

In Hungary, the National Institute of Pharmacy is the registration authority and it also coordinates the national drug information service. It publishes the Guide for drug prescribing, which contains the data sheets of all drugs marketed in the country, and Formulae normales for drugs compounded in pharmacies. A monthly journal, Gyógyszereink, is produced for doctors and pharmacists, and the NIPh Bulletin contains more specialized news of regulatory decisions, guidelines for trials, etc. A central drug information service is based on the NIPh library and answers written and telephone enquiries. It is linked to a national drug information pharmacists' network comprising 50 specially trained community and hospital pharmacists who are in touch with local hospitals and general practitioners.

In Czechoslovakia, the State Institute for Drug Control has built up a computer database of drugs used in all countries represented on the Council for Mutual and Economic Assistance (CMEA). A "micro-version" of this database system has been developed, which covers all drugs registered or undergoing clinical trial in the country and requires only a 10 Mb hard-disk memory. It will be used on personal computers in all centres of clinical pharmacology and in the larger pharmacies.

In Sweden, the regulatory authority is the Läkemedelsverket (LV). It approves the text of data sheets for professionals and for patients, compendia of which are published by the industry. Drug information centres in Sweden are coordinated by the National Corporation of Pharmacies (Apoteksbolaget), which also publishes much material for patients, pharmacists and prescribers. LV holds workshops where national experts discuss the treatment of various conditions, and distributes the reports of these to all doctors. The ADR data in the LV computer are freely accessible to the public. Since they ceased to be secret, they have been of no interest to journalists and the main users are drug information centres.

Other sources of drug information

Prescribers get information about drugs from a variety of sources, including: textbooks of pharmacology and of therapeutics, formularies (local or national) and officially approved data sheets; more or less promotional material from the industry; drug bulletins independent of the industry; medical journals of all kinds; and specialized books, for example about adverse effects of drugs or about the management of particular conditions.

Books take a long time to produce and are therefore liable to be out of date. This is to some extent true of formularies too, but can be more easily remedied. Material in bulletins and in medical journals, on the other hand, is produced relatively quickly and can be updated during production. Data-sheet information often has to be negotiated between a company and the regulators, and this often causes delays.

Advertisements and other promotional matter can provide much useful information, but their primary

purpose is to advocate the use of a drug and to sell it - not to help prescribers use it with discrimination and skill. Companies will often be biased in their selection of promotional information and such information is not always subjected to critical scientific scrutiny. This kind of material cannot readily be published in good, peer-reviewed journals, and if published at all may appear in sponsored journals, special symposium supplements, or presentations at congresses.

Even educational activities, which can be of great value to doctors, and some post-marketing research sponsored by industry are ultimately intended to increase sales, albeit indirectly, e.g. by giving company representatives access to prescribers who would otherwise not receive them. It must, however, be said that the medical and research departments of some companies are collaborating in a very positive way with academics and clinicians to make certain types of information, for example on ADRs and drug use in pregnancy, more comprehensive and usable.

Books, medical journals, formularies, data sheets and bulletins are typically used in quite different ways. Books are good for giving discursive general background information, and for treating broad or narrow subjects in depth. Review articles in medical journals also do this in a more limited way, but some journals have a regular slot for critical articles on therapy (for example the Danish, Dutch and Norwegian medical journals). These articles fulfil the same functions as drug bulletins (see below, p. 11).

Formularies guide the prescriber to varying degrees. Some are comprehensive, showing the range of drugs that can be used for a particular purpose, and may explain how to make good choices from this range; others offer a selection of preferred drugs. They may also give the essential information needed to use the drugs, but can rarely give much background.

Data sheets provide more detailed information about individual drugs, expressed from the viewpoint of the manufacturer and the regulatory authority, but the information may be difficult for prescribers to translate into action. The main objective of long lists of side effects in the data sheet might be to protect the manufacturer against liability claims.

Drug bulletins approach the prescriber differently: they examine therapeutic problems and drugs from the prescriber's standpoint. They may give brief background orientation, discuss the evidence for the value of a drug or a treatment, make comparative assessments, and suggest conclusions about when and in what way a treatment is worth using. Bulletins aim to be independent of the pharmaceutical industry and as far as possible of governmental authorities, and to present readers with impartial, unbiased professional material. They can discuss controversial subjects which the industry or an official government publication may not be able to raise. If necessary they can criticize individual advertising claims, therapeutic recommendations and sometimes even official licensing decisions. Of course, general medical journals can also do all this, but the dependence of many journal publishers on income from pharmaceutical advertising may inhibit editorial policy.

Most drug bulletins publish a wide range of material: assessments of individual drugs, especially new ones, and of groups of related drugs; evaluations of new treatments in relation to established ones; the management of particular therapeutic problems; adverse effects of treatment and their effect on the way the treatment is best used; costs of treatment; what information patients need from health professionals about particular treatments; the relationship of drug and non-drug treatments in particular conditions; the monitoring of drug treatment; review of old and perhaps obsolete drugs; discussion of prescribing policies and

of regulatory issues. The International Society of Drug Bulletins (ISDB), founded in 1986 with the support of the WHO Regional Office for Europe, aims to promote the international exchange of information of good quality on drugs and therapeutics, to encourage and assist the development of professionally independent drug bulletins in all countries, and to facilitate cooperation among bulletins.

In addition to printed information in formularies and drug bulletins, prescribers often need direct individual help when facing a new problem in prescribing. Pharmacists meet similar problems. A drug information service based in a university hospital or a large regional centre and staffed jointly by pharmacists and clinical pharmacologists can provide a broad spectrum of well founded and helpful advice to doctors and pharmacists in its region. It is, however, an expensive way of using scarce resources: clinical pharmacologists are few and busy, and their expertise is needed to benefit the medical community at large rather than the tiny proportion of practitioners who realize that they have a problem and know whom to ask. The logistic inefficiency of such a drug information service could be mitigated by publishing the most important and interesting questions and answers for all prescribers and to pharmacists.

Dangers and consequences of inadequate information: conflicting interests

When a drug is first introduced into medical practice, relatively little is known about it. It is important for registration authorities, investigators and also prescribers to be aware of potentially serious gaps in information. Incompleteness is related to the standards or expectations of the recipient; one authority may require over 100 volumes of data, another

only one - but more information does not necessarily lead to better decisions. Inconsistency between the information for different preparations of the same drug is a type of incompleteness which creates difficulties for everyone.

Some missing items of information may exist but be unpublished because their importance is unrecognized, or because a company is unwilling to acknowledge them. This happens most often in the case of suspected ADRs, where data are very soft. But such data should be treated very seriously. As they accumulate and are critically evaluated, the way the drug is used may have to be modified. Strict and well enforced regulations are therefore needed on the reporting of adverse events possibly caused by a drug or device.

The other side of this coin is the abuse of data on ADRs and quality defects concerning a product or group of products for the promotion of competing products. Repeated campaigns claiming the unreliability of generic products have been prominent examples.

Inadequate or incorrect information in promotional materials may or may not infringe one of the industry's national codes of marketing practice, which now exist in a number of countries, or the international code administered by the International Federation of Pharmaceutical Manufacturers Associations (IFPMA), which applies to all companies that are members of constituent associations throughout the world. Self-regulation by the industry has shown a modest improvement in some countries during recent years but is far from effective. Two reasons are that where the codes exist they are operated by the industry in private and they lack adequate sanctions.

Recommendations

The following recommendations are intended to help national drug regulatory authorities.

1. Information on drugs should be considered freely available and open to all users unless there are specific reasons for certain categories of information which have to be restricted.

2. In providing such information, regulatory authorities should work to the same standards.

3. Collaboration on drug information matters between national authorities is most desirable. The development of compatible systems for exchanging information will facilitate this.

4. In countries newly moving to a market economy, the need to register large numbers of new products could greatly increase the workload and this may require an increase in trained staff and other resources. One way of funding the increased work is by charging realistic application fees.

5. Official information about drugs should always include details of the prices of medicines, both in the national health system and bought privately.

6. All European drug authorities should work towards the adoption of GCP guidelines. This will entail training of the staff of regulatory agencies, of investigators and of people working in pharmaceutical companies.

The responsibility of ethics committees under the GCP guidelines will also need special consideration.

7. The preclinical data about a drug need central evaluation before a clinical trial, but to minimize delays a clinical-trial exemption scheme deserves consideration.

8. The increasing adoption of international norms for trials should reduce the need for local trials which merely replicate previous work.

9. The cost-effectiveness of different treatments, however, can differ markedly in different countries, and cost-effectiveness studies should therefore be encouraged.

10. The scientific and ethical quality of work undertaken has to be evaluated by institutional, regional, and/or national ethics committees in accordance with the local laws.

11. Drug utilization data at different levels - individual practices, health unit, region and country - are an essential ingredient of successful drug information management.

12. Drug information provision is essential to proper therapeutic audit. Audit of treatment in practice will highlight needs for particular types of drug information and their relative priorities.

13. Independent information prepared professionally on drugs and their therapeutic use is essential for the critical evaluation of information and claims about specific products. Independent drug bulletins, review articles in general medical journals, and special publications from professional organizations and regulatory bodies all have a part to play.

14. During undergraduate, postgraduate and continuing education in medicine, training in rational pharmacotherapy needs much greater emphasis.

15. As part of this training, students and doctors should be taught how to read and analyse scientific publications - particularly reports of drug trials - and how to assess promotional material.

16. The reporting by doctors and pharmacists of suspected adverse reactions to drugs and devices should be encouraged. Regional and local ADR reporting schemes may improve participation by practitioners. Feedback of relevant data, preferably evaluated, to those reporting ADRs is often an acceptable reward.

17. Data sheets and information for patients for different brands of the same drug should be identically worded except where the special characteristics of a product have to be described.

18. Company representatives who visit doctors should be encouraged to make their presentation to groups of doctors working together rather than to individual practitioners.

19. While standards for truthful, complete and relevant promotional information require legal backing, the pharmaceutical industry should be required to set and maintain standards of high quality in this respect.

Annex 1

BACKGROUND PAPERS

The following is a list of summaries and full texts of presentations made at the Meeting. Please contact the Pharmaceuticals unit at the WHO Regional Office for Europe* if you wish to receive copies.

ICP/DSE 165/6	Clinical trial assessment - epidemiology and statistics, by Dr L. Offerhaus
ICP/DSE 165/7	The general medical journal as a source of drug information, by Dr L. Offerhaus
ICP/DSE 165/8	The regulatory authorities' view and the European Community, by Dr E. Hvidberg
ICP/DSE 165/9	Clinical trials and drug information: European Community and Nordic Council GCP guidelines, by Dr E. Hvidberg
ICP/DSE 165/10	The pharmaceutical industry as a source of drug information, by Dr H. Kopera
ICP/DSE 165/11	The Hungarian drug information service, by Dr T. Paal
ICP/DSE 165/12	Local clinical trials as a source of information by, Dr E. Ludwig

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ICP/DSE 165/13 Dangers and consequences of inadequate information: conflicting interests, by Dr R.C. Hall

ICP/DSE 165/14 Drug bulletins as sources of drug information, by Dr A. Herxheimer

ICP/DSE 165/15 Problem-oriented drug information service: the link between clinical pharmacology and pharmacy, by Dr F. Follath

ICP/DSE 165/16 The regulatory authorities' view: EFTA/Nordic Council countries, by Dr P. Manell

ICP/DSE 165/17 Drug information systems in North-western Europe, by Dr P. Manell

ICP/DSE 165/18 Quality control of drug information and the IFPMA code of pharmaceutical marketing practices, by Mr H. Mandahl

ICP/DSE 165/19 The regulatory authorities' view: Eastern and Central Europe, by Professor J. Svihovec

Annex 2

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[a] Participation expenses not paid by WHO.

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[a] Participation expenses not paid by WHO.