WORLD HEALTH ORGANIZATION

Regional Office for the Eastern Mediterranean

ORGANISATION MONDIALE DE LA SANTÉ

Bureau régional pour la Méditerranée orientale

SYMPOSIUM ON DRUG EVALUATION AND LICENCING

Alexandria, 30 October - 2 November 1978

EM/SYM.DRG.EVL.LIC./4

28 September 1978

# EVALUATION OF TECHNICAL DATA

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This century has seen a revolution in the treatment and control of disease by the use of synthetic drugs and purified biological derivatives. Any potent and effective medicine, however, carries a risk, either from being wrongly used, or because of its toxic effects. Similarly, an effective product even if relatively safe, is potentially hazardous if it is used in serious conditions where an alternative more effective treatment is available. As the potential for harm as well as the benefits of modern medicine have been realized there has been an increasing demand for adequate protection for the consumer.

Until the early sixties, government control of medicines in Europe varied considerably, some countries having had fairly rigorous control on new products for decades and others relying almost entirely on the integrity of the pharmaceutical industry to carry out adequate testing. However, matters were brought to a head by the Thalidomide tragedy when it was realized that the drug, given in early pregnancy, was directly responsible for gross deformities in the developing foetus.

In the last fifteen years, since the need for adequate safety control over drugs was brought so sharply into focus, there has been another revolution, this time in the safety standards imposed as legal requirements on the manufacturers and promoters of medicinal products.

Each government within Europe exercises an independent control over the medicines allowed for sale within its territory but the countries of the European Economic Community have, since 1965, been working towards a position of uniformity or 'harmonisation' in respect of the statutory requirements for marketed medicines.

I shall return later to the EEC intention of 'establishing a common position' on the marketing of medicinal products but first I will describe in some detail the system for licensing medicines which has been established in the United Kingdom.

The Medicines Act 1968 empowered the Department of Health to set up a Licensing Authority in order to:

a) control, through a system of product licensing, the supply of all medicinal products, whether for marketing or for use in the clinical trials;

b) control, through a system of manufacturers licences, the conditions under which products are manufactured, prepared and assembled for sale, and

c) introduce other measures such as controls over advertising, labelling, information to doctors and patients, with a view to assisting the safe and appropriate use of medicines.

The 'medicinal products' to which the Act applies are defined as substances or articles (but not instruments, apparatus or appliances) which are used to treat or prevent disease, and for the purpose of diagnosis, inducing anaesthesia, contraception, or preventing or interfering with normal physiological function. Products for use both in humans and in animals are covered by the Act and a similar licensing scheme is operated for veterinary as well as human medicines. However, this paper is concerned essentially with human medicines.

Licensing of medicines in UK began in 1971 and replaced the former system under which the industry, by voluntary agreement, submitted data on all new drugs for examination by the Committee on Safety of Drugs (The Dunlop Committee).

Since 1971, therefore, authorization has been required before a product can be imported, marketed or supplied for use in clinical trials. The 'authorization' takes the form of a "Product Licence" for marketing or a "Clinical Trial Certificate" for trials. In order to obtain a licence or certificate the applicant must satisfy the Licensing Authority that the product is sufficiently safe and efficacious, and is of suitable quality for the intended use.

The Department issues 'Notes for Guidance' for prospective licence holders and a copy of this (MAL 2) is included as an appendix to this paper. The Notes give details of the type of information required to compile an application. The application consists of four separate parts.

Part 1 is an application form which includes the basic product description and particulars; name, constituents, uses, dosage, warnings, etc. These details later form the schedule to the licence if the application is successful. Supplementary administrative and background information, relevant to the determination of the application, is also included.

Parts 2, 3 and 4 contain the technical, experimental and clinical evidence from which the safety, quality and efficacy of the product have to be assessed. The following summarises the data required for a marketing application and references are given to the relevant sections in the Appendix MAL 2.

Part 2: Pharmaceutical Data

This section is concerned with the quality control exercised over the product and the pharmaceutical development work carried out to verify that the quality is satisfactory.

1. FINISHED PRODUCT

A description and full declaration of the composition is required including both active and inactive ingredients, colours, flavours and preservatives. Details of the container are required and a description of any formulations used in clinical trials, where these are reported in support of the application.

2. MANUFACTURE OF THE DOSAGE FORM

The manufacturer must be described in sufficient detail to indicate those stages of the process where control is required to ensure that the end product is of uniform quality and not affected adversely by the conditions e.g. where heating or grinding is involved. For sterile products considerable detail of the sterilization process is required with information of the checks that are carried out.

3. 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.

Ingredient specifications (3.1) are required for each of the constituents showing the tests which will be carried out on each batch of ingredient and the limits which must be met before the material is accepted for use. If an ingredient is the subject of a monograph in the British Pharmacopoeia or European Pharmacopoeia it must comply with the specifications given in the monograph.

Details of in-process control (3.2) carried out during manufacture are required, with information on sampling. This section should include any tests which are carried out prior to analysis of the finished product, e.g. moisture content of granules before tabletting, tests on tablet cores prior to coating.

A detailed description is particularly important when the finished product specification does not include tests for all ingredients (e.g. in some multi-ingredient products) and other cases where the quality control of the finished product depends on in-process control tests.

The finished product specifications (3.3) must also be given in detail. This is the protocol of testing to be applied to each manufacturing batch. It would normally include an indentity tests for the active ingredients, physical test, e.g. disintegration, hardness, viscosity, tests for impurities and contaminants, and assay to check on the quantity of active ingredient present.

4. DEVELOPMENT PHARMACEUTICS AND BIOLOGICAL AVAILABILITY

The foregoing sections (1-3) describe procedures and controls which are carried out routinely once the product has been developed and formulated. In order to establish the validity of these controls, and the suitability

of the product we also require the applicant to include results of development work carried out during the formulation of the product, but not necessarily carried out routinely.

The type of information required will vary according to the nature of the product. For example, where products contain bacteriostats or preservatives, tests should be carried out to demonstrate that the additives are effective. If unusual or specialized analytical methods are used for quality control, evidence of the validity of the method and, where relevant, a standard deviation will be required. In addition to this, where bioavailability problems are known or suspected, in vitro and in some cases in vivo testing is required to demonstrate satisfactory release of the drug substance from the dosage form. In vitro tests may take the form of dissolution tests (e.g. for tablets and capsules) or diffusion tests (for topical preparations). In vivo tests demonstrate, usually by blood level studies, the absorption characteristics of the formulation either in animals or man.

5. STABILITY

One area of development work which must be carried out in all cases, is the determination of shelf life and stability. Before a product can be released for clinical trials or marketing, tests must have been carried out to demonstrate that the formulation is sufficiently stable for its intended use. For clinical trial products only, short shelf life may need to be demonstrated if the trial is to be short but for marketed products a shelf life of three years would be expected. If the shelf life is less than this, an expiry date must be included on the label.

Accelerated stability trials are often carried out to estimate the shelf life of products. These are studies in which artificially high storage temperatures are used, or products are exposed to extremes of light and humidity. Stability data from such trials is acceptable, provided suitable assay methods are used, but longer term tests under normal storage conditions should then be continued to confirm the results.

6. CONTAINERS

Information is required on those aspects of the containers and packs which are critical to the stability and quality of the product (e.g. type of glass or plastic, nature of closure) or are concerned with uniformity of dosage (accuracy droppers, aerosol delivery systems, etc). Details are also required of any inserts such as cushioning, desiccants, fillers, which are in contact with the product.

Part 2 Addendum: Chemistry of the Drug Substance

The information outlined under headings 1-6 is require, in full, for every new medicine, whether the product contains new or established drug substances. There are however additional requirements for pharmaceutical data when a new drug substance is involved; data must be supplied on the chemistry of the drug and evidence of impurity levels and stability.

7. IDENTITY OF MATERIAL

For reference purposes details of the nomenclature, chemical structure and physical characteristics of the drug are required.

8. MANUFACTURE

An account of the synthetic route and manufacturing process is required with information on tests carried out on starting materials and intermediates.

9. DEVELOPMENT CHEMISTRY

This section 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 in this section should be reflected in the drug substance specification by which batch-to-batch uniformity is controlled. The type of information may include: NMR, Mass Spectroscopy, IR, etc., as evidence of structure; discussion of polymorphism and crystal structure; isomerism.

10. IMPURITIES

Impurity control should always be included in the specification. This section on impurities is intended to supplement this by describing the research programme which has been undertaken to demonstrate that the methods used in the specification are valid and sensitive.

11. SPECIFICATION

A complete statement is required under this section of the tests which will be carried out routinely on each batch of material at the time of manufacture. For a typical synthetic drug substances the following criteria, at least, should have been considered for inclusion in the specification:

a) Appearance, colour, odour, texture, crystallinity.

b) Identity tests - IR, UV, melting point, chemical tests.

c) Physico-chemical tests - solubility, pH, moisture, loss on drying, particle size, optical rotation, test for polymorphic form.

d) Purity tests - chromatography, ash level, heavy metals, trace elements, e.g. those used as catalyst residual solvents, moisture.

e) Assays - an assay method which is sufficiently specific and sensitive to be useful. For complex molecules two or more assay methods which measure different chemical groups in the molecule may be appropriate.

12. BATCH ANALYSIS

Results are required from recent typical production batches to demonstrate the actual results obtained when the testing specification (11 above) is applied.

13. STABILITY REPORTS

This section is additional to Section 5 above which concerns the formulated product. The information required in this section concerns the inherent stability characteristics of the drug substance, i,e, whether it is light sensitive, degraded by moisture, etc.

The nature of any degradation products should be investigated.

Part 3: Experimental Biological Studies

1. PHARMACOLOGY

This section of the application documents the laboratory work carried out on the product or the drug substance. Where the application concerns a new drug substance, full information is required on the pharmacology, pharmacokinetics, animal pharmacology and reproduction studies. In some cases, where the medicine is for long term administration or the drug substance is related to a known carcinogen, carcinogenicity studies may also need to be carried out.

1. 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 experimental models, e.g. mouse, rat, hamster, guinea pig, rabbit, cat, dog, monkey.

The data on pharmacology should demonstrate the actions of the drug which relate to the proposed therapeutic use (1.1). In addition, the action of the drug on other systems should be demonstrated (1.2). For example, the central nervous system, the autonomic system, the cardiovascular system, etc. Data is also required (1.3) on interactions with other compounds where this is relevant to the proposed therapeutic usage.

2. PHARMACOKINETICS

The aim should be to establish the pattern and time course of absorption, distribution, biotransformation and excretion of active drug and as far as practicable its metabolites in animals and, during clinical trial stage, especially in man.

Plasma levels of drug and metabolites should be determined (2.1) including peak plasma levels, plasma half lives or clearance time. The degree of plasma protein binding is important. In addition studies have to be carried out on distribution (2.2) and excretion (2.3) of drug and metabolites.

Pharmacokinetic studies may be required for new combinations of known substances if the toxicity tests and therapeutic studies indicate that interaction occurs.

3. ANIMAL TOXICOLOGY

This section is divided into single dose studies and repeated dose studies. Single dose or acute toxicity studies should include $LD_{50}$ by each of the proposed clinical routes of administration.

In addition at least one route should be used which would ensure systemic absorption of the drug, i.e., intravenous, intramuscular or subcutaneous. At least two species should be investigated using equal numbers of each sex.

Data from repeat dose toxicity studies in at least two species is normally required; the dosing should have been conducted by tne proposed clinical route of administration in man and the duration of dosing should be appropriate to the proposed clinical use of the drug. These studies should be conducted with at least three dose levels; the lowest dose level should be in the therapeutic range, and the highest should have been selected after preliminary dose ranging studies to reveal the target organ. Throughout the toxicity studies repeated haematological and serum biochemical monitoring is essential, and at the completion of the study, the animals should be autopsied and histopathological examinations of the major tissues performed.

4. REPRODUCTION STUDIES

All new drugs have to be tested for teratogenic potential in reproduction studies. The tests are designed not only to show any effects of the drug on the foetus and neorate but also on fertility and are divided as follows:

a) Dosing throughout the period of embryogenesis (4.1) in two species, one of which should be other than a rodent.

b) A fertility study (4.2) should be conducted in at least one species. Dosing should commence in male and female animals at a sufficient time before the propose mating so that any effects of the drug on gametogenesis could be revealed. After mating the females should continue to be dosed throughout pregnancy; half the females should be killed during gestation, preferably some days before expected date of parturition, and the fetuses removed by caesarean section and examined. The remainder of the females should be allowed to litter normally and rear their progeny.

c) A prenatal study in which dosing covers that period of gestation in which dosing is not conducted in (a) above, and should extend throughout the period of lactation up to weaning.

Part 4. Studies in Humans

1. HUMAN PHARMACOLOGICAL STUDIES

The inclusion of studies on human pharmacology will be determined by the nature of the compound. Information is often obtained from volunteer studies although these are not mandatory since, in some cases, the studies might be unethical.

2. CLINICAL TRIALS

Clinical trial data is required to substantiate the safety and efficacy of the product.

In establishing the efficacy of a medicinal product it is expected that controlled studies will have been conducted, and that evidence of efficacy has been objectively measured. Extensive safety monitoring on patients treated during clinical trials is expected. The design of the trial to demonstrate efficacy and the nature of the monitoring to establish safety under the conditions ofproposed clinical use will of course vary from product to product and no rigid requirements can be laid down in these respects.

In the presentation of clinical data for a product licence, it is expected that during the clinical evaluation of the drug any interaction with other drugs with which the new agent is likely to be used concomittantly should have been investigated.

In reporting the results of trials, individual case histories are not asked for; summaries only need be presented but the patient records must be kept for five years.

Assessment of Applications

The UK Licensing Authority receives about 800 applications a year to market new products or carry out clinical trials. Up to one hundred of these may relate to new drug substances whilst the others concern ingredients which are already available in other medicinal products. The applications are dealt with initially by the permanent medical and pharmaceutical staff of Medicines Division. The data in the applications is assessed and summarized into a report with a recommendation on whether or not the application should be granted.

These reports are then referred to a committee, The Committee on Safety of Medicines, which consists of doctors and pharmacists from Universities, Research Establishments, Hospitals and General Practice. The Committee meets once a month to consider the Product Licence and Clinical Trial Certificate applications and the scientific evidence. The Committee has several sub-committees which also consider the applications and advise the Main Committee on specialist aspects where appropriate:

a) The Sub-Committee on Toxicity, Clinical Trials and Therapeutic Efficacy considers experimental biological and clinical data;

b) The Sub-Committee on Chemistry, Pharmacy and Standards considers the pharmaceutical and quality control data;

c) The Sub-Committee on Biological Substances deals with the products which cannot be controlled by chemical means: vaccines, blood products, some enzymes, hormones and antibiotics.

d) The Sub-Committee on Standards for Herbal Products considers the quality of herbal medicines.

The final decision on whether or not a licence should be granted rests with the Licensing Authority but, in practice, all major applications are referred to the Committee for advice.

Product Licensing in the EEC

As mentioned earlier, the European Community is endeavouring to achieve a uniform standard in the control of medicines. Directives have been drawn up which require all Member States of the Community to establish a system of licencing for Proprietary Medicinal Products and to control and inspect the premises on which medicines are manufactured. Standards are laid down for the type of information which must be provided in support of an application for marketing authorization and this is essentially similar to that described for the UK system.

One of the aims of the Community is to remove the barriers to free trade and therefore, if this is to apply equally to the movement of medicinal products, it is important to establish common standards in requirements for an evaluation of safety, quality and efficacy.

We are not yet approaching a stage where an authorization to market a product in one of the EEC countries automatically allows marketing in other EEC States, nor are there any moves to set up a central Registration Authority for the whole of the Community. Each country has an independent system for product authorization but all are required to work within the guidelines set out in the Directives.

A system has however been agreed whereby applications can be made simultaneously to five or more EEC countries, once registration has been obtained in one Member State, and consideration and discussion of the application is co-ordinated through a central committee, the Committee for Proprietary Medicinal Products. The opinion of the Committee is not binding on any Member State but it is intended that discussion in this way should help to resolve differences of approach and establish greater uniformity.

The European Committee procedure has not been in operation long enough to establish whether or not the objectives will be achieved but it is evident that there will be considerable problems to overcome due to differences in scientific and clinical practice between countries. The purely administrative difficulties of co-ordinating the procedure and the problems of language and terminology can also give rise to considerable difficulty.

In summary, therefore, the situation within the EEC is that each country has an advanced system of licencing of medicines in which comparable standards are applied, but that complete harmonization has yet to be achieved.

Licensing of Old Products

The procedures and requirements described so far apply to newly marketed products and it is important to realise that there are many thousands of products available in Europe which have been marketed for many years and may never have been the subject of a fully documented application since the current procedures have been introduced relatively recently.

In the UK, when licensing was introduced in 1971, there were over 20 000 products already on the market. Under the Medicines Act these products were allowed to continue to be sold provided brief details of each were registered with the Licensing Authority. This registration did not require the submission of any data relating to quality safety or efficacy, as with new products, but merely enabled the Licensing Authority to compile a record of the basic particulars (name, active ingredient, indications, dosage, etc.) of all products on the market.

The safety of products on the market is constantly monitored by the maintenance of a register of adverse reaction reports. On the basis of these reports, the Committee on Safety of Medicines advises on action to be taken whenever a drug or product appears to be giving rise to problems. However, it has been realized that there is an additional need for a thorough review of all the "Licences of Right" products and such a review has commenced in UK.

The total register of products is to be scanned in order to identify any products which are considered to be undesirable on safety grounds and these will be brought forward for action at an early stage. At the same time, a systematic review on products according to therapeutic categories is being undertaken starting with the analgesics/anti-inflammatory agents and psychotropic drugs.

Licence holders have provided quality control data on all products and are being asked to supply other data on safety, quality and efficacy as the review proceeds. In due course all products will have been assessed in a similar manner to that applied to new products and therefore, in time, the differentiation between fully licensed products and those which hold only a licence of right will disappear.

A review of all products is also required under the EEC Directives and is scheduled to be completed in all Member States by 1990 (15 years from the time of implementation of the Directives). The amount of work involved in carrying out a thorough review of all products is however immense and it is yet to be seen whether this target can be achieved.

SUMMARY

The situation in the UK, which is typical of most of the advanced European countries, is that medicinal products can only be marketed in accordance with a marketing authorization or product licence. Obtaining a licence involves detailed documentation of the product with evidence of safety, quality and efficacy. The evidence is evaluated by a team of experienced professional staff within the Department of Health who are advised by Committees of experts from outside the Department.

Not all products on the market have been fully documented and evaluated in this way but a review is under way which is intended to ensure the uniformity of standards for all products.

**APPENDIX**

MAL 2

# NOTES ON APPLICATIONS FOR PRODUCT LICENCES

(Medicines for Human Use)

# MEDICINES ACT 1968

## NOTES ON APPLICATIONS FOR PRODUCT LICENCES

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**These notes are only a general guide and must not be treated as a complete or authoritative statement of the law on any particular case.**

**Copies of the Medicines Act and of regulations made under the Act can be bought from Government bookshops.**

# MEDICINES ACT 1968

## NOTES ON APPLICATIONS FOR PRODUCT LICENCES

## SECTION 1 - INTRODUCTION

### 1. BACKGROUND

1.1 The general arrangements for licensing medicinal products are explained in the "Guide to the Licensing System" (MAL 1). These notes are intended to give a more detailed account of the manner in which product licence applications should be compiled. Leaflet MAL 4 gives similar details for clinical trial certificate applications. These notes deal only with applications for products that have not previously been licensed. If a product has been the subject of a product licence, or a product licence of right, but a new application is necessary (because responsibility for the product has been transferred to a new person, or because there has been a substantial change in the product particulars or the activities covered by the licence) a different procedure may be necessary. In these cases, applicants should contact Medicines Division for advice.

### 2. THE SCOPE OF LICENSING

2.1 Broadly speaking licensing applies to any material in a pharmaceutical form suitable for administration as a medicine, and to a small number of biological or antimicrobial substances used as ingredients in the manufacture of medicines. (See paragraph 2.3 of MAL 1). Toilet preparations, disinfectants, foods and cosmetics may be subject to licensing in certain circumstances, though instruments, apparatus and appliances are generally not. Medicines Division will be glad to advise on the status of any particular product.

2.2 A product licence authorises its holder, in relation to the product or products named in the licence, to:-

a. sell, supply or export the product;

or b. procure the sale, supply or exportation of the product;

or c. procure the manufacture or assembly of the product for sale, supply or exportation;

or d. import or procure the importation of the product in accordance with the provisions of the licence.

2.3 A product licence also enables the product to be manufactured or assembled in accordance with the provisions of the licence, provided that the manufacturer or assembler -

a. holds a manufacturer's licence, and

b. acts to the order of the product licence holder (or is himself the product licence holder).

2.4 Until an order is made under Section 48 of the Act, no product licence is required for a product made solely for export, unless it consists wholly

or partially of antigens, antisera, sera, antitoxins, toxins or vaccines.

3. WHO MUST HOLD THE LICENCE

3.1 An application for a product licence should be made by the person responsible for the composition of the product* or, in the case of a product imported into the United Kingdom, the person who imports the product. If a substance first becomes a medicinal product at some time after manufacture or import, the application should be made by the person who first sells or supplies it as a medicinal product.

*See paragraph 3.3 of MAL 1.

3.2 Foreign companies are advised to apply through an agent in the United Kingdom.

4. WHERE TO APPLY

4.1 Applications for licences for products for human use should be sent to:-

Applications Section
Department of Health and Social Security
Medicines Division
Finsbury Square House
33/37a Finsbury Square
London EC2A 1PP

(Tel No. 01 638 6020).

4.2 Applications relating to products for use both in human and in veterinary medicine should be sent to the same address in the first instance. A covering letter should draw attention to the dual use.

5. DOCUMENTATION

Details of the content of applications for product licences are dealt with in Section 2 but the following general points should be observed in all cases.

5.1 Presentation

All data submitted in support of an application must be suitably bound or stapled. Every page, including reprints, diagrams, tables and other data, should be numbered serially with a separate series for each volume of the submission.

Applicants are particularly asked to ensure that the method of reproduction used, such as photostat or xerographic copying, should be such as to secure legible presentation of the text and of relevant drawings or illustrations with their captions. A4 size should be used.

Parts II, III and IV of the application (See Section 2) must be presented as separate documents or volumes and each should be prefaced by a copy of Part I.

All information must be in English. Where part of the supporting data is based on material in another language, this should be translated. One copy of the document in its original language should accompany the application.

The application must be signed by the prospective holder of the licence in the space provided in form MLA 201.

5.2 Number of Copies

In all cases the following will be required:

1 copy of Part I - MLA 201

3 copies of Part IA and IB.

The number of copies of the supporting information, Parts II, III and IV will vary according to the type of application. The regulations allow for up to 27 copies to be requested but this is not usually necessary.

Where the application relates to a 'new drug' (i.e. a substance not currently licensed in the UK) 18 copies will be required.

Where an 'abridged' application is appropriate 3 copies only of the supporting evidence may be required. Appendix A deals with the circumstances and the way in which applications may be 'abridged' and also gives an indication of the number of copies which are likely to be required in such cases.

This should, however, only be taken as a general guide and where there is doubt as to how many copies are needed, three copies should be submitted initially: initial scrutiny by professional staff of the licensing authority may lead to a request for further copies if needed.

5.3 Manuals

Where applicants are involved in compiling information on products which are pharmaceutically similar they may find that data on, for example, excipient specifications, standard analytical methods, are being reported from application to application (see Section 2, Part II, Heading 3.1). In order to avoid unnecessary duplication this information can be assembled in the form of a manual which will be held by the Department and to which reference may be made in subsequent applications, (but see Section 2, paragraph 22).

Only one copy of each manual is required and it must be clearly headed with the company name and the title e.g. "Manual - Ingredient Specifications".

Note

Many licence holders have already lodged manuals of information with the Department as part of the information required to up-date licences of right under the Product Licence Review (see MAL 35 for details). Reference can be made to these manuals when applying for product licences.

All manuals should be clearly indexed and references made to them must be specific and accurate.

5.4 Repetition of documentation

Apart from the circumstances described above there may be cases where large sections of information submitted in support of a previous application are relevant to a current application e.g. when a product licence application follows a clinical trial certificate application. The data should not be re-submitted; a copy will have been held on file by the Department and a clear cross reference to it is all that is

required. This also applies in the case of simultaneous applications for different formulations where much of the supporting data are common to both (e.g. oral and parenteral formulations of the same 'new drug' substance). The basic data which are common (e.g. chemistry and toxicology) should not be duplicated; they should be given in full in one application and cross referenced in the other.

5.5 Multiple Applications

In general, a separate application is required for each separate medicinal product. A composite application may, however, be made in respect of:

a. Two or more products with the same pharmaceutical form and which -

(i) contain the same active constituent in different strengths;

or

(ii) consist of a mixture in different strengths of the same two or more active constituents in the same proportion.

b. Allergens, where -

(i) two or more attenuations of the same allergen extract (or the same mixture of allergen extracts) are to be used for the treatment of allergies;

or

(ii) two or more allergen extracts are manufactured by the same method and are to be used for testing allergic responses to specific substances.

c. Two or more products to be administered in the same clinical trial or medicinal test on animals.

5.6 In these cases the different products can be described on the same application form (MLA 201) and the supporting evidence for all the formulations can be included in the same application.

5.7 In other cases where there seem to be good reasons for including two or more products on the same form, this should be discussed with the licensing authority before the application is made.

6. SPECIAL CASES

Section 2 sets out the format and information required for a product licence. The notes are intended primarily to cover the typical situation involving medicinal products containing chemically controlled synthetic or semi-synthetic ingredients. There will, however, be cases where the nature of the medicinal product is such that some of the information detailed in these notes may not be relevant and additional information on other aspects may be required. Two specific categories are given below.

6.1 Biological Substances

A leaflet "Additional Notes for Guidance - Biological Medicinal Products"

(MAL 41) is available from the Department and should be read in conjunction with these Notes whenever application is made relating to a product consisting of or including biological substances. The application should follow the general format set out in Section 2 but the technical content should be modified to include any additional requirements of MAL 41.

6.2 Products containing Herbal Ingredients

Special considerations also apply to products containing herbal ingredients and these are set out in the leaflet MAL 39 obtainable from the Department on request.

7. CONDITIONS ATTACHING TO PRODUCT LICENCES

All product licences are subject to the relevant provisions in the Medicines (Standard Provisions for Licences and Certificates) Regulations which are currently in force and are reproduced in Appendix B to these Notes. For biological products which contain the substances listed in paragraph 1 to 35 of Schedule I of the Medicines (Control of Substances for Manufacture) Order 1971 (S.I.1971 No. 1200) additional standard provisions contained in Schedule 5 to the Medicines (Standard Provisions for Licences and Certificates) Amendment Regulations 1977 (S.I.1977 No. 675) will also apply.

SECTION 2

INFORMATION TO BE INCLUDED IN APPLICATIONS

1. INTRODUCTION

1.1 This section describes the information which is required in support of a product licence application and gives the order in which the data should be arranged.

1.2 The notes have been set out in the following manner. Under each main heading, where appropriate, there is a general comment on the type of information required in that section. This is followed by details of the manner of presenting the data which has been set out in three columns. The first gives the headings to be used, the second describes the type of data required and the third includes comments for the guidance of applicants.

2. COMPLIANCE WITH EEC DIRECTIVES

2.1 Applications which are compiled in accordance with these Notes will fulfil the requirements of EEC Directive 75/318/EEC. This is the Council Directive of 20 May 1975 on the approximation of the Laws of Member States relating to analytical pharmo-toxicological and chemical standards and protocols in respect of the testing of proprietary medicinal products.

2.2 There are certain sections of the Notes which recommend that applicants should refer to their previous applications or Manual of Analytical Methods and Specifications, rather than repeat data already submitted. However, where an application is intended to be forwarded, after licensing, to the Committee on Proprietary Medicinal Products for consideration, applicants are advised to include full data in the application and not to refer to other documents held by Medicines Division.

3. APPLICATIONS SHOULD BE DIVIDED AS FOLLOWS:

PART I

Application Form - MLA 201 - One copy of MLA 201 should be the original or a lithographic copy.

| | |
|---|---|
| IA Product Particulars - | Form MLA 201, P.2 |
| IB Supplementary Details | Stapled as one document<br>Three copies required |

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| PART II<br><br>Pharmaceutical Data on the Dosage Form<br><br>PART II ADDENDUM<br><br>Chemistry and Pharmacy of the Drug Substance<br><br>PART III<br><br>Experimental and Biological Studies | Parts II, III and IV are to be bound as separate volumes each prefaced by Part I. |

PART IV

Studies in Humans

The full information set out under all these parts will not be required in all cases. Depending on the type of product involved and the current licensing status of the active ingredients to which the application relates, certain sections may often be omitted and therefore the majority of applications will be "abridged" to some extent. In all cases the application form and Part must be completed.

A general guide to the circumstances in which abridged applications may be made is given in Appendix A to these Notes.

PART I - APPLICATION FORM

See details on attached form.

PART IA - PRODUCT PARTICULARS

See details on attached form.

This section provides for entries relating to the basic product particulars and they will normally appear in precisely this form as the schedule to the licence. As a photocopy of MLA 201 Page 2 as completed by the applicant may form part of the formal licence documents actual particulars under each heading should be given in as compact a form as possible: Page 2 of form MLA 201 has been approved for this purpose. Locally produced forms may be used by prior arrangement with the Licensing Authority.

These details cannot be subsequently varied without the agreement of the Licensing Authority. The Licensing Authority may, however, find it necessary to exercise some discretion as to whether all these details are inserted in the licence particulars. In general, data sheets and labels will be required to be in accordance with the licence and hence with the information given in this section. Each page of this section must be signed and numbered.

PART IA PRODUCT PARTICULARS

## Product Particulars

1. Name of Product:

   If the marketing name is not settled this should be left blank and the name notified later as available.

2. Pharmaceutical form:

   Describe the pharmaceutical form eg tablets, capsules, injoctions, and state whether the product is (a) in a form for administration to human beings: or (b) for use as an ingredient in preparing medicinal products.

3. Active constituents:

   Indicate the way in which the active ingredients and quantities will be declared on any leaflet, label or descriptive material. Each constituent should be described under (a) its approved name or monograph name: or (b) where there is no approved name or monograph name the non-proprietary designation or other descriptive appellation by which it can be readily identified: or (c) the trade name in other cases.

4. Uses:

   State recommended clinical use the proposed route(s) of administration and any directions for use to be included in labels and leaflets.

5. Recommended dose and dosage schedule:

   State the recommended dosage for:
   (i) adults and if appropriate (ii) children and infants by age groups. Where appropriate, distinguish between therapeutic and prophylactic doses and between dosages recommended for different clinical uses.

6. Contraindications, Precautions and Warnings:

   State particulars of contraindications, warnings and precautions to be included in the data sheet, container label, package label or any leaflets.

7. Method of retail sale or supply:

   State whether it is proposed to make the product available:
   (a) for general sale: or (b) only through registered pharmacies - (i) for over the counter sale: or (ii) as a prescription item or (c) through some other specified group of outlets eg hospitals, specialised clinics laboratories from automatic machines or herbal practitioners

8. Manufacturer of dosage form:

   State the name(s) and address(es) of the manufacturer(s) of the dosage form.

Applicants reference number (as on page 1)

Applicants signature.....

PART IB SUPPLEMENTARY DETAILS

1. PRODUCT LITERATURE

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| 1.1 | Labelling and package inserts | Details of the proposed labelling and package inserts. |
| 1.2 | Data sheets | The text of any data sheet should be given, if appropriate. |

This can be supplied at a later stage if it is intended to defer final drafting until the licence is granted.

Applicants should check that ALL labelling complies with the provisions of the Medicines (Labelling) Regulations 1976 (SI No. 1726) and data sheets comply with the provisions of the Medicines (Data Sheet) Regulations 1972.

The Department issues guides to these regulations which are available on request:

MAL 25 Notes on Data Sheets.

MAL 42 Notes on the Medicines (Labelling) Regulations 1976.

2. BACKGROUND

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| 2.1 | Applications in other countries | If authorisation to market this product has been granted, by the appropriate regulatory authority in any other country, give the country, date and outcome. | Any explanatory details that you consider relevant may also be given, including reasons for revocation or refusal of marketing authorisation in another country. |
| 2.2 | Background | Any other historical or background information which may assist in the assessment of the application should be given here. | For new drug applications it is often helpful to indicate whether the substance has been newly developed or whether the early development work was carried out some years back, since the techniques used may in some instances appear outmoded. |

3. PERSONS INVOLVED IN THE MANUFACTURE OF THE FINISHED PRODUCTS AND THEIR DISTRIBUTION IN THE UK

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| 3.1 | Manufacturer(s) and Assembler(s) | The name and address of each place at which each stage of the manufacture and assembly takes place indicating briefly the manufacturing or assembly operations involved. For UK companies give the manufacturer's licence number for each company. | |
| 3.2 | Arrangements for storage | The arrangements made for storage of the product by the proposed licensee or on his behalf and the address of each place of such storage. | Only a brief outline of the storage arrangements is required. |
| 3.3 | Importer | The name and address of the actual importer if this is other than the licence holder. | |
| 3.4 | Responsibility for quality control | State:<br>(a) whether the licence holder will be responsible for deciding if any batch of the product is acceptable for release for marketing; if not, who will be responsible.<br>(b) where the quality control will be carried out. | |

PART II PHARMACEUTICAL DATA ON THE DOSAGE FORM

## 1. FINISHED PRODUCT

**This section must include a complete declaration of the composition for each of the products to be covered by the product licence. This declaration must include all excipients, colours, flavours, preservatives etc. and any constituents intended to be ingested or otherwise administered to the patient e.g. capsule shells.**

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| 1.1 Description | Describe the physical characteristics of the product. This should include where appropriate:- Shape, size, superficial marking for identification purposes; colour odour, taste, consistency, type of tablet coating (e.g. delayed release, enteric, film-coated, sugar coated etc.) | When describing a liquid preparation it should be clearly stated whether this is in the form of a solution, suspension or emulsion. |
| 1.2 Complete formula<br>1.2.1 Active Constituents<br>1.2.2 Other Constituents | The formula should be set out under the heading shown in the first column giving a list of the constituents with the quantity per dose unit against each. For products such as ointments, lotions where there is no unit dose, a percentage composition should be given. For products with a measured dose, such as metered aerosols, oral liquids, drops etc. the percentage formula and quantity per unit dose should be given. For injectable preparations the composition in terms of weight per ml should be given and also the weight of each active ingredient in the unit container, taking into account the usable volume of the product. | It is important in stating the composition of the dosage form to identify the constituent accurately by name and therefore the following rules should be adopted:-<br>1. If the constituent is the subject of a Ph Eur or BP monograph the name in English from the head of the monograph must be used; otherwise use:<br>2. The International Non-Proprietary Name (INN) or British Approved Name where such exists. (If the INN and BAN differ, both should be given); or<br>3. Another non-proprietary designation (e.g. USAN) or a simple chemical name by which it can be accurately identified; or<br>4. A proprietary designation; e.g. the trade name may be given for certain proprietary excipients which contain a mixture of components. |

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| | Metric units should be used to express the quantities. Where an active ingredient is present as a salt or ester the quantity should also be declared in terms of the base equivalent. This is particularly relevant where more than one salt or ester exists. | 5. Where colouring matters are used the substance should be identified by using the EEC code number.<br><br>Exact quantities are not required for ingredients used in tablet coating or capsule shells although the constituents of these must be declared. |
| 1.2.3 Overage | Where an overage is included this must be declared and it should be stated whether this is intended to cover losses during manufacture, loss of potency on storage or both. Reference should be made to other sections of the application which include information relevant to the need for an overage e.g. stability data Part II Heading 5. | The inclusion of an overage normally applies only to active ingredients, preservatives etc. For excipients, where a slight variation in quantities may be required from batch-to-batch the quantitative declaration of formula can include a suitable range. |
| 1.3 Containers | Give a brief description of the type of containers to be used and indicate the proposed pack sizes which the licence is required to cover. | Only a brief outline is required here as full details are given under Section 6. |
| 1.4 Formulation used in clinical trials | This heading is only applicable in cases where clinical evidence is submitted in support of an application. The composition of the products used in those trials must be declared. The formulae should be set out as in 1.2 above. | If the formulations used in the reported trials were identical to those given under 1.2 this should be stated and the formulae need not be repeated. |

## 2. 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.

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| 2.1 | Manufacturing formula | Give the actual manufacturing formula with quantities of all substances used. The quantities of some excipients, e.g. those used in tablet coating need only be given in approximate terms. Substances which are removed in the course of manufacture should be included. | |
| 2.2 | Manufacturing process | A description of all the stages involved in the manufacture of the dosage form is required. This should include sufficient detail to cover the essential points, such as steps in the process which involve comminution of the active ingredient, fluid media used in moist granulation procedures; drying processes; temperatures used, e.g. in preparation of ointments, sterilisation conditions and procedures. | It should be remembered that, whereas UK manufacturers are subject to licensing, and regular inspection, overseas manufacturing establishments may be less well known to the Licensing Authority; it is therefore advisable to give as full an account as possible of the manufacturing processes in these cases, especially where a sterile product is involved.<br><br>If, at the time of application, the manufacturer has prepared complete "operator instructions" or a "Master Formula and Method" it may be more convenient to include this to cover sub-headings 2.1 and 2.2. |
| 2.3 | Assembling process | Give a brief description of the assembly of the product into the final containers with information on any special precautions which are required. | |

## 3. 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 (MAL 41) must be included.

### 3.1 Specifications of Constituents

A specification is required for each of the constituents (active and other) used in each of the products.

Indicate whether the ingredients are bought to a purchase specification with a certificate of analysis, or tested by the manufacturer for compliance with the specifications.

The specification should be annotated to indicate the tests which will be carried out routinely and those which may only be checked on an occasional basis to ensure compliance with the specification.

### 3.1.1 Constituents Complying with Pharmacopoeial Monographs

The specifications should be given as follows:

a. Where any constituent complies with the specification in Ph. Eur., BP or BPC monograph, a reference to the monograph is sufficient (but see Note 1 opposite).

b. Where a constituent complies with pharmacopoeial monograph which is published in the English Language e.g. USP, USNF, a reference to that monograph is sufficient. (But see notes 1 and 2 opposite).

Note 1
The applicant's attention is drawn to Appendix A which outlines circumstances under which additional information on active constituents as set out in Part II Addendum may be required for ingredients even when they are the subject of pharmacopoeial monograph.

Note 2
Where an ingredient is the subject of an Ph. Eur., BP or BPC monograph, but is controlled using a specification from another source, information should be given on

a. whether the material would comply with the relevant Ph. Eur., BP or BPC Monograph, or
b. if not, in what respect(s) it differs from the monograph.

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| | c. Where a constituent complies with a pharmacopeal monograph which is not in English, a translation of the specifications must be provided (see also Notes 1, 2 and 3). | It should be noted that it is a requirement under EEC directive 75/318 that the monographs of the Ph. Eur. shall be applicable to all substances appearing in it. |
| | d. For constituents which are the subject of a Ph. Eur., BP or BPC monograph but are tested according to the company's own "in-house" specification, full details of the specification are required. (see Notes 2 and 3). | Note 3<br>Where full specifications and analytical methods have to be supplied the possibility of including them in a Manual of Specifications described under Section I Heading 5.3 should be considered to avoid unnecessary duplication of data in subsequent applications. It should be noted that EEC directive 75/318 requires that the description of the assay for non-pharmacopoeial ingredients should be in sufficiently precise detail so as to be reproducible in control tests carried out at the request of the competent authority. |
| 3.1.2 Constituents not in a pharmacopoeia | a. Full details of the testing specification is required with details of the analytical methods (see Note 3)<br>Part II Addendum<br>Where an ingredient is a new drug substance, not previously licensed in UK full supporting evidence to verify the specification is required as set out in Part II Addendum. Other circumstances under which the data may be required are set out in Appendix A. | Note 4<br>Where reference is made to a Pharmacopoeia or Codex, this will be taken to mean the current edition of that compendium unless otherwise stated.<br><br>Note 5<br>Where necessary, information on constituents can be supplied direct and in confidence to the Licensing Authority by the supplier. It is however the responsibility of the applicant to arrange for this information to be sent and care should be taken that the supplier clearly indicates the application to which this information relates. |

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| | b. For proprietary flavouring or perfume compounds, the name of the supplier must be given and arrangements should be made for details of the constituents of that compound to be placed on file with the Licensing Authority (see Note 5).<br><br>c. For colouring compounds the dyes must be identified by the EEC number(s) or, where none exists by the 1971 Colour Index Number(s) (but see Note 6). Where a propriety colour is used the name of the supplier should also be given. | Note 6<br>The EEC directive 78/318 limits the use of colouring matters in proprietary medicinal products to those permitted under the Council Directive on Colouring Materials.<br><br>Advice should be sought from the Secretariat before applying for a licence for a product containing a colouring substance without an 'E' code or which is not in the permitted list. |
| 3.1.3 Suppliers of active Ingredients | Give the names and addresses of the manufacturers or suppliers of the active ingredients. | This information will not normally be required for substances meeting BP, BPC or Ph. Eur. specifications and bought on the open market, except in cases indicated in Appendix A where additional information on the drug substance is required under Part II Addendum. |
| 3.2 In-Process control | | |
| 3.2.1 Analytical control | Specify any analytical controls which are applied to the product during manufacture giving limits or criteria of acceptance and analytical methods. | This sub-heading should include any tests which are carried out prior to analysis of the finished product e.g. moisture content of granules before tabletting tests on tablet cores prior to coating.<br><br>A detailed description is particularly important when the finished product specification does not include tests for all ingredients (e.g. in some multi-ingredient products) and other cases where the quality control of the finished product depends on in-process control tests. |

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| 3.2.2 | Sampling for quality control | Indicate the stages of manufacture at which sampling is carried out. | |
| 3.3 | Finished product specification | Details of the tests which will be carried out on each batch of material are required. Where applicable (see next column) a clear distinction should be made between:<br><br>a. <u>The Release Specification:</u> The requirements for each batch at the time of manufacture and<br><br>b. <u>The Check Specification:</u> The requirements with which any sample should comply during its shelf life. | A different Release and Check specification is often necessary where a product tends to be unstable <u>especially</u> where a stability overage has been included.<br><br>Note: Where preservatives, stabilisers, antidoxants etc. are included, identity and assay methods may need to be included in the specification, particularly the 'release' specification. |
| 3.3.1 | Tests and Limits applied | Give a list of tests which will be carried out and state the limits or criteria of acceptance for each test.<br><br>Where the finished product is the subject of a monograph in the BP, BPC or a pharmacopoeia in the English language a reference to the pharmacopoeia is all that is required and 4.2 may be omitted. If additional tests are carried out however, or tighter limits are imposed at the time of manufacture, details should be given. | The specification for all products which are the subject of a product licence application will be expected to include a suitable identity test. Where the type of dosage form (tablet, capsule etc) is the subject of a general monograph in the Ph. Eur., BP or BPC the product would be expected to comply with the requirements of the General Monograph. (e.g. disintegration rates for tablets and capsules, uniformity of weight, content etc.) Where pyrogen testing, abnormal toxicity tests, sterility testing etc. are carried out routinely or on each batch these should be included in the specification with an indication of the frequency of testing. |

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| 3.3.2 | Specify the analytical methods which are used. Where these are methods from the Ph. Eur., BP or BPC a reference to the appropriate compendium is all that is required. Reference may also be made to USP and USNF methods and other pharmacopoeias which are published in the English language. Where a method is not included in a pharmacopoeia or where the pharmacopoeia is not in English, full details of the method will be required. | Note 1<br>Wherever reference is made to a Pharmacopoeia or Codex this will be taken to mean the current edition of that compendium, unless otherwise stated.<br><br>Note 2<br>Where details of methods or translation need to be supplied and they are likely to occur in subsequent applications a possibility of including these in a Manual as described under Section I Heading 5.3 should be considered.<br><br>It should be noted that EEC directive 75/318 requires that the description of the techniques for analysing the finished product shall set out in sufficiently precise detail (so that they can be reproduced readily) the methods used for identification and assay of the active ingredient(s) either in a representative sample from the production batch or in a number of dose units analysed individually. |

## 4. DEVELOPMENT PHARMACEUTICS AND BIOLOGICAL AVAILABILITY

This section is intended to describe the development work which has been carried out to establish that the proposed formulation(s) detailed under Section I are satisfactory for the purposes specified in the application. The information should, as far as possible, be arranged according to the headings given in Column 1 below.

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| 4.1 Formulation Studies | An account should be given of the criteria which have been taken into consideration in formulating the product.<br><br>A discussion of the following aspects, where relevant, has previously been shown to be useful. | Where the application also includes Part II Addendum (full information on the active ingredient) there should be a correlation of the characteristics reported in that part with the factors considered in the pharmaceutical development. |

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| 4.2 | Analytical Development | The analytical methods and assay procedures selected for routine control of the formulation should be discussed. This should include evidence to show the validity of the methods which are used e.g. standard error of assay methods, results of single tablet assays to show uniformity of content, copies of spectra or GLC traces where these are used for assay or identification purposes. | The emphasis here should be on demonstrating that the proposed specifications and methods are adequate to ensure batch-to-batch uniformity of the product. |
| 4.3 | Analytical Results | Give the results of recent, representative batches of the dosage form which have been manufactured as described in the application. Where results from more than one batch are available, the results should preferably be tabulated. The details should include:<br><br>Date of manufacture<br>Batch size and number<br>Place of manufacture<br>Results of analytical tests<br><br>If the batches have been used in clinical trials which are reported in support of the application, this information should also be recorded. | A brief explanation should be included of any apparently anomalous results or batches which have not been tested according to the specification given in Sub-Heading 3.3. |
| 4.4 | Availability Studies | Where it has not been considered necessary to carry out studies on the availability of the drug substance, because of the nature of the active ingredients or formulation, this sub-heading may be omitted providing that the reasons for doing so are clearly stated. | |

a. Clinical requirements where the clinical use of the product indicates that a special formulation is necessary, e.g. controlled release tablets, enteric coating, depot injections etc.

b. Physical characteristics of the active constituent, e.g. whether the bulk density or crystal form of the drug substance have created special formulation problems.

c. Particle size control where this is necessary, e.g. for satisfactory uniformity of content in low dosage tablets etc.

d. Solubilising agents where these are required to produce a satisfactory solution or influence absorption.

e. Compatibility of the drug substance with any excipients used.

f. Patient acceptance where special modifications to the formula are required on the grounds of palatability, pain on injection etc.

g. Inclusion of preservatives, antioxidants etc. Where the nature of the formulation or its use make this necessary, information should be given on challenge tests etc. which have been carried out to confirm the suitability of the selected age in the particular formulation.

This applies particularly to the physicochemical characteristics reported in subheading 9.2 and the metabolic data summarised in heading 14.

For abridged applications where Part 2 Addendum is not included, reference should be made to characteristics of the drug; solubility, pH, absorption etc.

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| 4.4.1 | In Vitro Tests | Describe the tests which have been carried out <u>in vitro</u> to establish the release of the active constituent from the formulation under standard conditions, e.g. dissolution tests, diffusion tests etc. | Any information on the correlation of <u>in vitro</u> and <u>in vivo</u> results should be included. Where an <u>in vitro</u> test is included in the specification to ensure batch-to-batch uniformity, particularly in the case of controlled release formulations, the basis for choosing this particular test should be discussed in relation to the required clinical performance. |
| 4.4.2 | In Vivo Tests | Give an account of any work which has been carried out to demonstrate the absorption characteristics of the formulation either in animals or in man. If this work is reported in detail elsewhere in the application i.e. in the experimental or clinical sections, a summary need only be given here with the cross reference to the appropriate section. Information must be given however, on the exact formulations which were used in the study.<br><br>Where the formulations used in clinical trials, which are reported as part of the application, differ from the formulation proposed for marketing the equivalence of the formulations should be discussed and any appropriate data included. | |

5. STABILITY

Evidence is required to demonstrate that the proposed formulation is stable for the purposes covered by the product licence application and that it will meet the finished product (check) specification throughout its shelf life. As far as possible, the information should be set out using the headings in Column 1 below.

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| 5.1 | Batches examined | State the number of batches and batch reference numbers. | |
| 5.2 | Conditions of storage | State the time, temperature, humidity, light conditions, etc. under which the product was tested. | |
| 5.3 | Containers | State the containers in which the samples were stored for the purpose of the trials. | If the containers used in stability trials differ from those proposed for the marketed product, the significance of the differences should be discussed. (See also Note under 6.1 regarding the quality control of containers). |
| 5.4 | Results | Details of the actual results obtained when the samples were tested must be given and should preferably be tabulated and presented graphically where appropriate. | |
| 5.5 | Analytical Methods | Details are required of the analytical procedures used to monitor stability during the trials. When these methods are the same as those described under the specification, reference to the relevant section can be made. Where other methods have been used, they must be described in full. | It is important that the analytical methods used in the stability trials should be sufficiently specific and sensitive to detect deterioration. Reported non-specific assays, without supporting data on levels of degradation are not sufficient. Results should also include information on physical characteristics during storage. |
| 5.6 | Summary of Results | A summary and discussion of the results should be given with the conclusions which have been drawn from the stability trials. | The discussion should cover such aspects as:<br>a. Suitability of the analytical procedures as stability determining methods.<br>b. Whether it has been considered necessary to carry out toxicity tests on stored material because of the presence of significant amounts of degradation products (in such cases, results should be reported). |

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| 5.7 | Proposed shelf life | Give the proposed shelf life and details of any expiry date to be included on the label. | An expiry date is required for any product which has a shelf life of less than three years. See Medicines (Labelling) Regulations 1976 (S.I. No. 1726). |
| 5.8 | Storage conditions to be included on the label | Give details of any recommendations for storage which will be included on the label, packaging, promotional literature data sheet, etc. | |
| 5.9 | On-going stability trials | Indicate whether stability trials are still in progress and give a protocol of the testing which it is proposed to carry out. | Under certain circumstances a licence can be granted when only limited stability data is available provided assurances are given that suitable tests are in progress and that results will be forwarded at regular intervals. |

## 6. CONTAINERS

This heading covers those aspects of the containers and packs which are critical to the stability and quality of the product or are concerned with uniformity of dosage. Details are also required of any inserts such as cushioning, desiccants, fillers, which will be in contact with the product.

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| 6.1 | Type of Container | Details of the container should include, where applicable:<br><br>Fabric of container, i.e. the type of glass, type of plastic, composition of strip, packaging etc.<br><br>Nature of closures details of liners, caps etc.<br><br>Dosage measurement<br>Where the container or a component is designed as a dose-measuring device this should be described in detail and information will be required on the accuracy of measurement. | Where the nature of the containers is critical to the stability and satisfactory storage of the product it is important that the information under this heading is given in adequate detail. In some cases information may also be required on the tests which are applied to ensure suitability and batch-to-batch uniformity of the containers and closures. For example, this will always be required for injection solutions in plastic containers and may be necessary for other plastic containers especially for liquid and semi-solid preparations where such testing is critical. |
| 6.2 | Packaging Inclusions | State whether any desiccant or other inclusion is present in the container in contact with the product and give | |

the following information:

| | | |
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| 6.2.1 | Description and Composition | It is important that any inclusion should be readily distinguishable from the product by a suitable combination of size/shape/colour/weight/texture to ensure immediate dissimilarity by sight or by touch. |
| 6.2.2 | Duration of Satisfactory Performance (for desiccants) | This should be related to the shelf life/ expiry date and desiccant stability. |
| 6.2.3 | Instructions to Users of Product | These may be printed on the inclusion itself (e.g. "This is a drying agent. Not to be taken") or on the label of the product containers. |

PART II ADDENDUM; CHEMISTRY OF THE DRUG SUBSTANCE

(See Part II Sub-heading 3.1.2)

## 7. IDENTITY OF MATERIAL

This section deals with the identity, nomenclature and chemical structure of the drug substance which is the subject of the application. Only brief details of physical characteristics are required here, as full details and proof of structure are given later.

### 7.1 Nomenclature

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| British Approved Names (BAN)<br>International Non-Proprietary Name (INN)<br>US Adopted Name (USAN)<br>Laboratory Code(s)<br>Chemical Name(s)<br>Other Names (e.g. Proprietary) | List of names against the appropriate headings, indicating where there is no name, or the heading is not applicable. | An application for the British Approved Name should be made, if none exists, for an active ingredient which is the subject of a product licence application. Application to:<br>The British Pharmacopoeia Commission,<br>8, Bulstrode Street<br>London W1M 5FT |

### 7.2 Description

| | | |
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| Physical form<br>Structural formula<br>Molecular formula<br>Molecular weight | Give a brief description of the appearance of the material. Where relevant, give the structural formula diagrammatically with molecular formula and molecular weight, otherwise a detailed description of the nature of the substance should be given. | The molecular weight of the base or acid should also be included where the substance is a salt. |

## 8. MANUFACTURE

A concise but comprehensive account of the manufacture of the drug substance is required. The headings given below should be followed where the drug concerned is a totally synthetic product. Some modification may be required where the molecule is only partially synthetic e.g. Penicillin derivatives. For substances which are wholly or partially of biological origin additional requirements relating to these products are itemised.

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| 8.1 | Synthetic route | When a complete or partial chemical synthetic is involved, this should be represented by diagrams of the chemical reactions in the form of a flow sheet. | |
| 8.2 | Description of Process | Give a brief description of each stage of the manufacture, including, where applicable:-<br><br>Solvents and reagents used<br>Catalysts used<br>Conditions of reactions where these are critical<br>Information on intermediates which are isolated and purified.<br>Details of the final purification and the solvents involved. | The description of the process should indicate the scale of manufacture. It is often helpful if an indication of the yield produced at each stage is given.<br><br>The description must be complete i.e. alternative steps or alternative solvents should not be given without a clear indication of the circumstances under which alternatives will be used. If alternative methods and reagents for synthesis are to be used, evidence may be required under headings 4 and 5 above to show that the quality of the material produced by each method does not differ significantly. |
| 8.3 | Quality Control during Synthesis | | |
| 8.3.1 | Starting Materials | Describe the analytical controls which are applied to ensure that the starting materials used, or any reagents which make a significant contribution to the molecular formula are correctly identified and are of a satisfactory quality.<br><br>Indicate the criteria for accepting or rejecting batches of these materials. | The control of starting materials should be designed to detect isomeric or other impurities which are potentially reactive and could be carried through to the final product of the synthesis. |

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| 8.3.2 | Intermediate Control | Describe the quality control checks which are carried out at each stage of the process and on the isolated intermediates. | A statement of the analytical method and criteria for acceptance should be given for each stage. |

## 9. DEVELOPMENT CHEMISTRY

This section 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 in this section should be reflected in the drug substance specification by which batch-to-batch uniformity is controlled (heading 5 above).

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| 9.1 | Evidence of Chemical Structure | A scientific discussion of the chemistry of the molecule should be given and should include, where applicable evidence of structure, configuration, conformation and potential isomerism. Where relevant the information might include such evidence as:<br>Elemental Analysis<br>Infra-red spectra, with interpretation<br>Nuclear magnetic Resonance spectra with interpreation<br>Discussion of UV characteristics including acid-alkaline shifts<br>Mass Spectrum with interpretation and discussion of results<br>Discussion of the synthetic route as evidence of structure<br>Evidence of structure of Key intermediates of synthesis (e.g. using IR, NMR etc)<br>Characteristic chemical reactions which are diagnostic of the structure of the molecule.<br>X-Ray crystallography with interpretation and discussion of results<br>Optical rotation with discussion of optical purity in the case of d-or l-isomers. (Absence of optical rotation should be reported when this serves to illustrate that an asymmetric molecule is racemic). | A summary and discussion of the evidence of structure by the experts involved can often provide useful additional background information. Care should be taken that the visual evidence of spectra is completely legible when reproduced in the copies of the application.<br>It is important that the evidence of structure should be related to the actual material to be used in the marketed product, especially for highly complex molecular structures. Where the data included in this sub-heading are from a source or synthetic process other than that covered by the application, evidence may be required to confirm the structural identity of the different materials. This is particularly important where toxicity work has been carried out on material from a different source (see also Batch Analysis below).<br>Where the synthetic route and structure of the intermediates are cited as evidence of structure, references to relevant published papers in the literature would be helpful. |

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| 9.2 | Physico-chemical Characteristics | Information set out under the following headings in Column 1 should cover all aspects of physico-chemical characteristics which have been investigated, whether or not they are included in the specification. | |
| | 9.2.1 Solubility | Give solubility in water, acid, alkali, chloroform and other relevant solvents. Where possible numerical values for the solubility should be given. | |
| | 9.2.2 Physical Characteristics | Indicate whether the substance is crystalline, amorphous, etc. and give, where relevant, information on particle size, solvation, melting point, or boiling point etc. | |
| | 9.2.3 Polymorphism | Where relevant the presence of polymorphic forms and the methods of detection and control should be discussed, or their absence confirmed. | |
| | 9.2.4 pKa and pH values | Where relevant the pKa value of the drug substance should be given and the pH in solution. In the case of a salt, this information should be given for the corresponding base or acid. | |
| | 9.2.5 Other Characteristics | Any other relevant information should be given. | |
| 9.3 | Analytical Development | Any critical aspects of analytical development relevant to the specification should be mentioned. | The discussion here should highlight any unusual aspects of the tests for identity, physico-chemical characteristics and content which are used in the specification. (Tests for purity and freedom from contamination will be discussed under the section on impurities). Discussion of the precision and accuracy of assay methods is particularly applicable to substances where biological control is necessary. (See also MAL 41). |

## 10. IMPURITIES

The purpose of this section is to give a broad outline of 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. Methods which have been tried but have proved unsuccessful for the detection of impurities should be stated.

### 10.1 Impurities

Give a list and brief discussion of the products which have been considered as impurities arising from the synthesis. State in each case whether actual samples have been synthesised for test purposes and which of the analytical methods described under sub-heading 4.2 have been used to detect that impurity.

The term "impurities" in this context includes:

a. By-products of the synthesis arising from side reactions, impurities in the starting materials or isomerisation.
b. Residual solvents and reagents
c. Trace elements arising from the use of catalysts or from other sources
d. Degradation products.

### 10.2 Analytical methods

Describe the analytical methods which have been used to detect each of the likely impurities considered in 10.1 above or other related impurities, the exact identities of which may be unknown.

In describing several different chromatographic methods which have been used to detect impurities, a tabulation of results is often helpful. The information which is required is listed opposite but the actual format in which it is supplied is left to the applicant's discretion.

#### 10.2.1 Chromatography

Description of chromatographic methods (TLC, PC, GLC, HPLC, etc) must include information on:

a. Sensitivity and limits of detection for the methods.
b. Separation of potential impurities e.g. Rf values.
   Note: Where relative Rf values are given state the actual Rf value of the reference sample.
c. Actual loadings of samples and potential impurities onto the column, plate, paper etc.
d. Method of detection or visualisation of results
e. Methods of quantifying results

Visual evidence of chromatographs should be supplied.

Photographic or diagrammatic representations of TLC plates and paper chromatography are acceptable. These help to show the shape and size of the spots obtained under laboratory conditions and to illustrate that separation of spots is satisfactory when Rf values are close. For GLC, Column Chromatography and HPLC copies of the actual chromatographs should be included.

#### 10.2.2 Other methods

Where other methods have been used to detect impurities, e.g. chemical methods

spectroscopy or atomic absorption for trace elements, these should be described and where appropriate details should be supplied on the sensitivity and specificity of the methods used.

10.3 Summary of Results

10.3.1 Impurities found — A summary should be given of the impurities which have been detected in the batch samples of the material. The levels found should also be reported.

The criteria for selecting the limits and methods used for impurity control in the specification (Heading 11) might usefully be discussed here.

11. SPECIFICATION

A complete statement is required under this section of the tests which will be carried out routinely on each batch of material at the time of manufacture.

Tests which are used, but not necessarily for every batch, should be included with a clear statement of the frequency or circumstances in which they would be applied.

Note: The additional information which is required in the case of Biological Substances is set out in MAL 41.

11.1 Tests and Limits applied — Give a list of tests which will be applied to each batch of drug substance with the limits or criteria of acceptance for each test.

For a typical synthetic drug substance the following criteria, at least, should have been considered for inclusion in the specification:

1. Appearance, colour, odour, texture, crystallinity.
2. Identity tests - IR, UV, melting point, chemical tests.
3. Physico-chemical tests:
   Solubility, pH, moisture, loss on drying, particle size, optical rotation, test for polymorphic form.
4. Purity tests:
   Chromatography, ash level, heavy metals, trace elements (e.g. those used as catalyst residual solvents, moisture).
5. Assays:
   An assay method which is sufficiently specific and sensitive to be useful. For complex molecules two or more assay methods which measure different

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| | | chemical groups in the molecule may be appropriate.<br><br>Note: If alternative assay methods are included in the specification it is important to explain the criteria for selecting one method rather than the other. |
| [illegible] | Information is required on the analytical procedures for each test included in the specification. | Where standard pharmacopoeial methods are used or where the analytical procedure is fully described in some other document submitted by the applicant (e.g. a Manual or previous application) reference to the relevant document is all that is required (see paragraphs 5.3 and 5.4 of Section 1). |
| [illegible] | [illegible] the use of a Reference Standard for the drug substance a full characterisation of that Standard with Spectra and analytical results should be given. | If this is used as a control in a chromatographic test, it may be important that visual evidence of the impurity profile is included in the application either here or under the impurity section. |

## 12. BATCH ANALYSIS

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 purposes covered by the Product Licence;

b. Batches of material used in the toxicity tests and clinical work reported in support of the application.

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| 12.1 Laboratory reports | The results should preferably be tabulated and should include where known<br><br>Date of manufacture<br>Batch size and number<br>Place of manufacture<br>Results of analytical tests<br>Use of batch | As far as possible the results should give actual figures for tests on, for example, impurity levels. Results which merely state that the material "complies" with the test are often not sufficiently informative, especially where a relatively wide limit is allowed in the specification.<br><br>The batch analyses should include all the tests set out in the specification. There may however, be cases where earlier batches of material were tested using a slightly different specification. In these cases a brief explanatory note should be included. |
| [illegible] Discussion of results | Any apparently inconsistent or anomalous results in the batch analyses should be explained. | |

13. STABILITY REPORTS

This section refers to stability tests on the drug substance; information on the stability of formulated products is given under Section 5 of Part II. As far as possible the information should be set out using the headings in the first column below.

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| 13.1 Batches examined | The number of batches with the batch numbers. | |
| 13.2 Conditions of Storage | Give the temperatures, humidity, acid, alkaline and light conditions etc., which were used to assess the stability of the compound, with details of the length of time of storage. Details of the container should also be given. | The stability tests on the bulk chemical should be designed to determine the inherent stability characteristics of the molecule. The findings should be reflected in the formulation work on the dosage form (see Development Pharmaceutics - heading 9 above). |
| 13.3 Analytical Methods | Describe the analytical control procedure used to monitor the stability of the product. Where these are the same as in the specification, reference to the relevant section can be made. Where other methods have been used these should be described in full. | In all cases there should be a discussion of the analytical methods with evidence to show that they are suitable and sensitive methods for detecting deterioration of that particular compound. |
| 13.4 Results obtained | The results of the tests carried out on samples during the stability trials must be given in detail and should preferably be tabulated. The levels and (where possible) identity of degradation products should be given.<br><br>A summary and discussion of the results should be included. | The discussion should cover such aspects as:<br><br>a. The inherent stability characteristics of the compound (e.g. photo-sensitivity, hygroscopicity, thermolability.)<br><br>b. Storage conditions required for bulk drug.<br><br>c. Whether it has been considered necessary to carry out toxicity tests on stored material because of the presence of significant amounts of degradation products. (In such cases results should be summarised). |

## 14. 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 heading of the Experimental Studies should be avoided but relevant data from Section 3.1 of Part III should be reproduced as indicated under 14.2 below.

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| 14.1 Metabolic Pathways | The metabolic pathways if partially or fully determined should be represented schematically and described briefly. If these are known for the different species of animals used in the experimental data and for man, these should be given for comparison. | |
| 14.2 Measurement of Plasma levels of drug or metabolites (See Sub-heading 3.1 Part III) | Data should be presented as to the technique of measurement, and, where metabolic studies are conducted using labelled material, the position of the label and the specific activity of the labelled material should be given. Peak plasma levels and plasma half lives or clearance time of the drug should be given. | Where the information given under heading 3.1 in Part III is extensive it need not be reproduced in full. A summary may be given but this <u>must</u> include details of analytical techniques and information on the labelled material used. A cross reference to the Section containing the full data should then be made. |
| 14.3 Synthesis of Labelled Compounds | Where labelled compound(s) have been used an outline of the synthesis of the labelled compound should be given. Information on the specification and radioactive stability of the material should also be supplied. | |

PART III EXPERIMENTAL AND BIOLOGICAL STUDIES

In the interpretation of the following guidelines it must be appreciated that they are not rigid requirements and may not be universally applicable. Interpretation should therefore be flexible and related to the proposed use of the drug.

## 1. 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 experimental models. Data usually should be reported under the following headings in the following species order: Mouse, Rat, Hamster, Guinea Pig, Rabbit, Cat, Dog, Monkey, other animals.

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| 1.1 Actions relevant to the proposed therapeutic use. | Description of the experimental systems used, species and strain of animal, dose level(s), route(s), and frequency must be given. | Comparison with other standard drugs of the same therapeutic class is desirable. Where possible, it is desirable to present data that establish the mechanism of the principal pharmacological action. The validity of the models used should be established where practicable. Some evidence of pharmacological activities should be demonstrated by proposed clinical routes of administration. Results should be expressed in quantitative terms (e.g. dose-effect and time-effect cures). |
| 1.2 Other actions demonstrated or sought | These should be classified under systems e.g.<br><br>1.2.1 Central Nervous System<br>1.2.2 Autonomic System<br>1.2.3 Cardiovascular System<br>1.2.4 Respiratory System<br>1.2.5 Gastro-intestinal System<br>1.2.6 Other Systems where relevant<br><br>Both in-vitro and in-vivo data should be presented systematically in species order.<br><br>A general pharmacological profile of the substance is required, with special reference to collateral effects. More extensive investigation is required if the doses producing secondary effects approach those producing the primary therapeutic effect. | |

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| 1.3 Interaction of drug with other compounds where relevant to proposed therapeutic usage | | These interaction studies may have to be conducted with respect to excipients e.g. sympathomimetics with freon propellants. |
| 1.4 Other data | | |

2. PHARMACOKINETICS

The aim should be to establish the pattern and time course of absorption, distribution, biotransformation and excretion of active drug and as practicable its metabolites in animals and, during clinical trial stage, especially in man. (Studies in man may in certain circumstances be more appropriately reported under human pharmacological studies Part IV, heading 1.)

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| 2.1 Plasma levels of drug of metabolites | Data should be presented as to the technique of measurement, and where metabolic studies are conducted using labelled material the position of the label and the specific activity of the material should be given.<br><br>Peak plasma levels and plasma half lives or clearance time of the drug should be given. Degree of plasma protein binding should be determined. | A method of radio labelling should normally be chosen in which the radio-active atoms are not easily disengaged from the parent molecules by known metabolic routes. (See Part II Addendum, heading 14, clear cross referencing to this Section should be made.)<br><br>In certain circumstances it may be desirable to choose a radioactively labelled form which does lose its label through a specific metabolic reaction, since this could be the simplest way of following such a reaction.<br><br>It is desirable that these metabolic studies should be conducted on the species used in the toxicological and reproduction studies by the proposed clinical route of administration. Repeat dosing to detect possible cumulation, or enzyme induction or inhibition, is essential. Should enzyme induction be caused by a dose relevant to that likely to be employed in man, and if the drug will be administered for a prolonged period, it may be necessary to determine its effect on appropriate endogenous substrates and its interaction with other compounds. |

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| 2.2 | Distribution of drug or metabolites | Autoradiography or measurement of actual drug levels in the major organs are acceptable depending on the techniques available for each particular compound. | Studies conducted in some pregnant animals are desirable to assess to what level of drug the fetus has been exposed. (See MAL 36 - Notes for Guidance on Reproduction Studies). |
| 2.3 | Excretion of drug or metabolites | Total urinary and faecal excretion following a single dose of the drug should be presented, the time of urinary and faecal collection should be adequate to obtain a reasonably complete recovery. Identification or separation of urinary metabolites should be conducted as far as is technically reasonable. Any evidence for enterchepatic recycling of the drug should be presented. | It is appreciated that full analysis of the metabolic pathways of new drugs is not always technically possible but this should be presented as far as it is reasonably practicable to determine. |

Pharmacokinetic studies may be required for new combinations of known substances if the toxicity tests and therapeutic studies indicate that interaction occurs.

## 3. ANIMAL TOXICOLOGY

To be reported under the headings -

(i) Single dose studies

(ii) Repeated dose studies subdivided as

(a) sub acute
(b) intermediate term and
(c) chronic or long term

Under each of these headings reports are to be made in the following order -

Route of administration i.e. intravenous, intramuscular, subcutaneous, intraperitoneal, oral, topical, per rectum.

In each sub-section reference to results should appear in the following species order:

Mouse, Rat, Hamster, Guinea Pig, Rabbit, Cat, Dog, Pig, Monkey, other animals.

It is essential that in addition to the summary, details should be given of, and conclusions drawn from the original data. The reporting toxicologist or pathologist should give an interpretation of their findings in the light of the control evidence and the incidence of any abnormality in the colonies used. The autopsy report should begin by outlining the procedure adopted including a list of the organs to be studied. A report on each animal is required, but where no abnormalities were detected in a number of organ systems, these can be grouped together so that those systems in which abnormalities were found can be easily identified. The significance of any abnormality found should be discussed in detail.

An analytical specification of the batch of the drug used for toxicological studies should be included and compared with those batches intended for human use. (This specification should also be included in the volume on Chemistry and Pharmacy). Any excipient used for the first time in the pharmaceutical field should be investigated in a similar manner to an active ingredient.

Wherever meaningful and practicable the product in its final pharmaceutical formulation should be subjected to toxicity testing; a minimum of an acute study should be presented.

In the case of substances in combination the studies should be conducted in such a way as to determine whether or not potentiation or novel toxic effects occur.

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| 3.1 Single dose studies | Full information should be supplied must include –<br><br>3.1.1 Number and source of animals<br>3.1.2 Species and Strain used<br>3.1.3 Sex of animals<br>3.1.4 Diet used<br>3.1.5 Number of animals dying in each group, and the mode of death, if observed. Mortality 24 hours and 7 days after dosing should be recorded.<br>3.1.6 Autopsy findings<br>3.1.7 Method of statistical analysis to calculate the $LD_{50}$ (including the 95% fiducial limits).<br><br>The above details should be supplied in the case of all species used, for each sex and for each route studied. | Acute toxicity studies should include $LD_{50}$ by each of the proposed clinical routes of administration. In addition at least one route should be used which would ensure systemic absorption of the drug i.e. intravenous intramuscular or subcutaneous. Equal numbers of each sex should normally be used, and at least 2 species investigated. If SPF animals are used this should be stated. |

3.2 Repeated Dose Toxicity

Subacute
Intermediate term
Chronic or long-term

The drug should be administered to animals by the route or route proposed administration to man. Normally three dose levels should be employed. These should relate at the lowest dose to the proposed therapeutic daily dose in man, the top dose should be chosen from preliminary dose ranging studies so that target organ toxicity is revealed. The intermediate dose(s) should be spaced logarithmically. The studies should be carried out in at least two mammalian species, one of which is non-rodent. It is essential that as much detail as possible should be supplied in connection with these studies. Full information on the following should be supplied.

Adequate control groups should be included in all studies to allow statistically meaningful assessment of any differences caused by treatment to be made.

[illegible] duration [illegible] acclimatisation [illegible] for guidance".

Dosing should normally be conducted seven days per week by the proposed routes of administration. If oral dosing is given by adding drug to the diet it is expected that the amount of drug in the food mix will be modified at regular intervals as necessary, in relation to total food intake, throughout the study to achieve a constant dosage in terms of mg/kg/day of drug.

3.2.1 The species, strain source and sex of animals, also diet, age, weight, housing conditions and numbers of animals used at each dose level should be given.

If SPF animals are used this should be stated.

In selection of a species of toxicological assessment of a compound it is desirable that the agent demonstrates pharmacological activity in that species and strain.

In selection of species for long-term studies prior to marketing, it is desirable that the species should metabolise the drug in a manner as closely similar to man as possible within the usual spectrum of laboratory animals.

If melanin binding of a drug is demonstrated, special attention should be paid to ophthalmic toxicity and ototoxicity.

It is therefore suggested that albino animals are not used for toxicological evaluation of drugs that demonstrate melanin binding.

3.2.2 The route of administration if different from that proposed in man, should be discussed.

3.2.3 The method of dosing (i.e. whether the drug has been mixed in diet, given by intubation and whether 7 days dosing per week has been employed.) In all cases, the amount of drug should be expressed in mg/kg/body weight/per day.

3.2.4 Monitoring during the study should include -
Food consumption
Body weight
Behaviour and condition of the
Haematology
Biochemistry and Urinalysis
Ophthalmological monitoring is also desirable.

Tabular summaries of the mean(s) for each group should be provided: full data on all parameters measured should be provided for any animal with any value outside the range of normal for the laboratory in which the estimation was made.

It is desirable that pre-treatment data be obtained from all animals and that repeat measurements are conducted at intervals through the dosage period on an adequate number of animals from each dosed group.

Pre-treatment estimation of all variables in small rodents may not be feasible, in view of their small size, the stress of blood sampling and the numbers of animals involved. Complete pre-treatment values are not essential if the strain is well-known and there is adequate background data from that particular colony of animals.

3.2.5 Autopsy
All animals dying during the experiment should be autopsied. A record of the findings should be given and, where possible, the cause of death established. On completion of dosing a full post-mortem should be carried out on all animals and histopathological studies undertaken on control and all dosed groups.

Reversibility studies are useful to enable the significance of positive toxicity findings to be assessed. Comparative studies with other standard drugs may be also helpful in the interpretation of any toxicity found.

3.3 Oncogenicity Studies and Mutagenicity Studies

Detailed Notes for Guidance on Oncogenicity and Mutagenicity Studies are being prepared and applicants are referred to the EEC Norms and Protocols Directive reproduced below.

Tests to reveal carcinogenic effects shall be essential:

1. In respect of substances having a close chemical analogy with known carcinogenic or cocarcinogenic compounds;

2. In respect of substances which have given rise to suspicious changes during the long term toxicological tests.

Such tests may also be required in respect of substances to be included in proprietary medicinal products likely to be administered regularly over a prolonged period of a patient's life.

4. 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 offspring in later life.

It is expected that results on studies which have involved dosing during the period of embryogenesis 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 perinatal study should be presented.

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| 4.1 Dosing during period of embryogenesis | It is expected that dosing will be conducted at three dose levels in two species. The top dose usually should be such that some minimal maternal toxicity is produced.<br><br>Dosing should include the proposed clinical route of administration where practicable though it may be necessary to extend this with studies by other routes.<br><br>Reports of examinations should be made of the fetuses from the animals dosed during the period of embryogenesis. Animals should be killed and the fetuses removed by Caesarean section. | Applicants should consult Notes for Guidance on Reproduction Studies (MAL 36) for further details.<br><br>Adequate control groups should be included in all studies. |

In these animals the following should be reported:

4.1.1 The number of implantation sites
4.1.2 The number of resorptions
4.1.3 The number, weight and sex of individual fetuses
4.1.4 The individual fetuses should be examined for external abnormalities and adequate examination of the skeleton or viscera or both on all fetuses. Where obvious abnormalities are found further appropriate examination should be conducted, these should be reported in detail.

4.2 Fertility Study

A fertility study should be conducted in at least one species. Dosing should be by the proposed route of administration of the drug in man. Dosing should commence in male and female animals at a sufficient time before the proposed mating so that any effects of the drug on gametogenesis could be revealed. After mating the females should continue to be dosed throughout pregnancy; half the females should be killed during gestation, preferably some days before the expected date of parturition, and the fetuses removed by Caesarian Section and examined. The remainder of the females should be allowed to litter normally and rear the progeny.

In the fertility study dams killed during the period of gestation should have their fetuses delivered by Caesarian Section and the following information should be recorded:

4.2.1 Number of corpora lutea
4.2.2 The number of implantation sites
4.2.3 The number of resorptions

4.2.4 The number, weight and sex of individual fetuses

4.2.5 All fetuses should be examined for skeletal and/or visceral abnormalities

From animals dosed during the fertility study and allowed to litter normally and rear their progeny to the stage of weaning, a large enough number of the progeny should be reared to maturity to enable the following investigations to be made:

4.2.6 Late effects of the drug on the progeny in terms of the auditory, visual and behavioural function should be reported in detail.

4.2.7 Reproductive function should be determined in the progeny by allowing at least one male and one female from each litter of dosed animals to breed and produce one litter (within litter mating is not envisaged).

4.3 Perinatal Study

Prenatal dosing should cover that period of gestation in which dosing is not conducted in 4.1 above, and should extend throughout the period of lactation up to weaning.

The dams dosed through the pre and post natal period should be allowed to litter spontaneously and the progeny examined at weaning. All animals killed at the end of lactation should be subjected to a thorough autopsy examination. Under certain circumstances some of the progeny may be

reared to maturity so that their reproductive capacity could be assessed and other late effects of the drug on the progeny in terms of behavioural, visual and auditory function determined.

Results of this study should be reported under the following headings:

4.3.1 Effects on the mother
4.3.2 Effects on parturition
4.3.3 Effects on the fetus or neonate
4.3.4 Effects on lactation and growth of the weanling
4.3.5 Late effects on the offspring

5. SPECIAL ROUTES

All the general considerations referred to under headings 1-4 are deemed to apply but the following comments are given for additional guidance. If the pharmacokinetics and metabolism of the formulated compound are similar after administration by other routes, only limited study of toxicity by the special route may be necessary.

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| (i) Intravenous<br>(ii) Intramuscular<br>(iii) Intraarterial<br>(iv) Intradermal<br>(v) Subcutaneous | Where the proposed clinical route of administration includes the intravenous, intramuscular or intraarterial route, toxicology of appropriate duration with respect to the proposed clinical usage should be conducted by these routes. | In addition to the routine histopathological examination at conclusion of the study particular attention should be paid to the injection sites with respect to any local reaction. |
| (vi) Intraperitoneal | Unless the proposed clinical route of administration is by this route, use of the intraperitoneal route for repeat dose studies is not recommended. | |
| (vii) Inhalation | Studies should be performed on two species using the proposed clinical formulation with respect to drug plus propellant system or drug plus dispersing agent. The propellant or dispersing agent alone should be given to an additional control group. | The studies should normally be conducted by techniques which do not involve whole body exposure, since this may permit absorption of the drug by other routes; but this technique is sometimes applicable. The frequency and the duration of dosing required in these studies is determined by the intended clinical use of the drug. |

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| | Local effects on the respiratory tract should be studied with respect to ciliary activity and mucus secretion following both single and repeated exposure to the preparation. | Ciliary activity may be studied by measurement of rate of transport of particles placed on the respiratory epithelium after acute or chronic exposure to the drug. Special staining techniques to show changes in mucus producing cell distribution and possible fibrotic changes in the lung are required.<br><br>In certain circumstances e.g. inhaled corticosteroids it is desirable to monitor serially the flora of the upper respiratory tract. |
| | Systemic effects should be studied as in any other toxicological study with respect to serial observation, haematological, biochemical monitoring etc. A full autopsy should be performed at the conclusion of the study. | |
| | The effectiveness of dosing by this route must be established and attempts should be made to measure the blood level of the drug and where appropriate the propellant. | An estimate of the amount of drug trapped on the turbinates in the mouth, and swallowed and that reaching the lower respiratory tract is desirable. |
| (viii) Topical | | |
| (a) Cutaneous | Studies should be conducted on two species using the formulation intended for clinical use. Studies on both intact and damaged skin may be desirable depending on the clinical use of the drug. | The duration and frequency of dosing per day, and whether or not occulsive dressings should be employed is determined by the proposed clinical use of the drug. |
| | Percutaneous absorption of the drug should be measured and systemic effects and local effects should be monitored; serial haematological and biochemical monitoring should be conducted on an adequate number of animals from each dosed group and a full autopsy should be performed at the conclusion of the study on all animals. | It is essential to clean the treated area before applying subsequent doses.<br><br>If absorption is negligible, repeated dose toxicity and reproduction studies by this route may be omitted, provided that data is presented which ensures that appreciable amounts of the drug are not systemically available. |

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| (b) Ophthalmic preparations | Tests for local toxicity are required for all ophthalmic preparations. The duration and frequency of dosing should be determined by the proposed clinical usage. Systemic effects following absorption should be considered for new chemical entities following ophthalmic administration. |
| (c) Other routes<br>e.g. aural, nasal, rectal, intravaginal etc. | Appropriate studies should be conducted for these routes. |

PART IV STUDIES IN HUMANS

1. HUMAN PHARMACOLOGICAL STUDIES

The inclusion of such studies and their nature will be determined by the nature of the compound. Any studies reported under this heading should clearly indicate the sex, age and weight of the subjects, the route by which the drug was given, the dosage, frequency and duration of dosage. (While studies in volunteers can be helpful, they are in no way mandatory, and in some cases it might be unethical to conduct such studies. If any studies have been undertaken, they must, however, be reported if they have any relevance to the drug's safety).

2. CLINICAL TRIALS

The data required for new combinations must substantiate the safety and efficacy of the combination. Testimonial statements on safety and efficacy which are not scientifically substantiated cannot be accepted as valid evidence. In most cases evidence of efficacy will be from controlled clinical trials. In addition, where a product is to be administered on a long-term (e.g. an oral hypoglycaemic agent) evidence of its long-term safety and efficacy in a substantial number of patients is needed. This can be provided from open trials in appropriate cases.

2.1 Summary of all clinical trials

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

2.1.1 Number of trials; specify number of comparative randomised trials and non-comparative (single series) studies.

2.1.2 Total number of patients entering trials and their diagnoses.

2.1.3 Number of patients receiving the test medication in the trials and number withdrawn before end of treatment period (reasons for withdrawal must be stated).

2.1.4 Daily dosage expressed as mean and range. Other therapy given concurrently.

2.1.5 Duration of dosage, or range of durations.
2.1.6 Summary results in terms of efficacy, and details of any statistical assessments.
2.1.7 Adverse reactions - all to be reported whether major or minor.
2.1.8 Conclusion and comment.

2.2 Summary relating to use of the drug in each of the proposed clinical indications

A summary relating to patients treated in each diagnostic category included under the proposed indications for use of the drug should be presented under each of the following headings:

2.2.1 Types of trial; state numbers of cross-over trials, comparative series trials and single series studies, specifying how many of each were double-blind, single-blind or open.
2.2.2 Total number of patients entering trials.
2.2.3 Number of patients receiving the test medication in the trials, and number withdrawn before end of treatment period (reasons for withdrawal must be stated).
2.2.4 Daily dosage expressed as mean and range. Other therapy given concurrently.
2.2.5 Duration of dosage, or range of durations.
2.2.6 Summary results in terms of efficacy, and details of any statistical assessments.
2.2.7 Adverse reactions - all to be reported whether major or minor.
2.2.8 Conclusion and comment.

2.3 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.

2.3.1 Type of trial (as in 2.2.1) with further details of design.

2.3.2 Number of sex of patients entering trials, and the selection, age-distribution and diagnoses of patients in both treated and control groups. Criteria for exclusion of patients.

2.3.3 Number of patients receiving the test medication in the trial. Details and reasons for patients withdrawn before end of treatment period must be stated.

2.3.4 Daily dosage, with mean and range if it varied. Other therapy given concurrently.

2.3.5 Duration of dosage, with range if it varied; duration of any follow-up after end of treatment period.

2.3.6 Nature of treatment of control group.

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

2.3.8 Adverse reactions reported during the study, both of major or minor character. Reports of suspected drug dependence (including habituation, addiction or difficulty in weaning patients off the drug) or interactions must be submitted in detail.

2.3.9 Conclusion and comment by the clinician responsible for the care of the patients should be included with respect to the efficacy and safety of the treatment.

Where possible details should be given of the results of treatment of patients who may be at increased risk - e.g. elderly patients, children, pregnant or menstruating women, or patients whose physiological or pathological condition requires special consideration.

| | | |
|---|---|---|
| | The original documents or microfilm copies which form the basis for associating those documents with the patients in question, must be kept for 5 years from the date of application. | |
| 3. ADVERSE REACTIONS | Any information available on adverse reactions reported during clinical use of the drug in any country. | A commentary on these reports may be helpful: it should assess the extent of adverse reactions reporting in the countries concerned. Individual case reports are not required unless the reactions were severe or of an unusual nature. |

## EXTENT TO WHICH APPLICATIONS MAY BE ABRIDGED

Table 1

The following table indicates the circumstances under which certain parts may be omitted from an application. This is intended as a general guide and is not comprehensive. In cases of doubt as to the form an application should take, applicants are advised to seek advice from the Secretariat.

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PART I Application Form

and

PART IA Product Particulars

REQUIRED — in all cases

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PART II Dosage Form - Pharmaceutical Data

REQUIRED — in all cases

If information on the identical formulation has been submitted in full, in support of a previous application, reference may be made to this.

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PART II Addendum: Chemistry of the Drug Substance

REQUIRED for — New drug substances (substances not previously licensed under the Medicines Act).
If a Product Licence application follows a recent Clinical Trial Certificate application, in which this section was completed, the information need not be repeated but should be up-dated. The drug substances specification, heading 11, must however be given in full.

SOMETIMES REQUIRED for

(a) Pharmacopoeial substances when there is reason to question the validity of the specification, e.g., when the material is obtained from a new source and differences in the synthetic route may give rise to a different pattern of impurities from those detected by the published specification. This is particularly applicable to drugs which come out of patent. Emphasis is on heading 8, 9, 10, 11 and 12.

(b) Non-pharmacopoeial substances where the material is not widely used and is not well documented in the literature. Evidence may be required under headings 8, 9, 10, 11 and 12 to establish the validity of the specification.

NOT NORMALLY REQUIRED for

(a) Simple, widely used and documented ingredients, especially where these are the subject of pharmacopoeial monographs;

(b) Ingredients which have previously been described in a 'new drug' application.

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PART III Experimental and Biological Studies

REQUIRED for

(a) New drug substances

If a Product Licence application follows a recent Clinical Trial Certificate application, in which the section was completed the data need not be repeated but should be up-dated if necessary and any additional studies included.

(b) New Route of Administration

Relevant sections of toxicity, irritancy and metabolism required for the new route.

(c) New Mixtures

Information in this section will be required on the toxicity of the new combination of ingredients.

SOMETIMES REQUIRED for

(a) New dosage level

Toxicity data may be necessary if the dosage is raised significantly.

(b) Little known ingredients which are not widely used and are poorly documented in the literature. Information in this section may be required before a Product Licence can be considered.

NOT NORMALLY REQUIRED for

(a) Well-established pharmacopoeial substances to be used by the normal route in standard dosage.

(b) Ingredients which have previously been the subject of a 'new drug' application for the same route and dosage.

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TABLE 2

The following table gives examples of the way in which applications may be abridged and indicates the number of copies which are likely to be required.

| Part of Application | | | | | Examples | No. of copies |
|---|---|---|---|---|---|---|
| I | II | IIA | III | IV | | |
| + | + | + | + | + | New drug application | 20 |
| + | + | + | - | - | Pharmacopoeial ingredient from new source (e.g. recently out of patent) | 20 |
| + | + | - | + | + | New mixture of 'established' ingredients | 20 |
| + | + | - | + | + | New route of administration or dosage | 20 |
| + | - | - | - | + | New use | 20 |
| + | + | - | - | - | Pharmacopoeial ingredient in normal dosage, use and route | 3 |
| + | + | - | - | - | Ingredient previous subject of a 'new drug' application - new dosage form, same route, use, dose | 3 |
| + | - | - | - | - | Clinical Trial on a product for which a full product licence or previous clinical trial certificate is held | 3 |

Key

\+ Section of application completed in full or part

\- Section omitted

PART IV Studies in Humans

REQUIRED for

(a) New drug substances

(b) New use of a licensed drug

(c) New mixtures of ingredients

SOMETIMES REQUIRED for

(a) New route of administration

(b) New dosage recommendations

(c) New formulations where a special formulation has been developed to modify drug release e.g. controlled release tablets and injections or where bioavailability may have been altered by the formulation.

(d) Little known ingredients which are not widely used and which are poorly documented in the literature. Evidence of efficacy may be required.

NOT NORMALLY REQUIRED for

(a) Well established ingredients, especially from the pharmacopoeias for use in the standard indications, routes, doses etc.

(b) Ingredients which have previously been the subject of a 'new drug' application for the same indications or other cases where full clinical data has previously been submitted.

## STANDARD PROVISIONS FOR PRODUCT LICENCES

1. The licence holder shall forthwith report to the Licensing Authority any change in his name and address and in any address at which there is carried on a business to which the licence relates.

2. (1) The licence holder shall forthwith inform the Licensing Authority of any material change that has been made or that he proposes to make, or that he proposes that another person shall make, in the particulars contained in or furnished in connection with his application, in relation to any medicinal product to which the licence relates, that is to say -

   (a) in the specification of the medicinal product,

   (b) in the specification of any of the constituents of the medicinal product,

   (c) in the composition of the medicinal product, or of any of the constituents of the medicinal product,

   (d) in the methods of manufacture or assembly of the medicinal product, or of any of the constituents of the medicinal product,

   (e) in the methods and procedures described in the application for ensuring compliance with such specifications, or

   (f) in the arrangements described in the application for storage of the medicinal product.

   (2) Where the particulars of any of the matters mentioned in the licence differ from the particulars relating to the corresponding matters contained in or furnished in connection with the application for the licence, the licence holder shall forthwith inform the Licensing Authority of any change to a material extent in the matters mentioned in the licence that he proposes to make, or that he proposes that another person shall make.

3. The licence holder shall forthwith inform the Licensing Authority of any information received by him that casts doubt on the continued validity of the data which was submitted with, or in connection with, the application for the product licence for the purpose of being taken into account in assessing the safety, quality or efficacy of any medicinal product to which the licence relates.

4. The licence holder shall maintain a record of reports of which he is aware of adverse effects in one or more human beings or animals associated in those reports with the use of any medicinal product to which the licence relates, which shall be open to inspection by a person authorised by the Licensing Authority, who may take copies thereof, and if the Licensing Authority so directs, the licence holder shall furnish the Licensing Authority with a copy of any such reports of which he has a record or of which he is or subsequently becomes aware.

5. The licence holder shall keep readily available for inspection by a person authorised by the Licensing Authority durable records of his arrangements -

(i) for procuring the sale, supply, manufacture, assembly or importation of any medicinal product to which the licence relates, and

(ii) for obtaining materials for the purpose of the manufacture of the assembly by him or on his behalf of any medicinal product to which the licence relates, and

(iii) for tests to be carried out on the materials used for manufacture or assembly of any medicinal product and on any medicinal product to which the licence relates,

and shall permit the person authorised to take copies of, or to make extracts from, such records. The records shall not be destroyed for a period of five years from the date when the sale, supply or exportation of the relevant batch of the medicinal product was authorised by or on behalf of the licence holder, without the consent of the Licensing Authority.

6. The licence holder shall keep such documents as will facilitate the withdrawal or recall from sale, supply or exportation of any medicinal product to which the licence relates.

7. Where the licence holder has been informed by the Licensing Authority that any batch of any medicinal product to which the licence relates has been found not to conform as regards strength, quality or purity with the specification of that product or with the provisions of the Act or of any regulations under the Act that are applicable to the medicinal product, he shall, if so directed, withhold such batch from sale, supply or exportation, so far as may be reasonably practicable; for such period not exceeding six weeks as may be specified by the Licensing Authority.

8. The licence holder shall notify the Licensing Authority forthwith of any decision to withdraw from sale, supply or exportation any medicinal product to which the licence relates, and shall state the reason for that decision.

9. (1) Subject to sub-paragraphs (2) and (3) below, the licence holder shall not issue, cause another person to issue or consent to the issue of advertisements relating to medicinal products to which the licence relates containing particulars as to the uses, nature or effects of such products or warnings concerning those products unless the terms of the advertisements in so far as they relate to such particulars or warnings correspond to, or differ to an extent that is not material from:-

(a) the terms of the provisions of the licence relating to such particulars or warnings, or

(b) where the provisions of the licence do not relate to such particulars or warnings, the terms stated in the application on which the licence was granted relating to such particulars or warnings, or the terms stated in a notice in writing given by the licence holder relating to such particulars or warnings and sent or delivered to the Licensing Authority not less than

42 days (or such shorter period as the authority may allow) before the first issue of the advertisements.

(2) The licence holder shall be required to comply with the provisions in sub-paragraph (1) above when (and only when) he has been so notified in writing by the Licensing Authority in respect of advertisements of any particular kind specified in such notification.

(3) Notwithstanding the provisions of sub-paragraph (1) above, where the terms of advertisements relating to such particulars or warnings as aforesaid have been stated in an application or notice in circumstances to which sub-paragraph (1)(b) above applies and the licence holder has been informed in writing by the Licensing Authority, not later than either the date on which the licence was granted or 21 days after the receipt of the notice under sub-paragraph (1)(b) above (whichever is the later), that, for any of the purposes referred to in section 95(4) of the Act, such terms ought not to be included in advertisements or ought only to be so included in a modified form, the licence holder shall not issue, cause another person to issue or consent to the issue of any advertisement of a kind specified in the notification under sub-paragraph (2) above containing such terms or, as the case may be, such terms other than in a modified form, unless the consent of the Licensing Authority has been given in writing.

10. The licence holder shall, whenever so required by the Licensing Authority furnish particulars of any advertisement it is proposed to issue in respect of any medicinal product to which the licence relates, such particulars to include the contents and form of the proposed advertisements, the means, medium or media by which it is to be issued and the time and manner of such issue.

11. The licence holder shall, as soon as is reasonably possible, comply or take all steps that are in the circumstances necessary to ensure compliance with any direction in writing given by the Licensing Authority that, for any of the purposes referred to in section 95(4) of the Act:-

(a) advertisements of any particular kind specified in such direction relating to medicinal products to which the licence relates, ought not to be issued or, if such advertisements have already been issued, ought not to be issued again, or ought not to be issued or issued again except in circumstances specified in such direction, or

(b) the terms or form of such advertisements or the manner in which such advertisements are, or are to be, issued ought to be modified in a manner specified in such direction, or

(c) precautions as to the use, or warnings as to the effect, of such products ought to be included in such advertisements.