

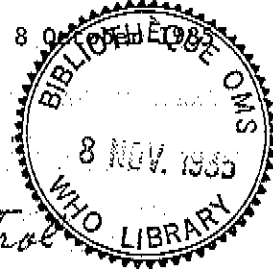


CONFERENCE OF EXPERTS ON THE
RATIONAL USE OF DRUGS

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CONTROL AND DISTRIBUTION OF HUMAN MEDICINES IN THE UNITED KINGDOM

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CONTROL AND DISTRIBUTION OF HUMAN MEDICINES IN THE UNITED KINGDOM

DRUG MARKETING PRACTICES

Regulatory control of medicines

1. The United Kingdom has a comprehensive system of controlling human medicines which has developed over the years.
2. High standards generally existed in the pharmaceutical industry, although until 1964 there was no necessity for a manufacturer to seek approval from an independent body before commencing clinical trials or putting a new drug on the market in the United Kingdom. These matters did not come under control until the Committee on Safety of Drugs was established in January 1964 in consultation with the medical and pharmaceutical professions and with the pharmaceutical industry following the thalidomide disaster.
3. Although the terms of reference of the Committee were to review the available evidence for new drugs and to advise on their toxicity, the Committee had no legal powers and operated strictly on a voluntary basis. A very important consideration to the successful operation of this system was that the major pharmaceutical manufacturers, members of the Proprietary Association of Great Britain (PAGB) and of the Association of the British Pharmaceutical Industry (ABPI) agreed to seek the Committee's approval before commencing clinical trials with a new drug and also before placing it on the market. The voluntary system worked well but it was realized that this was only an interim measure until comprehensive legislation could be established to provide legal controls over the supply and sale of medicines.
4. The Medicines Act (1968) is a comprehensive piece of legislation. It was implemented in September 1971 and exercises control over the manufacturer, importation, sale and supply, labelling and advertising of medicines. A Medicines Commission has been established to give general advice on the various aspects of the enforcement of the Act. It also functions as an appeal body for the activities of a number of expert advisory committees. In this context, the best known of these expert committees is the Committee on Safety of Medicines (CSM) which replaced the Committee of Safety of Drugs (CSD) in 1971.
5. The Biological Standards Act (1975) established the National Biological Standards Board. This Board, appointed by United Kingdom Health Ministers and funded by the Health Department, is responsible for standards and control of biological substances, i.e. substances whose purity and potency cannot be adequately tested by chemical means such as hormones, blood products and vaccines. The Board operates through the executive arm, the National Institute for Biological Standards and Control.
6. Before a clinical trial on patients can be conducted on a new drug or a new drug marketed in the United Kingdom, the supplier must hold a valid Clinical Trial Certificate (CTC) or Product Licence (PL). Studies in normal healthy volunteers are not subject to the Medicines Act and notification to the Licensing Authority is not required. In practice many clinical trials are carried out under the exemption scheme introduced in 1981 (see paras 14-17).
7. Licences are issued by the Licensing Authority which acts for the Health Ministers. In practice the licensing of human medicines is handled by the Medicines Division of the Department of Health and Social Security (DHSS), staffed by a total of 19 doctors, 81 pharmacists, 158 administrators and four lawyers.

8. The Act defines a medicinal product as a substance or article intended for use mainly or wholly for a medicinal purpose for administration to human beings or animals.

9. In determining whether licences should be issued, and the conditions under which they should be issued, the Licensing Authority obtains advice on the quality, safety and efficacy of medicines from various advisory committees and the National Institute for Biological Standards and Control as appropriate. These advisory committees consist of independent experts such as hospital clinicians, general practitioners, pharmacists and clinical pharmacologists, not the staff of the DHSS, and are appointed by Ministers on the advice of the Medicines Commission. The relevant advisory committees are:

(i) Committee on Safety of Medicines (CSM). This committee advises the licensing authority on questions of the safety, quality and efficacy of new medicines for human use. It is also responsible for collecting and investigating reports on adverse reactions to medicines already on the market. A number of sub-committees have been established to assist the main committee in its work.

(ii) Committee on the Review of Medicines (CRM). This committee advises the licensing authority on the review of the safety, quality and efficacy of products already on the market.

(iii) Committee on Dental and Surgical Materials (CDSM). This committee as its name implies, provides advice on a range of products which fall outside the expertise of the CSM.

10. The British Pharmacopoeia Commission (BPC) is responsible for preparing future editions of the British Pharmacopoeia and for selecting non-proprietary names for medicinal substances.

Clinical Trial Certificates

11. A clinical trial in the terms of the Act is an investigation, or series of investigations, consisting of the administration of one or more medicinal products, where there is evidence that they may be beneficial, to a patient by one or more doctors or dentists for the purpose of ascertaining what effects, beneficial or harmful, the products have.

12. The Licensing Authority does not lay down rigid requirements concerning the data which must be provided before authorization can be given for the clinical trial of a new drug. It issues guidelines for applicants. Essentially the application will consist of a detailed clinical trial protocol together with the supporting experimental animal data. The latter will include: the chemistry, pharmacy and pharmacological activity; pharmacokinetic studies in animals which provide information on the likely absorption, distribution and excretion in man; preliminary metabolic studies in man may also have been performed. Other data received at this stage will include acute and chronic toxicity studies and information on possible effects on reproduction. Taken together these data give information on the therapeutic potential of the new drug and on its likely margin of safety. Details of animal and clinical studies performed abroad are relevant and will be considered.

13. These data are assessed by the professional pharmaceutical and medical staff of Medicines Division of the Department of Health and Social Security (DHSS) and are then referred to the relevant Sub-Committees of the Committee on Safety of Medicines. Most applications are referred to the Sub-Committee on Chemistry, Pharmacy and Standards and to the Sub-Committee on Safety, Efficacy and Adverse

Reactions. A separate Sub-Committee considers Clinical Trial Certificate applications for biological substances. If the data are considered to be satisfactory, the Committee on Safety of Medicines will advise that a Clinical Trial Certificate can be issued by the Licensing Authority for the supply of the drug for the specified trials and clinical indications detailed in the application. It is important to note that the holder of the certificate has an obligation to inform the Licensing Authority of any serious or unexpected adverse effects which occur during the course of the trial. Rights of appeal against a decision to refuse a Clinical Trial Certificate are the same as detailed in the section on product licences.

Clinical Trial Exemption Scheme (CTX)

14. The Clinical Trial Exemption Scheme (CTX) came into operation on 11 March 1981 to provide the statutory basis for a new scheme under which pharmaceutical companies may secure exemption from the need to hold a Clinical Trial Certificate and proceed to rapid clinical trial for chemicals of interest as prospective medicinal products. This has been a major advance in permitting studies of promising compounds at an early stage so that manufacturers can decide whether to continue with further expensive studies or to discontinue work on the compound. The scheme also effectively encourages clinical trials to be performed in the United Kingdom rather than elsewhere. Since its inception the scheme has been well received by industry and has been an undoubted success.

15. The basis of the CTX scheme is that together with a detailed clinical trial protocol, summaries of chemical, pharmaceutical, pharmacological, pharmacokinetic, toxicological and human volunteer studies may be submitted instead of the additional details normally required for a CTC or PL application.

16. This exemption scheme is based on the requirement that: (a) a doctor must certify the accuracy of the data; (b) the supplier undertakes to inform the Licensing Authority of any refusal to permit the trial by an ethical committee; and (c) the supplier also undertakes to inform the Licensing Authority of any data or reports concerning the safety of the product.

17. The Licensing Authority has 35 days in which to consider and object to the application if it wishes; an additional 28 days may be invoked if necessary. If the Licensing Authority refuses the exemption then the applicant has no right to make representations but will need to apply for a Clinical Trial Certificate in the usual way.

Product Licences

18. A Product Licence authorizes the holder to sell and supply the named product. A Product Licence also applies where the licence holder has made arrangements for a supply which is manufactured elsewhere. The Product Licence thus covers all the main activities associated with the marketing of a pharmaceutical preparation.

19. Applications for Product Licences are made to the Licensing Authority. They must be accompanied by the relevant supporting data relating to pharmaceutical quality, safety and efficacy for the proposed indications. Detailed guidelines on quality, pre-clinical testing and clinical trial requirements are issued by the DHSS. The Licensing Authority must satisfy itself regarding the quality, safety and efficacy of the product before issuing a licence. The "need" for the product, its price and its efficacy compared to existing products are not considered. Applications are assessed by the professional staff of Medicines Division and referred to the appropriate advisory committee, usually the Committee on Safety of Medicines. If the Licensing Authority wishes to refuse an application the

applicant has the right to make representations, in writing or orally, to the Committee; the applicant also has the right to make further representations to the Medicines Commission if the Licensing Authority still intends to refuse the application after considering the representations made before the Committee. In all cases the various advisory bodies only provide advice - the Licensing Authority is the only body with power to grant or withhold licences, although the advice of the advisory committee is nearly always accepted.

Adverse reactions voluntary reporting system

20. A most important aspect of the United Kingdom regulatory system is the scheme provided by the voluntary reporting of adverse reactions to marketed drugs.

21. Since most serious adverse reactions are rare events they are unlikely to be detected in early clinical trials. The problem is essentially one of numbers since relatively small numbers of patients are exposed to a new drug before it is released on to the market. Marketing may, therefore, be the first adequate safety trial.

22. The main functions of the adverse reaction reporting system are (i) to provide an alerting signal of a risk due to a particular drug, (ii) to provide confirmation of an alert detected by some other method and (iii) to provide data to assist in the evaluation of comparative risks of related drugs.

23. The input to the system is essentially derived from the spontaneous voluntary reporting of adverse reactions by practising physicians on the prepaid postage reporting forms which are distributed widely to the profession and to the pharmaceutical industry. Other important sources of information are the Government's Office of Population Censuses and Surveys (death certificates, congenital abnormalities, cancer registers and mortality statistics), professional publications and the WHO adverse reaction monitoring system in Uppsala, Sweden.

24. Approximately 12 000 reports are received per annum and some 145 000 have been entered into the Adverse Reactions Register since it was initiated in 1964. It must be emphasized that all reports are treated in the strictest confidence and the identity of the patient or reporting doctor is not revealed without the written permission of the latter. The information is stored by computer after evaluation by the medical staff of the DHSS. Problems signalled by this system may lead to immediate action or initiation of special studies involving follow-up by a team of 200 part-time medical officers who can interview doctors in any part of the United Kingdom. After consultation with the pharmaceutical company and presentation of the problem to the Committee on Safety of Medicines through the Sub-Committee on Safety, Efficacy and Adverse Reactions (SEAR), action may be taken voluntarily by the manufacturer, or the Committee may decide to issue a letter in the medical journals or to send an individual letter to every doctor (and possibly dentist and pharmacist) in the United Kingdom, or to publish a statement in the Adverse Reaction series (which first appeared in 1964) or in Current Problems (which first appeared in 1976). This may be accompanied by the publication of a scientific paper in the case of a detailed study. Occasionally, this action will result in a variation to the Product Licence for the drug concerned or, rarely, to withdrawal.

25. Since the reporting of adverse reactions by the practising doctor is voluntary, the most serious limitation of the system is under-reporting, since only a proportion of those adverse reactions which actually occur are reported. An indication of drug usage is often valuable in assessing the importance of a problem, and prescribing statistics from a sample of prescriptions in general practice are often helpful.

Harmonization within the European Community

26. The United Kingdom became a member of the European Community in 1973. There are four major Directives on human medicines. Council Directive 65/65 involves arrangements for granting marketing authorizations. Council Directive 75/318 involves requirements for pre-clinical testing, pharmaceutical quality and manufacture.

27. A move towards harmonization within the European Community was taken when Council Directive 75/319 was adopted in 1975. It provides for the setting up of a Committee for Proprietary Medicinal Products (CPMP) in Brussels, and a procedure for obtaining marketing authorizations throughout the community. The CPMP is made up of one official from each of the member states. It discusses problems of common interest, particularly on exchange of information on adverse drug reactions, and it plays a central role in the community procedure for obtaining marketing authorizations. This procedure is invoked when a company obtains a marketing authorization in one member state and wishes to obtain similar authorizations in five or more other member states. The application is forwarded by the first member state to the EEC Commission and to the other states in question. The various states concerned have 120 days in which to grant marketing authorizations or raise objections.

28. In November 1985 Council Directive 83/570 comes into force. This Directive amends the earlier ones with respect to the format and data requirements for applications for marketing authorizations. It also changes the procedure for obtaining marketing authorizations throughout the community CPMP procedure.

Brand and generic names

29. The British Pharmacopoeia Commission is authorized by the Medicines Act 1968 to assign generic names to drug substances and to other materials used in the formulation of medicines. The names are known as British Approved Names (BAN).

30. This work is carried out in very close collaboration with other national nomenclature agencies, such as the United States Adopted Names Council. The endeavours of such national agencies are co-ordinated by the World Health Organization which publishes most of the names as International Nonproprietary Names (INN). The Member States of WHO are then encouraged to accord official recognition of INN in their domestic drug legislation.

31. In contrast to generic names which relate to ingredients, brand names relate entirely to the finished product, and serve to identify the manufacturer. In the absence of a brand name or of a visually distinctive assembly, identifying the source of a product can be a serious problem. Brand names are usually, but not necessarily, based on a registered trade mark which confers upon the manufacturer certain protective rights akin to patents rights.

The labelling of medicinal products

32. The labelling of medicinal products in the United Kingdom is strictly controlled by the Medicines Act and subordinate legislation. These controls exist to ensure correct description and identity of medicinal products, to prevent false or misleading information, to give proper instructions and warnings and generally promote safety. Existing regulations are comprehensive and cover all categories of medicines. As well as statutory warnings (e.g. keep out of reach of children) for over-the-counter medicines, some specific label warnings are required through individual product licences. All labelling must be in English, though other languages are not prohibited and must be clear and indelible.

33. Various campaigns exist for medicines to be labelled with warnings relating to driving, pregnancy, overuse of steroids, etc. The Department of Health and Social Security policy is that medicines bought over-the-counter need full warnings but that it is for the doctor to decide what is to be labelled on medicines obtained via a prescription. The British National Formulary (the prescribers' handbook) contains authoritative advice to prescribers about the labelling of the products. Because of their size, labels can only contain a limited amount of information and it is important therefore that this is of relevance to the patient concerned. One statutory addition to labelling currently under consideration is a declaration of certain additives to which some patients are allergic (e.g. tartrazine).

Packaging

34. At the present time United Kingdom legislation requires solid-dose aspirin and paracetamol preparations, intended for use in over-the-counter retail sale, to be packed in child-resistant containers.

35. United Kingdom legislation is supplemented by a voluntary agreement between the medical and pharmaceutical professions which states that all solid dose oral preparations should be dispensed in child-resistant containers. Ordinary containers are also provided at the patient's specific request. This voluntary scheme has been in operation since March 1981 and according to independent research carried out by the Pharmaceutical Society of Great Britain has been implemented by virtually all pharmacists. There is no doubt that child-resistant packaging has been very effective in reducing the number of cases of accidental poisoning.

36. Child-resistant containers are currently manufactured to a minimum British standard. The United Kingdom is actively participating in negotiations with other countries aimed at achieving an international standard for child-resistant packaging. The United Kingdom has no regulations in force at present relating to tamper resistance so far as medicines are concerned. Most manufacturers of over-the-counter products subscribing to the Proprietary Association of Great Britain are moving towards tamper resistance which is described as "security packaging".

DRUG DISTRIBUTION SYSTEM

37. There is a well-defined system of drug distribution in the United Kingdom which is controlled by a licensing system covering manufacture, wholesale and retail supply. For every medicinal product there has to be a Product Licence and the product may only be manufactured (or imported) and distributed for sale in accordance with that licence. In addition, manufacturers are required to hold a Manufacturer's Licence and those who deal in medicines wholesale must hold a Wholesale Dealer's Licence.

38. An important factor in the control of the manufacture of human medicines in the United Kingdom is the activities of the Medicines Inspectorate of DHSS. Inspection of premises is carried out before the granting of a Manufacturer's Licence and at regular intervals thereafter. Withdrawal of licences and, rarely, prosecutions can result if standards are not maintained. In this respect DHSS gives detailed guidance regarding good manufacturing practice (GMP).

39. The distribution of medicines from manufacturers to retailers is mainly a private enterprise function, the wholesaler covering his costs and earning his profit through the margin allowed to him in the retail price. Wholesalers must hold a Wholesale Dealer's Licence which amongst other things, seeks to ensure adequate record keeping in case a batch of medicines has to be recalled.

Retail supply

40. There are three ways in which medicinal products may be distributed at retail level in the United Kingdom: (a) "prescription only medicines" (POM) supplied only by or under the supervision of a pharmacist and in accordance with a doctor's or dentist's prescription; (b) "pharmacy medicines" (P) may be sold over the counter only at pharmacies by or under the supervision of a pharmacist; and (c) "general sale list medicines" (GSL) may be sold at any shop such as a village store. Mention should also be made of hospital pharmacies, which supply prescription medicines to hospital patients and to patients attending hospital clinics.

41. "Pharmacy medicines" are the usual form of sale. The decision whether a medicine should be restricted to prescription only or should be allowed on general sale is taken by Ministers and published in statutory orders. Ministers are guided in this by independent expert advisory bodies - in particular, the Medicines Commission, which advises on broad issues of policy, and the Committee on Safety of Medicines, which advises about the safety of particular drug substances or products.

42. As a broad guide, medicines are included in the Prescription Only Medicines List where, in the Ministers' opinion, treatment with them needs to be supervised by a doctor because of (a) a known or potential toxicity hazard to the user, or (b) a likelihood of producing drug dependence, or (c) some danger to the health of the community at large. There is a small amount of movement of drugs from prescription only to non-prescription status as drugs which are initially included in the list only because they were new, become older and doubts about their safety are resolved. The Medicines Act classifies medicines as P unless restricted to POM or relaxed to GSL. Every new chemical entity is classified as POM but reverts to P status after an initial period, usually at renewal of Product Licence, unless specifically retained as a POM medicine.

43. Although "pharmacy medicine" status is the norm, the Medicines Act empowers Ministers to specify in a General Sale List those medicines which in their opinion could with reasonable safety be sold freely at non-pharmacy premises. The medicines which have been listed in this way are, broadly, those considered suitable for self-medication, where the hazard to health, the risk of misuse and the need to take special precautions in handling are all thought to be small and to be outweighed by the convenience to the public of wider sale: e.g. the well-tried home remedies such as cough mixtures, laxatives, antiseptic creams, indigestion tablets and (in small packs) analgesics. There is a large number of such products which can legitimately be sold from non-pharmacy outlets, and it is constantly being added to as new products suitable for self-medication come into the market, and, after very careful and thorough scrutiny, are assessed as reasonably safe for general sale.

44. Medicines on the General Sale List may be sold by self-service methods in any lockable shop or other premises occupied by the seller, but the medicine must have been pre-packed elsewhere and must be sold unopened. General Sale list medicines may also be sold by means of automatic machines, provided the machine is located on premises which can be closed at certain times so as to exclude the public.

Prescribing

45. In the United Kingdom, prescriptions are required for all medicines supplied under the National Health Service and for all prescription only medicines. For such medicines prescriptions may only be written by a doctor or dentist if registered in the United Kingdom.

46. The United Kingdom National Health Service (NHS) is financed primarily out of taxation and is available to all residents. Most people are registered with a general medical practitioner, in contract with the NHS and paid mainly on a capitation basis, who provides primary care and is the normal route of referral to hospital and specialist services, whether in the NHS or private sectors. A small minority of the population obtain some or all of their medical treatment privately, mainly through insurance schemes.

47. As part of primary care, the general practitioner is free to prescribe virtually any medicine which he considers desirable for his patient, with the exception of medicines in certain therapeutic categories referred to below.

48. In some mainly rural areas the doctor may also dispense the medicines he has prescribed but more usually the patient takes the prescription to a community pharmacist, also in contract with the NHS, who dispenses the medicines and claims reimbursement at predetermined rates. Unless exempt, the patient pays at the time of dispensing a prescription charge of £2 for each item on the prescription. In practice, however, more than 70% of prescriptions are exempt from the charge on grounds mainly of young or old age, pregnancy, low income or for those suffering from specified diseases. Under the National Health Service, medicines for patients in hospital are provided free of charge.

49. From April 1985, within certain therapeutic categories, general medical practitioners have been restricted in the medicines they may prescribe under the NHS to those included in a selected list. The medicines concerned are generally those which can be purchased directly by the patient without a prescription, i.e. cough and cold remedies, tonics, vitamin preparations, antacids, laxatives, and minor analgesics, but also include some prescription items such as benzodiazepine sedatives and tranquillizers. The principle underlying this economy measure is that in the therapeutic categories concerned, the only medicines prescribable at NHS expense should be those which meet real clinical need at the lowest cost. The list will remain under review by an expert advisory committee, the Advisory Committee on NHS Drugs. For medicines no longer available under the NHS but for which a prescription is necessary it is open to the doctor to prescribe these and to the patient to pay for them privately.

50. The prescribing practices of general practitioners are monitored. Because after dispensing the prescriptions are sent to one central point for authorization of reimbursement, it is possible to analyse each practitioner's prescribing habits and costs. A summary is sent to each practitioner together with a note of the area and national averages. If a practitioner's costs are significantly higher than the average, this may be discussed with him by a doctor from the Regional Medical Service of DHSS.

Control of prices

51. Prices of medicines supplied under the National Health Service (NHS) are controlled mainly through the Pharmaceutical Price Regulation Scheme, a non-statutory agreement between the industry and the Department of Health and Social Security (DHSS). Under this scheme companies supplying medicines for the NHS are in effect reimbursed the costs incurred and are allowed to earn an agreed level of profit expressed as a return on the capital employed. The scheme operates on the basis that since the health departments are effectively monopolist buyers of all prescribed medicines sold in the United Kingdom, the prices of individual products are not for practical purposes significant if the overall costs and profits of the company producing these medicines are reasonable; a high profit on one product will be offset by a low profit on another.

52. In practice, a company is allowed itself to set the initial price of a new product but subsequently has to seek approval before increasing the price of this and other existing products. Approval is given only if DHSS is satisfied that the increase sought would not enable the company to exceed its profit target and that the costs as declared are reasonable. In considering the latter, DHSS recognizes the importance of research and development and makes an appropriate allowance for this in the costs.

53. Each company is required to submit an annual financial return which enables DHSS to check in retrospect whether the level of costs and profits was reasonable and, if the profit target was exceeded, to negotiate an adjustment. Among the allowable costs is that for distribution from the manufacturers to the community pharmacists through the wholesalers.

54. While companies supplying generic medicines are formally within the Price Regulations Scheme, in practice the prices of generics are determined by competition in the market place. Medicines used in hospitals may be bought through wholesalers but for large-user items tenders are usually invited. The price then depends on the terms negotiated. Many hospitals have special committees composed of doctors and pharmacists to formulate lists of drugs which may be prescribed and consequently which medicines will be purchased.

Controlled drugs

55. Special arrangements apply to the prescribing of drugs of dependence in the United Kingdom under the provisions of the Misuse of Drugs Act 1971.

56. Drugs controlled include cocaine, dipipanone, diamorphine (heroin), methadone, morphine, opium, pethidine, phencyclidine, lysergide (LSD), amphetamines, barbiturates, cannabis, codeine, pholcodine and certain drugs related to the amphetamines such as chlorphentermine and diethylpropion.

57. For all controlled drugs, prescriptions must be signed and dated by the prescriber and the following particulars included in the prescriber's own handwriting: name and address of patient, form and strength of preparation as appropriate, total quantity in both words and figures, and dose.

58. Only medical practitioners who hold a special licence issued by the Home Secretary may prescribe diamorphine, dipipanone or cocaine for addicts; other practitioners must refer the addict to a treatment centre. This stipulation only applies to addicts and does not preclude the prescription of diamorphine or cocaine for the relief of pain due to organic disease or injury.

DRUG PROMOTIONAL PRACTICES

Provision of information to prescribers

59. Information to prescribers can be broadly divided into that sponsored by the pharmaceutical company marketing the drug and that sponsored by the government. While the activities of the pharmaceutical company are commercially oriented and directed at the promotion of their product, government-sponsored publications aim to adopt a critical approach and to present data on new drugs in comparison with existing remedies. Regulations and codes of practice exist to ensure that promotional material from pharmaceutical companies is presented in a fair and objective way.

60. Medical journals represent an important source of pharmacological and therapeutic information for prescribers, particularly on new drugs. Journals such as The Lancet and the British Medical Journal are highly regarded, concerning the quality and independence of the clinical data reported. Journals such as Pulse and Doctor, which are circulated exclusively to doctors, provide an independent source of information, news and comment on medicines. Although these journals are not funded by the pharmaceutical industry they are entirely dependent on advertisements of various types (not solely pharmaceuticals) for their revenue.

61. Pharmaceutical companies provide a wide variety of material on their products. Non-promotional material includes data sheets and specialized information packages for researchers, prescribers and patients. Promotional activities include journal advertisements, printed communications such as letters, booklets and brochures, audiovisual communication, symposia and activities of medical representatives. Under the PPRS (see para. 51) only a limited amount of expenditure on sales promotion may be reflected in the prices of NHS medicines; from April 1985 the limit has in broad terms, been 9% of turnover.

62. Data sheets provide an important source of information to prescribers. A data sheet is a concise document containing basic information about the composition, uses, dosage, side-effects, contraindications and warnings relating to a medicinal product. Detailed regulations under the Medicines Act specify the form and content of data sheets. The data sheets for new products are inspected by Medicines Division of DHSS as are the data sheets of older products as they are reviewed. If a product is promoted to doctors a data sheet must be sent or delivered within the previous 15 months, to any doctor likely to see the advertisement. Any information in an advertisement must be consistent with the particulars on the data sheet. In practice most data sheets are included in an annual compendium compiled by the Association of the British Pharmaceutical Industry (ABPI) which is sent to all doctors. The current edition (1985-86) contains 1037 pages. Mention must also be made of the Monthly Index of Medical Specialities (MIMS), a commercially-produced publication which provides compact information on proprietary medicinal products and is distributed free to all general practitioners.

63. Advertising controls are provided by a mixture of statutory measures and by means of various voluntary codes of practice. The main regulatory powers are contained in the Medicines Act (1968) under which it is an offence to issue false or misleading representations. Advertising claims have to be consistent with the Product Licence. Detailed regulations apply to the information which must be contained in normal advertisements and abbreviated advertisements.

64. Where advertising to the professions is concerned, the Association of the British Pharmaceutical Industry operates a code of voluntary marketing agreed with DHSS which has been in existence for 23 years, to which their members subscribe and to which most pharmaceutical companies who are not ABPI members also elect to adhere. The code emphasizes the importance of providing the medical profession with accurate, fair and objective information. The code is enforced by a Code of Practice Committee chaired by an independent chairman who is a QC. The ABPI Code of Practice Committee submits detailed reports of infringements to the Pharmaceutical Journal and the British Medical Journal for publication. To complement these arrangements the DHSS monitors advertisements generally and investigates all complaints. This joint control between government and industry has proved to be highly successful.

65. The Department of Health and Social Security (DHSS) in the United Kingdom produces very little information on medicines directly, but has a strong interest in encouraging effective and economical prescribing by doctors and exerts its

influence by sponsoring certain independent publications. Two publications are paid for by the DHSS, but are produced independently: Prescribers Journal and the British National Formulary (BNF). The former produces short authoritative independent review papers on therapeutic subjects and is produced every two months. The BNF is a long-standing joint publication by the British Medical Association (BMA) and the Pharmaceutical Society of Great Britain (PSGB) which was radically revised in 1981 and is now a unique, compact source of information intended for those concerned with prescribing, dispensing and the general administration of medicines. It includes most medicines, especially commercial products, available in the United Kingdom but has retained a small formulary section for providing extemporaneous preparations. Revisions are produced every six months and the BNF is distributed free to all medical students and practising doctors.

66. More recently the DHSS has sponsored the free circulation of Drug and Therapeutics Bulletin and Adverse Drug Reaction Bulletin to doctors and final year medical students. The former is published fortnightly by the Consumers Association and the latter every two months by Adverse Drug Reactions Research Unit, Shotley Bridge General Hospital. Drug and Therapeutics Bulletin provides up to date assessment of products or therapeutic practices.

67. The DHSS also distributes copies of the BNF and other literature to other governments on request. On this basis, copies of Martindale's Extra Pharmacopoeia were distributed in 1984.

Employment of medical representatives

68. The employment of medical representatives or detail men is permitted in the United Kingdom and forms an essential part of the promotional activity by the pharmaceutical company in respect of their medical products.

69. The activities of medical representatives are subject to the Code of Practice for the Pharmaceutical Industry mentioned earlier. This code covers such activities as the training and ethical conduct, the proper basis for claims for products and the frequency, timing and duration of calls on doctors and the security of medical products. The code also recommends that representatives are paid a fixed basic salary and that commission on sales should not constitute an undue portion of their remuneration. An important aspect of the training of medical representatives is that detailed briefing material must be provided on the technical aspects of any product that is to be promoted and that a copy of such material must be available to the Licensing Authority on request.

70. Medical representatives undergo a training programme and examination under the auspices of the ABPI. Examinations take place twice yearly. There are currently about 3000 medical representatives employed by the various pharmaceutical companies operating in the United Kingdom, one for every 25-30 doctors compared with one for every two doctors in Japan.

The supply of samples

71. The Code of Practice for the Pharmaceutical Industry (ABPI) also gives specific guidance on the supply of samples to the medical profession.

72. Samples should be provided to a doctor only in response to a signed request unless intended solely for identification or demonstration purposes. Wherever practical, an individual sample should not represent more than four days' treatment for an individual patient. Samples of products restricted to supply on prescription must be handed direct to the doctor or his authorized representative

and a strict system of accountability should be established. In addition, distribution of samples in hospitals should comply with any individual hospital regulations.

Holding of symposia

73. The holding of symposia is a recognized part of the promotion of a new drug. Many such symposia are held in Postgraduate Medical Centres situated in hospital grounds. The Association of the British Pharmaceutical Industry, the National Association of Clinical Tutors and the Advisory Committee of Deans of the Council for Postgraduate Medical Education have agreed that meetings sponsored by a pharmaceutical company may be allowed in a Postgraduate Medical Centre at the discretion of and arranged through the Clinical Tutor or Local Postgraduate Medical Education Committee. It is recommended that some vetting of lecture material or films be undertaken and that a doctor sufficiently experienced in the topic should always be available at such meetings to give an independent opinion. Publicity by the pharmaceutical company is allowed but it is recommended that this should be separate from the educational content of the meeting. Sponsorship by the pharmaceutical company should be limited to the provision of light refreshments and the printing of programmes.

SUMMARY

74. The clinical trial and marketing of new drugs in the United Kingdom first came under voluntary control when the Committee on Safety of Drugs was established in 1964. A statutory system now operates through the Medicines Act (1968) which was implemented in 1971 and, for biological substances, through the Biological Standards Act (1975) via the National Biological Standards Board and its executive arm, the National Institute for Biological Standards and Control. So far as safety, quality and efficacy of medicines are concerned, the United Kingdom has a comprehensive set of controls, consistent with those of other members of the European Community and most other developed countries, governing the import, manufacture, testing, labelling, advertising, distribution and retail sale of medicines. A well developed system for the reporting of adverse reactions feeds information to WHO and to other regulatory authorities. The export of medicines is not controlled under United Kingdom medicines legislation. Progress continues towards harmonization with the European Community, but there is some way to go before this process can be completed.

75. Medicines are available to the population of the United Kingdom either through over-the-counter purchase of approved medicines or by supply through the National Health Service. For the most part doctors are free to prescribe under the NHS medicines of their choice. A recent development, however, has been the introduction of a selected list of medicines prescribable mainly for relatively minor ailments. Except for a standard prescription charge, from which there are extensive exemptions, prescribed medicines are supplied free of charge. Prices to the NHS are controlled under a non-statutory scheme agreed between the government and the industry. The way in which companies may promote their medicines is regulated by a mixture of statutory controls, self-regulation by the industry and by financial pressures exerted through the price control scheme. The United Kingdom government seeks in various ways to encourage doctors to prescribe effectively and economically, including the prescribing of generic forms of branded medicines.