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SOME ASPECTS OF THE CONTROL OF MEDICINES IN THE UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND

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ABSTRACT

The main aspects of the control of medicinal products in the United Kingdom following the publication of the Medicines Act 1968 are shown against the background of the work of the Medicines Division, Department of Health and Social Security, and its consultative and advisory bodies. Brief mention is made of the cooperation with international bodies.

CONTENTS

INTRODUCTION

This paper provides information on some aspects of the control of medicines in the United Kingdom. It is not an exhaustive description of the legislation used to implement this control but simplified notes to enable the reader to obtain an overall view of the situation. An outline of the work of the Medicines Division of the Department of Health and Social Security is given. No mention is made of the inspection activities of the Pharmaceutical Society of Great Britain nor of local Food and Drug Authorities both of which activities are provided for under the Medicines Act. The control of veterinary medicines is administered in a way similar to that for human medicines but this paper refers only to medicines for human use.

These notes should not be treated as an authoritative or complete guide to the law in any particular case. Copies of the Medicines Act and the Regulations and Orders made under it are available from Her Majesty's Stationery Office. Explanatory leaflets are available from the Medicines Division, Finsbury Square House.

HISTORICAL BACKGROUND

Legislation in relation to the control of medicines goes back to the mid-sixteenth century when the physicians of London were empowered to appoint inspectors of 'drugs' among other things. In the early seventeenth century these inspecting doctors were joined by representatives of the Society of Apothecaries. During the nineteenth century the Pharmaceutical Society of Great Britain was established and legislation was introduced to control the retail supply of poisons and the people who could do this. A book

of standards, the first British Pharmacopoeia, was later published and this has been followed at regular intervals by updated issues. Subsequently, various Acts of Parliament provided the legal framework for the control of different aspects of the preparation and distribution of drugs and drug products. In the early 1960's the need for further and coordinated legislation was under discussion when the teratogenic effects of thalidomide became evident. This highlighted the need for more effective measures to be taken in the control of medicines and the result was that in 1963 a Committee on Safety of Drugs was formed under the Chairmanship of Sir Derrick Dunlop. This 'Dunlop Committee', as it came to be known, began work with effect from January 1964.

The Committee had the full support of the medical and pharmaceutical professions. The pharmaceutical industry voluntarily agreed to submit data on new products to the Committee and to abide by its advice. New legislation to give statutory backing to the Committee's advice and to enable a comprehensive overhaul of all legislation relating to medicines was embodied in the Medicines Act which received the Royal Assent in October 1968. Licensing under the Act began on 1 September 1971, the 'first appointed day', but for a period following that date transitional exemptions enabled those engaged in the manufacture and distribution of medicinal products before licensing began to continue with their activities.

Most exemptions terminated on 1 September 1972 by which time licences 'as of right' had to be applied for. This licensing of right was simply a registration exercise to provide the Department with information necessary for the fuller implementation of the Medicines Act. Medicinal products on the market under a product licence of right have not been scrutinised by the Committee on Safety of Medicines with respect to safety, quality and efficacy. They can be varied, suspended or revoked by the Licensing Authority at any time pending the formal review by the Committee on the Review of Medicines which commenced its activities in October 1975 under the Chairmanship of Professor Sir Eric Scowen

THE MEDICINES ACT 1968

The Medicines Act is a comprehensive measure replacing most of the previous legislation on the control of medicines for human and for veterinary use. The Act is administered by the Health and Agriculture ministers of the United Kingdom.

This Act covers all aspects of the control of medicines other than the control of the misuse of certain medicines which are controlled under the Misuse of Drugs Act of 1971 administered by the Home Office.

The Medicines Act applies to medicinal products. These are defined as substances or articles (not being instruments, apparatus or appliances) which are used for administration to human beings or animals in order to treat or prevent disease, and for the purpose of diagnosis, inducing anaesthesia, contraception or preventing or interfering with the normal operation of a physiological function. Ingredients to be used in the preparation of medicines for dispensing in hospitals or pharmacies or by practitioners are also treated as being medicinal products as are herbal and homeopathic remedies.

There is also power under the Act to extend control to instruments, apparatus or appliances which are used for these medicinal purposes and to articles and substances which are not medicinal products but which may constitute a potential health hazard. Control has already been extended by the power given by this provision to cover surgical sutures and certain other surgical materials, to certain substances which are used as active ingredients in medicinal products and which cannot be fully assayed chemically, and to antibiotics when used for both medicinal and non-medicinal purposes. Action is currently being undertaken to make dental filling materials, contact lenses and their associated fluids, and intra-uterine contraceptive devices subject to the provisions of the Act.

As can be seen the whole of the Medicines Act was not implemented at once: it is an enabling act which allows further secondary legislation (known as Regulations or Orders) to be made

as and when necessary and practicable. Under the Act there is a statutory requirement for the Department to consult interested parties before secondary legislation becomes effective.

Early measures taken under the Act were the setting up of consultative and advisory bodies and the establishment of a licensing system to control the manufacture and marketing of medicinal products. This system is operated by the Ministers acting as the Licensing Authority with advice from the advisory bodies. The following sections give more details of these activities.

CONSULTATIVE AND ADVISORY BODIES

The Medicines Commission

The Medicines Commission was established in 1969 under Section 2 of the Act. It consists of a Chairman, Professor W.J.H.Butterfield and members appointed by the Ministers after consultation with interested organisations. Doctors, veterinary surgeons, pharmacists and others are included in the membership. A member's normal term of office is 4 years. Those currently serving are listed in the Annual Report.

The Commission's advice is sought on a wide variety of topics. They have advised Ministers on such subjects as the microbial contamination of intravenous fluids, the presentation of medicines in relation to child safety, the advertising of medicines and the provision of information to doctors, and the experimental use of animals in the pharmaceutical industry. When a particularly complex problem arises requiring examination in detail a committee to examine the issues involved may be appointed. Two such committees were set up when the Commission was asked to advise which medicines should be available on prescription and which should be permitted to be sold at shops other than registered pharmacies. The Committee on Safety of Medicines was appointed by the Ministers under Section 4 of the Act on advice from the Medicines Commission.

The Committee on Safety of Medicines

This Committee is in effect a continuation of the former committee on Safety of Drugs and it advises the Licensing Authority

on matters of safety, quality and efficacy of medicines for human use. It is also responsible for collecting and investigating reports on adverse reactions to medicines already on the market and for the issue of warnings about newly-identified hazards or reminders about those already recognised. The Committee has been under the Chairmanship of Sir Eric Scowen who retires from this post in March 1976 to be succeeded by Professor Graham Wilson. A list of other members is in the Annual Report.

The Committee established 6 sub-committees to consider matters in specialist areas. These are:

The Sub-Committee on Toxicity Clinical Trials and Therapeutic Efficacy which considers medical and biological data presented in support of an application for a Clinical Trial Certificate or Product Licence.

The Sub-Committee on Chemistry, Pharmacy and Standards which considers the chemical and pharmaceutical aspects of an application.

The Sub-Committee on Biological Substances which deals with immunological and blood products, hormones, enzymes and antibiotics.

The Sub-Committee on Standards of Herbal Products which considers the quality of herbal medicines.

The Sub-Committee on Adverse Drug Reactions which advises on the collection and evaluation of reports of adverse reactions to drugs.

The Sub-Committee on Antimicrobial Substances (established jointly with the Veterinary Products Committee) which advises on all aspects of the use of antibiotics and related substances.

The Committee on the Review of Medicines

The Committee on the Review of Medicines is the most recent of the consultative and advisory bodies to be set up under Section 4 of the Act. It has the mammoth task of reviewing all the medicinal products at present on the UK market whether licensed as of right or having full product licences. The former Chairman of the Safety of Medicines Committee, Sir Eric Scowen, and some other members from this Committee form the nucleus of this new committee. There is thus a continuity of approach and policy with reference to the criteria of

safety, quality and efficacy taken into account in the assessment of medicinal products. The whole range of products is being divided into categories by reference to therapeutic use. Categories under early consideration are:
Non-steriod anti-inflammatory drugs: Analgesics: Psychotropic drugs: Antibiotics: Immunological agents.

The basic pharmaceutical data to enable the Committee to begin its work is now on computer record. This is being updated as each category comes under review.

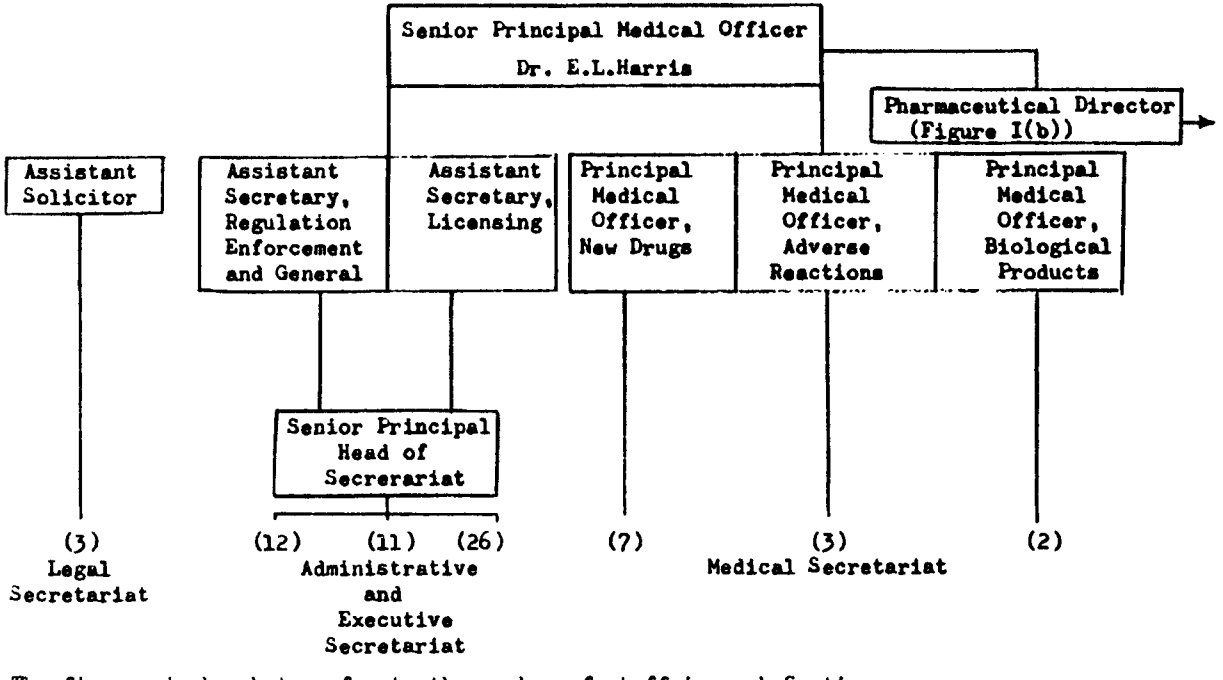
The British Pharmacopoeia Commission

The BP Commission has the responsibility, under the direction of the Medicines Commission, of preparing future editions of the British Pharmacopoeia in succession to the former body of the same title which performed this task for the General Medical Council. This publication will eventually, together with the European Pharmacopoeia, contain all the published standards for human and veterinary medicines (published in separate colums) and will also provide standards for formulated products, including any necessary to support formulae appearing in the British National Formularly. It is also responsible for selecting non-proprietary names for Medicinal Substances. To assist it the British Pharmacopoeia Commission has appointed 21 advisory committees and a number of special panels.

THE MEDICINES DIVISION

The functions of the Health Ministers of the United Kingdom under the Medicines Act are discharged on their behalf by the Medicines Division of the Department of Health and Social Security which is situated at Finsbury Square House, London. The Medicines Division takes advice from the Consultative and Advisory bodies mentioned above.

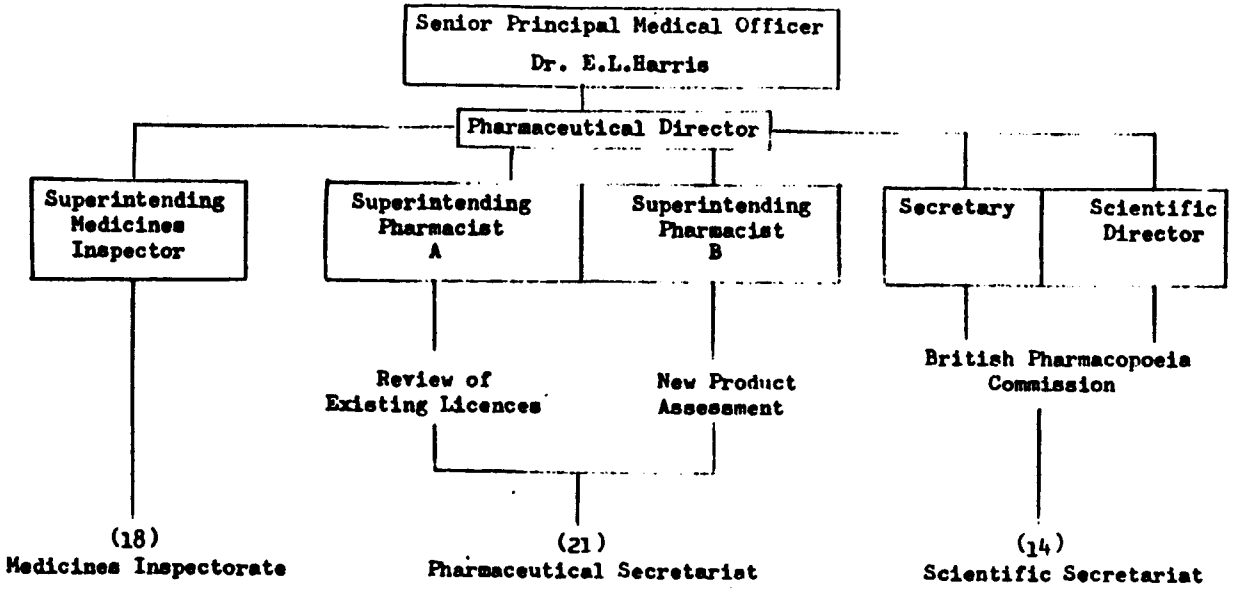
The Division is composed of doctors, pharmacists, scientists, lawyers, a dentist, administrative and clerical staff. The work of the Division is coordinated and directed by its senior staff meeting as the Divisional Management Group. Figures 1(a) and 1(b) and 2 show in diagram form the organisation of the Medicines Division and the inter-relation between the Division and other bodies respectively.



The figures in brackets refer to the number of staff in each Section.

FIGURE I(a)

ORGANISATION OF MEDICINES DIVISION



The figures in brackets refer to the number of staff in each Section.

FIGURE I(b)

ORGANISATION OF MEDICINES DIVISION

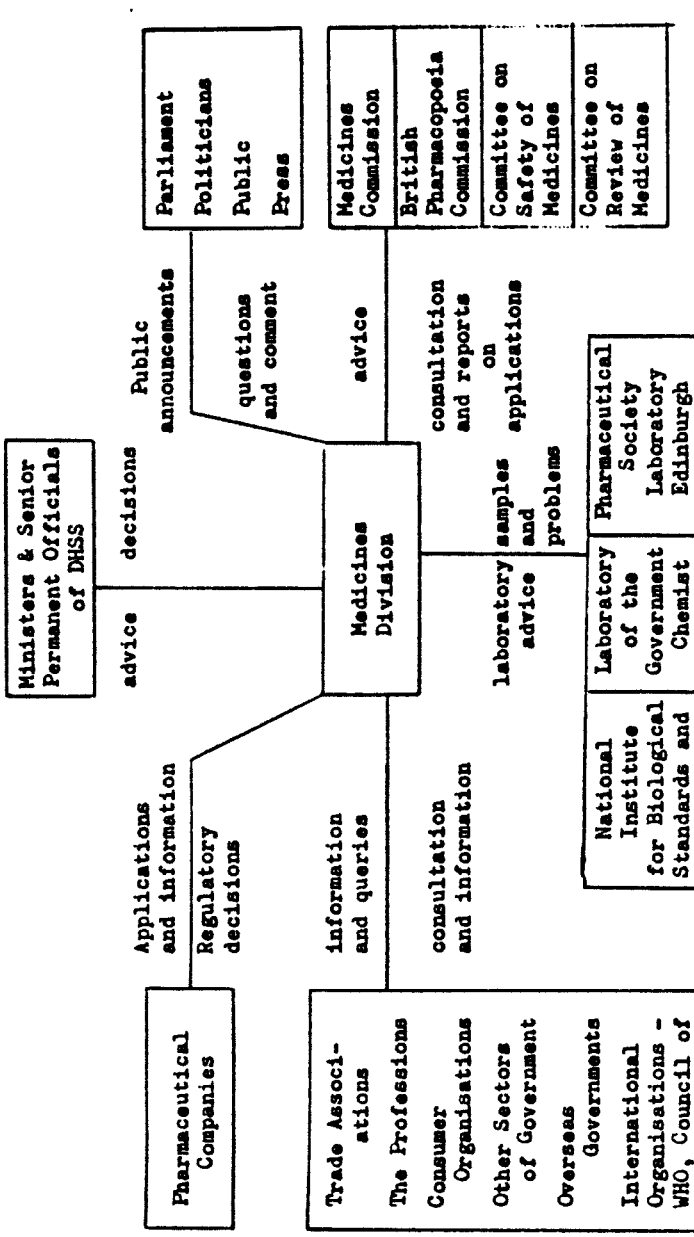


FIGURE 2

THE POLICY PROCESS

The main functions of the Division are:

As Licensing Authority

The Division is involved at every stage in the licensing of a medicinal product, its preparation and distribution.

(i) Applications for manufacturers' and wholesale dealers' licences are evaluated, on the basis of information supplied by the Medicines Inspectorate, to ensure that the premises are suitable for the proposed operations and to check that the appropriately qualified staff are employed.

Manufacturers' licences authorise the holder to manufacture or to assemble medicinal products. (Assembly means enclosing the product in a container, and labelling it after manufacture). Wholesale Dealers' licences are required for the sale of medicinal products to anyone other than the ultimate users.

(ii) Applications for Clinical Trial Certificates and Product Licences are considered initially by the professional secretariat. The scientific and technical data presented in support of an application and assessed with reference to Safety, Quality and Efficacy. At this stage informal discussion may take place between the secretariat and the applicant prior to a critical report with recommendations being prepared for the Committee on Safety of Medicines and its expert sub-committees. These reports together with the original data supplied by the applicant are presented to the committees to assist them in formulating their advice to the Licensing Authority. An outline of the information required in support of an application is set out in Appendix I.

A Clinical Trial Certificate is necessary to authorise the supply of a medicinal product for the purpose of a clinical trial in human beings as patients where it is expected that this will be of benefit (so-called human pharmacology studies, where no benefit to the volunteer is expected, are not controlled).

A Product Licence is required to authorise the importation sale of supply of a product and is held by the person responsible for the composition of the product (this is usually the manufact-

urer or, in the case of contract manufacture, the person or company to whose order the product is manufactured) or by the importer of the product.

Control of labelling and advertising is outlined in Appendix 2.

As Enforcement Authority

The Division is responsible for ensuring the enforcement of the Act. The Medicines Inspectorate acts as the main field force of the Ministers and inspects pharmaceutical manufacturing and wholesaling establishments in the UK and abroad. These visits have a two-fold purpose: first, to ensure the continued compliance by the licence holder with the conditions of the licence; and, second, to examine specific aspects of manufacture in accordance with a programme of priorities determined by the Division. During a visit samples may be taken. These are analysed either by the Pharmaceutical Society's Laboratory in Edinburgh, Scotland, or by the Laboratory of the Government Chemist in London. (The Medicines Division has no laboratory facilities of its own).

A separate group undertakes the inspection of biological products. They work in close conjunction with the National Institute for Biological Standards and Control which also tests batch samples where necessary. Because of the importance of in-process controls in the manufacture of these products, there is considerable overlap between the inspection function and the assessment function of applications for both manufacturers' and product licences.

When a visit results in the discovery of unsatisfactory arrangements at a manufacturers or wholesalers' premises, a report is submitted to the responsible group in Medicines Division, who decides what further action to take. This may include revocation or suspension of the licence, or prosecution if the terms of the licence have been breached.

The "Guide to Good Pharmaceutical Manufacturing Practice" (the 'Orange Guide' because of the colour of its cover!) describes measures for the control of quality during manufacture and assembly with particular reference to those aspects which are associated with safety. The Guide has no statutory force but is merely what

it says - a Guide. The object of quality control is to ensure that the product conforms to its specification and that the prescriber and user can trust it as being reliable for the therapeutic purpose for which it is intended.

As Adverse Drug Reactions Monitoring Centre

A team of medical and pharmaceutical staff works under the direction of the Committee on Safety of Medicines and its Adverse Reactions Sub-Committee in monitoring adverse reactions to medicinal products. Full-time staff in the Division are assisted by part-time staff around the country to follow up reports on adverse reactions and to make special enquiries if required to do so.

In the UK there is a conviction that the controls imposed before marketing are not in themselves a sufficient safety factor in the total assessment of a medicinal product. Hence the need for post-marketing surveillance.

Great importance is therefore attached to the monitoring of adverse reactions to medicinal products. Advice on this subject is given to the Medicines Division by the Committee on Safety of Medicines. A Register of Adverse Reactions has been established to which confidential reports about individual patients are made on a voluntary basis by members of the professions. Other data derived from sources such as the Pharmaceutical Industry, the Registrar General, or Coroners are also added to the Register. Summaries of information stored in the Register are provided routinely for those who report suspected reactions and are also available for certain classes of authorised persons who may enquire about them. All persons who report suspected adverse reactions are assured that no information is released which could identify a patient without written consent. This consent is occasionally sought in order to put research workers interested in specific problems in touch with each other.

A number of epidemiological monitoring programmes are also undertaken to identify possible hazards which might not otherwise be detected. One such programme is designed to monitor the drug histories of mothers of babies born with congenital abnormalities, and is

intended to detect any previously unidentified teratogenic hazards. Other programmes have investigated the role of drugs in certain types of tumours, aplastic anaemia and jaundice. The Committee's investigations of oral contraceptives are well-known.

Where indicated, information about adverse reactions is published in order to alert the professions to the possibility of adverse reactions to particular drugs and to the need for a closer observation of their effects. It is recognised that early action must sometimes be taken on what is scient fically not wholly conclusive evidence. It is preferable to give earl, warnings of possible hazards than to risk harm to patients while protracted studies are undertaken to establish causal relationship between a drug and a reaction or to obtain precise measurements of the incidence of reactions.

As Defect Report Centre

The Division operates a system for following up reports of defective batches of medicines and for issuing any warnings that may be required as a result. These reports may come from the manufacturer of the original batch, from hospitals, or from any other user of the material. After consideration of a defect report it may be decided to recall the faulty material. This is undertaken as appropriate, by the manufacturer, the wholesaler or the Department. Examples of recalled materials are: serious mislabelling, microbial contamination, incorrect constituents or level of constituents in a formulation, or where it is considered that administration of the product would constitute a serious health hazard.

INTERNATIONAL COOPERATION

World Health Organisation

The United Kingdom is a principal contributor to the WHO Register of Adverse Reactions. It also takes part in the preparation of the International Pharmacopoeia.

Council of Europe (Partial Agreement)

The United Kingdom was a founder signatory of the European Pharmacopoeia Convention. It plays an active role in the preparation

and revision of the Pharmacopoeia and also contributes to other meetings held under auspices of the Council of Europe

European Economic Community (EEC)

The United Kingdom licensing system under the Medicines Act 1968 very largely meets its provisions as regards marketing authorisations.

The draft "second" directive elaborates on Directive 65/65 in relation to the processing of applications and lays down minimum requirements for the granting of licences to manufacture proprietary medicinal products or import them from third countries. The draft standards and protocols directive sets out the technical information which should accompany licence applications regarding the specification, analysis and testing of the product. Two committees are to be established, one to keep the Directives under review and the second to coordinate the views of Member States on individual products.

Pharmaceutical Inspection Convention

The United Kingdom is a signatory of the Convention for the Mutual Recognition of Inspection in Respect of the Manufacture of Pharmaceutical Products, (now commonly referred to as the Pharmaceutical Inspection Convention) together with Austria, Denmark, Finland, Iceland, Liechtenstein, Norway, Portugal, Sweden and Switzerland. Under this Convention, members exchange information gained by inspecting manufacturers of pharmaceutical products.

CONCLUSION

In the United Kingdom the Regulatory Authority's aim is to maintain a flexible and sensible approach to the control of medicines and to do this in a spirit of partnership with all parties concerned.

APPENDIX I

The scientific information required in support of an application for a product licence. (The following is an abstract of the headings from the more detailed "Notes for Guidance" series MAL 2 mentioned in Appendix 3).

The required scientific information is classified under three headings:

(i) Chemistry and Pharmacy

(ii) Experimental and Biological Studies

(iii) Clinical Trials

CHEMISTRY AND PHARMACY

Drug Substance

Identity of Material

This is intended to give information which will clearly identify the drug substance which is the subject of an application.

Manufacture

A concise but comprehensive account of the manufacture of the drug substance is required.

Development Chemistry

This should indicate the research and development programme which has been undertaken on the drug substance to investigate the chemical and physico-chemical properties. The findings described here should be reflected in the drug substance specification by which batch-to-batch uniformity is controlled.

Impurities

The purpose of this section is to outline the research programme which has been undertaken to demonstrate that the methods used for impurity control in the drug substance specification are valid and sensitive. Negative information can sometimes be important, that is, methods which have been tried but have proved unsuccessful for the detection of impurities.

Specification

A complete statement of the tests which will be carried out routinely on each batch of materials at the time of manufacture.

Batch Analyses

This section serves to illustrate the actual results which have been obtained from routine quality control of the drug substances. Results should be given for (a) recent batches which are

representative of the product which will be supplied for the purpose covered by the Product Licence or Clinical Trial Certificate application, and (b) batches of material used in the toxicity tests and clinical work reported in support of the application.

Stability Reports

This section refers to stability tests on the drug substance: information on the stability of formulated products is given in the section on dosage form.

Metabolism

The purpose of this section is to demonstrate the validity of the metabolic work in terms of the analytical procedures and assay methods which have been used. Duplication of large sections of experimental data and results, which are reported in full in the Section of the Volume on Experimental Studies should be avoided.

Dosage Form

Finished Products

This section must include a complete delcaration of the composition of each of the products which is to be covered by the Product Licence or Clinical Trial Certificate. It should be remembered that a Clinical Trial Certificate is required to cover, in addition to the main product, any placebos or control products which are supplied for the trial.

Manufacture of Dosage Form

This section covers the manufacture and assembly of the finished product as it will be sold or supplied for the purposes covered by the application. The description should reflect the scale on which it is to be manufactured; that is, it should distinguish between pilot or laboratory scale production (eg, for clinical trials) and full scale production.

Quality Control

This section must give a complete account of the tests which will be carried out routinely on each batch of the product and its constituents and must state the specifications with which any sample, picked up in the course of an inspection, would be expected to comply.

Note: Where the product or any of the active ingredients are "biological substances" as defined in the 'Compendium of Requirements with respect to Biological Products' the relevant additional information, as set out in the Compendium, must be included.

Development Pharmaceutics and Biological Availability

This section should describe the development work which has been carried out to establish that the proposed formulation(s) are satisfactory for the purposes specified in the application.

Stability

Evidence is required to demonstrate that the proposed formulation is stable for the purposes covered by the Product Licence or Clinical Trial Certificate application and that it will meet the finished product (check) specification throughout its shelf-life.

Containers

Information is required on the containers, packs and any inserts such as cushioning desiccants, filters which will be in contact with the product when sold or supplied in accordance with the Product Licence or Clinical Trial Certificate.

EXPERIMENTAL AND BIOLOGICAL STUDIES

Pharmacology

Methods of pharmacological screening will vary with the type of preparation under investigation but the aim should be to establish a pattern of pharmacological activity within the major physiological systems using a variety of experientmal models.

Drug Kinetics

The aim should be to establish the pattern and time course of absorption, distribution and excretion of active drug and metabolites in animals and in human volunteers, where such data is available.

Animal Toxicology

To be reported under the headings:

(i) Acute Toxicology (or single dose studies)

(ii) Repeated dose studies (subacute, intermediate term and chronic or long term).

Under each of the headings reports are to be made in the following order of route of administration where appropriate, intravenous, intramuscular, subcutaneous, intraperitoneal, oral, topical, with in each subsection referring to route results should appear in the following species order:- Mouse, Rat, Hamster, Guinea Pig, Rabbit Cat, Dog, Monkey, Pig, other animals.

It is essential that in addition to the summary, details should be given and conclusions drawn from the original data. The reporting toxicologist or pathologist should given an interpretation of their findings in the light of the control evidence and the overall incidence of any abnormality in the colonies used.

Carcinogenicity Studies

In cases where carcinogenicity studies are applicable, it is suggested that these should be discussed with the professional staff associated with the Committee on Safety of Medicines and the Licensing Office.

Reproduction Studies

The study of drug effects on the fetus and neonate should be conducted in such a manner as would reveal the presence of any drug effect which might result in fetal abnormality or fetal loss or produce damage to the off-spring in later life.

It is expected that results on studies which have involved dosing during the period of embyrogenesis will be presented in two species one of which will be other than a rodent, a fertility study should be conducted in at least one species, and results of a peri-post natal study should be presented.

Other Studies

These should only be reported if they contain important general information or are relevant to the proposed clinical use of the drug as presented in the current application.

Reports should be given of other studies carried out, for example - skin irritation studies, sensitivity studies, eye irritation studies.

Human Pharmacological Studies

The nature of these will be largely dictated by the nature of the compound, any studies reported in this section should clearly indicate the sex, age and weight of the volunteers, the route by which the drug was given, the dosage, and frequency of dosage.

CLINICAL TRIALS

Summary of All Clinical Trials

An overall summary of the trials should be presented under the following headings:-

Number of trials, specify number of open studies, double blind studies etc.

Number of patients entering trials and their diagnoses.

Number of patients on test medication on completion of trials.

Daily dosage expressed as mean and range.

Duration of dosage.

Results of study in terms of efficacy and details of any statistical assessment.

Adverse reactions - all o be reported whether major or minor.

Conclusion and Comment.

Summaries of Each Individual Clinical Trial

Each study should be reported in sufficient detail to allow an assessment to be made of each conclusion drawn by the investigators. Where clinical, biochemical, haematological or other monitoring has taken place, tabulated summaries of individual reports should be provided.

Number of patients entering trial, and their diagnoses.

Number of patients on test medication on completion of trial.

Dosage employed expressed as a mean and as a range.

Duration of dosage.

Design of trial open, or controlled double blind etc.

Results achieved from the study, and details of statistical assessment.

Adverse reactions reported during the study, both major and minor.

Conclusion and comment.

Clinical Trials

For a clinical trial the requirements for chemistry and pharmacy are not so extensive as those for a product licence. Where the trial is small, of limited duration, and using material from one batch only, all that is required is for the material used to be adequately characterised and shown to be stable for the duration of the trial. Where a clinical trial has to be extended, using fresh material, it is necessary to show good replication from batch to batch of material used.

APPENDIX 2

Labelling

It is an offence under the Medicines Act to sell or supply any medicinal product which is labelled in such a way as falsely to describe the product, or to be likely to mislead as to its nature or quality, or uses and effects.

Proposed labelling regulations are currently the subject of consultations with the interests concerned. These will contain detailed requirements for the labelling of medicinal products for both human and veterinary use. The primary objective of these proposals is to ensure that labels bear the appropriate particulars at the final point of sale or supply, and the general requirements of the draft regulations specify certain particulars which must appear on containers and packages. These will include the name, composition and quantity of the product, directions for use, contra-indications, expiry date, special handling and storage conditions, and certain particulars concerning the product's and manufacturer's licences. It is proposed to make exceptions to the general requirements for ampoules and other small containers, strip packaging, surgical materials, advertising outers, packages for transit, import and export, containers for clinical and animal trials and certain products exempt from licensing. These would be covered by modified and special requirements.

In some cases the Licensing Authority may specify particular labelling requirements within the provisions of the product licence for an individual product.

Advertising

Under the Medicines Act it is an offence to issue false or misleading advertisements relating to medicinal products or to make false or misleading oral representations. Advertisements or representations which involve recommendation for the use of a product other than a use that has been specified in the product licence are also prohibited. In addition there are powers under the Medicines Act to prohibit the issue of advertisements relating to particular products or products falling within a class and to make general requirements about the form and context of advertisements.

From 1973, any advertisement or representation to a practitioner concerning medicinal products, whether written or oral, must be preceded or accompanied by a Data Sheet delivered not longer than 15 months before the representation. A data sheet is a statement in a set format about the product and its uses for the information of practitioners. In particular the information must be in accordance with the terms of the product licence.

Recently introduced standard provisions for product licences enable the Licensing Authority to exercise controls over the advertisments to be submitted in advance or by requiring that certain particulars should always be included, or by requiring that an individual advertisement be amended or withdrawn.

The Independent Broadcasting Authority controls advertisements appearing on Independent Television and Radio, and is advised by a Medical Advisory Panel. Such advertisements must conform with an agreed code of practice.

Some control of advertising of pharmaceutical products is carried out on a voluntary basis. The Proprietary Association of Great Britain, and the Association of the British Pharmaceutical Industry have codes to which their members subscribe. The British Code of Advertising Practice lays down detailed requirements which are to be observed by various newspapers and bodies involved with advertising.

APPENDIX 3

Bibliography

- The Medicines Act 1968 and its Regulations and Orders (see list below)
- The Annual Reports of the Medicines Commission, Committee on Safety of Medicines, Veterinary Products Committee, British Pharmacopoeia Commission, with a memorandum by The Medicines Division of the Department of Health and Social Security.
- Guide to Good Pharmaceutical Manufacturing Practice (currently being revised).

MAL (Medicines Act Licensing) Notes and Guides (see list below).

Dewar's Textbook of Forensic Pharmacy (6th Edition 1964).

Pharmacy, Law and Ethics by J.R.Sale and G.E.Appelbe (to be published April 1976 by Pharmaceutical Society of Great Britain.)

REGULATIONS AND ORDERS MADE UNDER THE MEDICINES ACT 1968

Statutory Instrument		Title
1970	No. 746	Medicines, The Medicines Commission and Committee Regulations 1970.
1970	No. 1256	Medicines (British Pharmacopoeia Commission) Order 1970.
1970	No. 1257	Medicines. The Medicines (Committee on Safety of Medicines) Order 1970.
1970	No. 1304	Medicines. The Medicines (Veterinary Products Committee) Order 1970.

- Her Majesty's Stationery Office.

Statutory Instrument		Title
1971	No. 972	The Medicines (Standard Provisions for Licences and Certificates) Regulations 1971
1971	No. 973	The Medicines (Applications for Product Licences and Clinical Trial Certificates) Regulations 1971.
1971	No. 974	The Medicines (Applications for Manufacturer's and Wholesale Dealer's Licences) Regulations 1971.
1971	No. 1153	The Medicines (First Appointed Day) Order 1971.
1971	No. 1198	The Medicines (Exportation of Specified Products for Human Use) Order 1971.
1971	No. 1200	The Medicines (Control of Substances for Manufacture) Order 1971.
1971	No. 1267	The Medicines (Surgical Materials) Order 1971.
1971	No. 1309	The Medicines (Exportation of Specified Veterinary Products) Order 1971.
1971	No. 1326	The Medicines (Importation of Medicinal Products for Re-exportation) Order 1971.
1971	No. 1410	The Medicines (Exemption from Licences (Food and Cosmetics) Order 1971.
1971	No. 1445	The Medicines (Retail Pharmacists-Exemption from Licensing Requirements) Order 1971.
1971	No. 1446	The Medicines (Data Sheet) (Transitional) Regulations 1971.
1971	No. 1447	The Medicines (Applications for Product Licences of Right and Clinical Trial and Animal Test Certificates of Right) Regulations 1971
1971	No. 1448	The Medicines (Applications for Manufacturer's and Wholesale Dealer's Licences of Right) Regulations 1971

Statutory Instrument		Title
1971	No. 1449	The Medicines (Fees) Regulations 1971
1971	No. 1450	The Medicines (Exemption from Licences) (Special and Transitional Cases) Order 1971
1972	No. 640	The Medicines (Exemption from Licences) Wholesale Dealing Order 1972.
1972	No. 717	The Medicines (Closing Date for Applications for Licences of Right) Order 1972.
1972	No. 788	The Medicines Act 1968 (Commencement No.1) Order 1972.
1972	No. 1198	The Medicines (Termination of Transitional Exemptions) (No.1) Order 1972.
1972	No. 1199	The Medicines (Exemption from Licences) Manufacture and Assembly Temporary Provisions) Order 1972.
1972	No. 1200	The Medicines (Exemption from Licences) (Special Cases and Miscellaneous Provisions) Order 1972.
1972	No. 1201	The Medicines (Applications for Product Licences and Clinical Trial and Animal Test Certificates) Amendment Regulations 1972.
1972	No. 1225	The Medicines Act 1968 (Commencement No. 2) Order 1972.
1972	No. 1226	The Medicines (Standard Provisions for Licences and Certificates) Amendment Regulations 1972.
1972	No. 2076	The Medicines (Data Sheet) Regulations 1972.
1973	No. 367	The Medicines (Extension to Antimicrobial Substances) Order 1973.
1973	No. 1120	The Medicines (Hexachlorophane Prohibition) Order 1973.
1973	No. 1164	The Medicines (Feeding Stuffs Additions) Order 1973.

Statutory Instrument		Title
1973	No. 1529	The Medicines Act 1968 (Commencement No.3) Order 1973.
1973	No. 1530	The Medicines (Labelling of Medicated Animal Feeding Stuffs) Regulations 1973.
1973	No. 1822	The Medicines (Pharmacies)(Applications for Registration and Fees) Regulations 1973.
1973	No. 1849	The Medicines (Pharmacies)(Appointed Day) Order 1973.
1973	No. 1851	The Medicines Act 1968 (Commencement No.4) Order 1973.
1973	No. 2079	The Medicines (Exemption from Licences) (Food and Cosmetics) Amendment Order 1973.
1974	No. 316	The Medicines (Exemption from Licences) (Emergency Importation) Order 1974.
1974	No. 498	The Medicines (Exemption from Licences) (Clinical Trials) Order 1974.
1974	No. 711	The Medicines (Interim Prescription Only) (No. 1) Order 1974.
1974	No. 832	The Medicines (Renewal Applications for Licences and Certificates) Regulations 1974
1974	No. 1082	The Medicines (Phenacetin Prohibition) Order 1974.
1974	No. 1149	The Medicines (Termination of Transitional Exemptions) (No.2) Order 1974.
1974	No. 1150	The Medicines (Exemption from Licences) (Ingredients) Order 1974.
1974	No. 1523	The Medicines (Standard Provisions for Licences and Certificates) Amendment Regulations 1974.
1974	No. 2167	The Medicines (Interim Prescription Only) (No.2) Order 1974.

Statutory Instrument		Title
1975	No. 298	The Medicines (Advertising of Medicinal Products) Regulations 1975.
1975	No. 366	The Medicines (Fees) Regulations 1975.
1975	No. 533	The Medicines (Dental Filling Substances) Order 1975.
1975	No. 681	The Medicines (Applications for Product Licences and Clinical Trial and Animal Test Certificates) Amendment Regulations 1975.
1975	No. 761	The Medicines (Termination of Transitional Exemptions) (No.3) Order 1975.
1975	No. 762	The Medicines (Exemption from Licences) (Wholesale Dealing in Confectionery) Order 1975.
1975	No. 1006	The Medicines (Committee on the Review of Medicines) Order 1975.
1975	No. 1326	The Medicines (Advertising of Medicinal Products) (No.2) Regulations 1975.
1975	No. 1473	The Medicines (Committee on Dental and Surgical Materials) Order 1975.
1975	No. 2000	The Medicines (Child Safety) Regulations 1975.
1976	No. 74(C2)	Medicines. The Medicines Act 1968 (Commencement No.5) Order 1976.

THE FOLLOWING LEAFLETS ON VARIOUS ASPECTS OF THE MEDICINES ACTS ARE CURRENTLY AVAILABLE

MAL 1 Guide to the Licensing System
MAL 2 Notes on Applications for Product Licences
MAL 4 Notes on Applications for Clinical Trial Certificates
MAL 5 Notes on Applications for Manufacturer's Ordinary Licences
MAL 6 Notes on Applications for Wholesale Dealer's Licences
MAL 7 Fees for Licences and Certificates
MAL 8 A Guide to the Status of Borderline Preparations under the Act.

MAL 9 Licensing Provisions affecting Retail Pharmacists

*MAL 10 Notes on Applications for Product Licences for Veterinary Medicinal Products.

*MAL 11 Notes on Applications for Animal Test Certificates

MAL 13 Notes on Licensing of Products sold as Chemist Own Brands

MAL 14 Special Dispensing Services

MAL 18 Licensing Requirements involved in the Packing and Labelling of Medicinal Products

MAL 19 Wholesale Dealer's Licences Limited to General Sales List Products

MAL 21 Notes on Licensing of Homoepathic Products

MAL 22 The Licensing of Ingredients

MAL 23 The Application of Licensing to Non NHS Hospitals

MAL 24 Supply in Course of Giving Advice as to Treatment

MAL 25 Notes on Data Sheets

*MAL 26 Guide to Provisions on Medicated Animal Feeding Stuffs

*MAL 27 Notes on Applications for Veterinary Product Licences for Substances or Articles to be used for incorporation in Animal Feeding Stuffs for a medicinal purpose

*MAL 28 Guide to provisions on Labelling of, and Supply of Leaflets with Medicated Animal Feeding Stuffs

MAL 29 Notes on Export Certificates

MAL 30 A Guide to Licensing Provisions affecting Doctors and Dentists

MAL 31 Clinical Trials arranged by doctors or dentists

MAL 32 Clinical Trials using Marketed Products

*MAL 33 A Guide to Licensing Provisions affecting Veterinary Practitioners

MAL 34 The Medicines Act - A note for Doctors

MAL 35 Review of Product Licences - Basic Product Information

MAL 36 Notes for Guidance on Reproduction Studies

MAL 37 The Promotion of Sales of Medicinal Products

*MAL 38 Notes for Guidance on Reproduction Studies Veterinary

MAL 39 Products Containing Herbal Ingredients

*MAL 40 Guide to the Enforcements of the Medicated Animal Feeding Stuffs Provisions

Requests for copies of these should be addressed to the Department of Health and Social Security, Medicines Division, Finsbury Square House, 33-37A Finsbury Square, London EC2A 1PP

* Requests for these MALs should be addressed to Ministry of Agriculture, Fisheries and Food, Government Buildings (North Block) Garrison Lane, Chessington, Surrey, England.