OCCASION

This publication has been made available to the public on the occasion of the 50th anniversary of the United Nations Industrial Development Organisation.

DISCLAIMER

FAIR USE POLICY

CONTACT

Please contact publications@unido.org for further information concerning UNIDO publications.

For more information about UNIDO, please visit us at www.unido.org

UNITED NATIONS INDUSTRIAL DEVELOPMENT ORGANIZATION
Vienna International Centre, P.O. Box 300, 1400 Vienna, Austria
Tel: (+43-1) 26026-0 · www.unido.org · unido@unido.org

D00260

United Nations Industrial Development Organization

IDO

Distr.
LIMITED
ID/WG.37/11
14 January 1970
ORIGINAL: ENGLISH

Expert Working Group Meeting on the Establishment of Pharmaceutical Industries in Developing Countries

Budapest, 4 - 10 May 1969

CURRENT LEGISLATIVE STATUS FOR EVALUATING QUALITY AND EFFICACY IN THE IMPORT AND EXPORT OF PHARMACEUTICALS IN SELECTED COUNTRIES 1/

by

Charles C. Stevens
Imperial Chemical Industries
Macclesfield, Cheshire
England

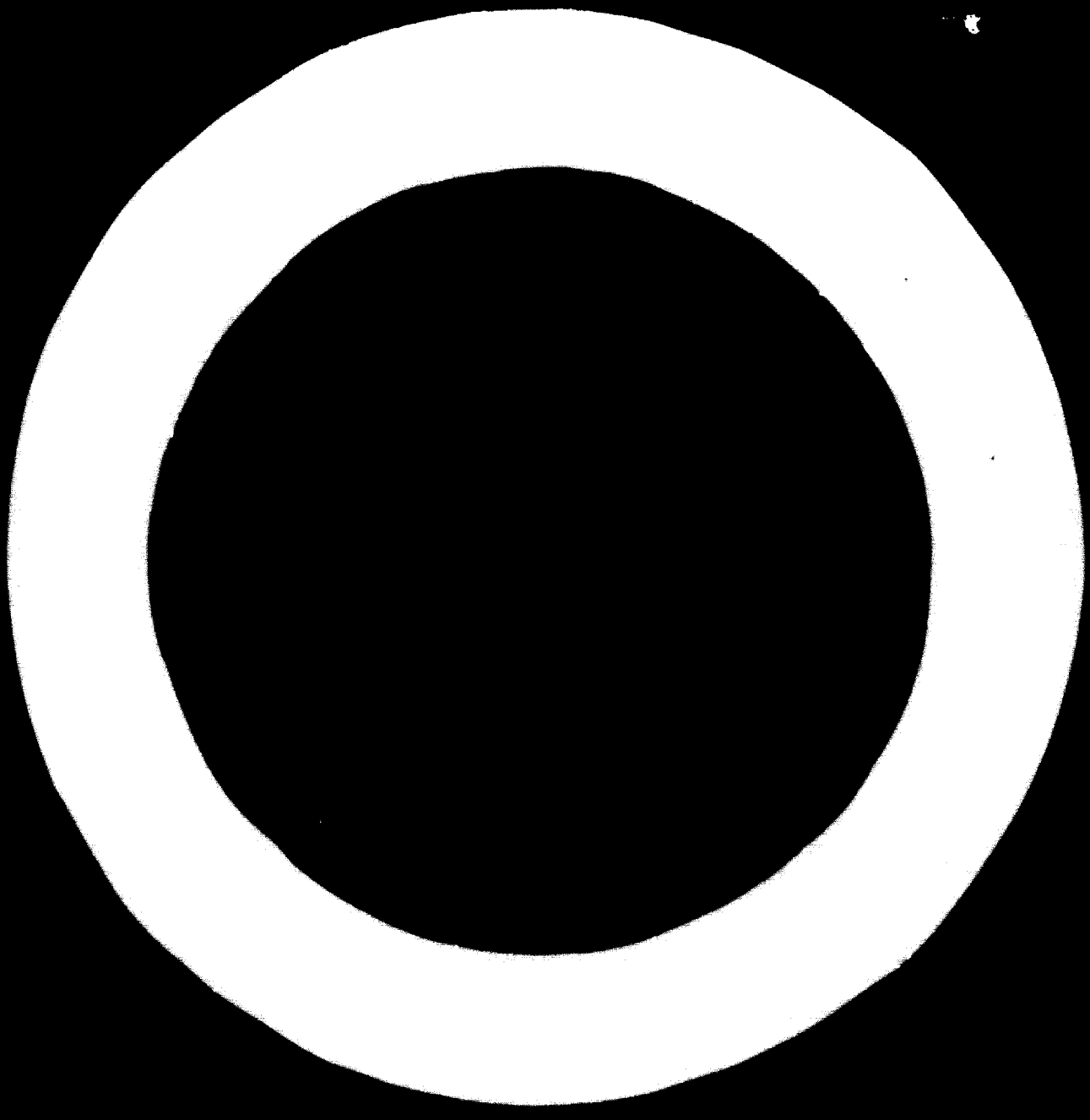
1/ The views and opinions expressed in this paper are those of the author and do not necessarily reflect the views of the secretariat of UNIDO. This document has been reproduced without formal editing.

id.70-279

CONTENTS

SELECTED BIBLIOGRAPHY

A Survey of Legislation on Medicines 1968	Pharmaceutical Industries Association in the E.F.T.A., Zurich.
Apotekens Forfattrisingssamlung 1960	Finlands Apotekareforenings Forlag, Helsingfors.
Arzneimittel Gesetz 1967	Verlag R. S. Schulz, Munich.
Code de l'Hygiene Publique 1951	Maison Ferdinand Larcier, Brussels.
Codice del Farmaco 1962	L di G Pirola, Milan.
Droit Pharmaceutique 1958	Libraires Techniques, Paris.
Federal Food, Drug & Cosmetic Act 1950	Kleinfeld & Dunn, Washington.
Journal Mondial de Pharmacie No. 1 1959	Federation Internationale Pharmaceutique, The Hague.
Legislacion de Farmacia Vigente en Espãna 1953	D Blas y Menada, Madrid.
Legislazioni Farmaceutiche d'Europe 1960	Societa Italiana di Scienze Farmaceutiche, Milan.
Leyes Reglamentos y Decretos 1958	Simon L. Guevara E., Caracas.
Manuel Pratique de Legislation Pharmaceutique 1968	Masson et Cie, Paris.
Rassegna Amministrative de la Sanita 1968	Publisci, Rome.
Symposium International sur le Control des Specialites Pharmaceutiques - Compte Rendus 1958	Association Pharmaceutique Belge, Brussels.
Traité de Droit Pharmaceutique 1953	Juris Classeurs, Paris.
Technical and administrative regulations on pharmaceutical products in O.E.E.C. countries 1960	Organisation for European Economic Co-operation, Paris.



SECTION 1 (a)

THE NEED FOR REGULATIONS COVERING LICENSING FOR SALE OF PHARMACEUTICALS IN RELATION TO QUALITY AND EFFICACY, WHETHER FOR EXPORT, IMPORT OR HOME MANUFACTURE.

The primary purpose of any control system in relation to pharmaceutical products is the protection of the public and safeguarding of their health. Emotional aspects apart, the health of the population should be, and is, a major concern of Government and any steps necessary to safeguard health should be taken. The increasing complexity of modern drugs, their potency and, as a corollary, possible side effects, mean that it is essential for adequate control of quality and efficacy to be instituted in order that no risk can arise. It is recognized that manufacturers will conscientiously themselves take all the necessary steps to ensure quality, efficacy and safety, but experience has shown that under modern conditions and with the vast inter-change of pharmaceutical products between nations, voluntary systems and control by conscience and reputation are not enough in themselves. As long ago as 1951 at a Symposium in Belgium to study international control of pharmaceutical specialities, it was stated "The problem of the control of the pharmaceutical speciality finds itself among the great social problems of our times. All have an obvious interest that the problem should be resolved clearly and without equivocation; the pharmacist because he has a professional responsibility; the pharmaceutical industry because it is a matter of its reputation and credit; the doctor because the whole value of therapeutic efficacy is in question, and finally, but most important, the patient, because the problem plays a definite part in his health and even his life."

Up until the time of the first World War, the problem of drug control was relatively simple, as nearly all medicaments that were

available were of an unsophisticated character, being mainly of vegetable or mineral origin or inorganic or simple organic chemicals. The synthetic and antibiotic drugs currently produced in such variety and number by the pharmaceutical industry were unknown. Furthermore, the drugs available at that time, although not particularly effective, were for the same reason not particularly harmful, except such classic poisons as arsenic or strychnine, etc., and slight variations in quality and potency in most cases had little effect. The development of the pharmaceutical industry and the pace of discovery since 1914, and particularly since the end of the second World War, has created an entirely new position. The result is that the doctor can no longer have a comprehensive knowledge of materia medica, and the pharmacist is no longer able in his own pharmacy to prepare and control the medicaments which he dispenses. The White Paper on legislation of medicines published by the United Kingdom Government in 1967 stated: "The pharmaceutical revolution of the last thirty years by introducing powerful and valuable new medicines, which have superseded most of the traditional medicines, has given rise to new problems for which our existing legislation was never designed. The need for greater safeguards has been recognised in many other countries."

Reference has already been made to the increasing international character of the pharmaceutical industry and the practice of medicine, which means that no longer can efficient control systems be limited to an individual country or even the major manufacturing countries, but a system must be devised that is adequate to give world protection. Countries without a pharmaceutical industry, or those developing countries in the initial stage of establishing an industry, must not only have adequate controls for their own manufacture, but must ensure that

products imported into their territory comply with equivalent standards. Furthermore, those countries which export need to know clearly the standards they must meet, and even where exporting to countries without standards as yet, must ensure there is no lowering of quality. This is not only for their own reputation, but is a duty, a duty which must be recognised in law by exporting and importing countries alike. This raises the question of standards for domestic use only and the question of reciprocity and uniformity in standards, which is dealt with in Section 4.

A few countries have used their control systems for ancillary purposes, such as to influence fiscal and economic aspects, for example, as a means of raising revenue or to protect a home industry. If there is a need to raise revenue or to give certain industries protection, this should be done by other means and not incorporated in legislation designed to ensure quality, efficacy and safety of pharmaceutical preparations.

SECTION 1 (b)

BRIEF REVIEW OF HISTORY OF MEDICINE CONTROL

Medicine control was relatively simple prior to the pharmaceutical revolution, and such control mainly consisted of measures to ensure that there was no adulteration of what were chiefly vegetable drugs. The knowledge of alkaloidal and other active contents of drugs was sparse, and the type of controls exercised until well into the twentieth century could be carried out by the pharmacist in the hospital or pharmacy.

With the development of manufacturing and wholesaling of drugs in the nineteenth century, it was considered necessary to establish some standards, and many of the pharmacopoeias originally prepared as books of recipes, reference and information for the medical and pharmaceutical profession were selected as legal standards. In many countries on the Continent of Europe, where the profession developed earlier than in the Anglo Saxon countries, not only national law but the professional rules of the Government bodies gave pharmacopoeias mandatory effect at an early date. In the Anglo Saxon countries there was a tendency to control food and drugs together, as being related items vital to the public for health and life. For example, in the United Kingdom there was a Food and Drugs Act of 1875 which instituted control, and control of drugs in the main has been under food and drugs legislation until the Medicines Act passed only in late 1968. Canada, Australia and New Zealand and other Commonwealth territories had similar food and drugs legislation. In the United States the first real Federal control was under a Food and Drugs Act of 1906, and even today, although drug control is most sophisticated and advanced, it is governed by a Food, Drug and Cosmetics Act. The relatively simple nature of the controls was shown by the requirement in most cases that the drugs sold "should not be to the prejudice of the purchaser".

Regulations covering quality and efficacy in a modern sense, under what is now known as a registration system, developed in the nineteen-twenties, and one of the first countries to recognize the need to set standards for pharmaceutical specialities was Spain, which instituted a registration system in 1924. Spain had regulated import of drugs in 1864 and prohibited certain advertising in 1865. A simple form of quality control had already been instituted in 1871.

The Latin American countries, possibly influenced by Spanish culture and practice, instituted registration of pharmaceutical specialities between 1920 and 1950, one of the first sophisticated systems being that of Venezuela, incorporated into law in 1943. After 1945 the registration system began to spread throughout Europe, among the last countries to establish it being Germany and Holland, following up the establishment of the Common Market with its need for harmonised pharmaceutical legislation. In the last ten years, registration systems have spread throughout much of Africa and most of Asia. Essentially, a registration system insists that all pharmaceutical products are registered with a Government Authority, and the registrant when applying for permission to sell must satisfy the Authority as to quality, suitable controls, safety and efficacy. New drugs systems, which require the clearance only of new drugs, started in the United States under the Food, Drugs and Cosmetics Act of 1938, and the system modified slightly was accepted in Canada a few years later. A similar system of new drug application is in force in India, Pakistan and the Commonwealth of Australia.

France, in 1941, instituted a particularly French system, known as the visa control, which will be dealt with more fully later.

It is fair to say at the present time, now that a legal system is in force in Great Britain, that all the countries manufacturing and

exporting pharmaceuticals have regulations covering quality and efficacy. A great number of the importing nations have regulations, but there is wide variation and in many cases these latter regulations are not designed specifically to take into account the needs of a modern, developing pharmaceutical industry.

SECTION 2 (a)

WORK DONE IN THE FIELD BY THE WORLD HEALTH ORGANIZATION AND AVAILABLE FOR DEVELOPING COUNTRIES

The World Health Organization has for a number of years taken a strong interest in the control of pharmaceutical specialities and has convened a number of meetings of expert groups to study the questions involved and make recommendations.

In the early nineteen-fifties the then Chief Pharmacist to the Organization made an informal arrangement with the major pharmaceutical manufacturers, principally in Europe but also in the United States, that they would send him copies of their Scientific Memoranda (technical data sheets) relating to new products. The information provided would be confidential, but made available in suitable form to help developing countries set up controls for pharmaceutical products. The Scientific Memoranda would also assist in the preparation of the International Pharmacopoeia, which has been published in two volumes and establishes standards for those countries which have so far not produced their own pharmacopoeia, or adopted the pharmacopoeias of other countries.

In 1957 a study group was established on the use of specifications for pharmaceutical preparations. This group consisted of Government experts, analysts from industry and the colleges, and their recommendations were published in the document "Use of Specifications for Pharmaceutical Preparations", Technical Report Series No. 138. The report covered a review of the situation in certain countries, the examination of pharmaceutical preparations and possible future action by the World Health Organization. Reference was made to the centre for authentic chemical substances, definitions were dealt with, and the essential requirements for the introduction on to the market of a pharmaceutical preparation were also covered in general part. Detailed statements were made on information

on analytical, physico-chemical, microbiological, pharmacological and other methods of control, together with statements on the organization of a national control authority.

In 1962 a technical meeting to deal with the quality control of pharmaceutical preparations was held, and the findings of this meeting were published in Technical Report Series No. 249 entitled "The Quality Control of Pharmaceutical Preparations". There was a review of the general situation regarding quality control, definitions were dealt with, and also the problem of controlling new pharmaceutical preparations. Observations were made on the responsibility of pharmaceutical manufacturers and the necessity to establish the safety of new pharmaceutical preparations prior to sale. Greater attention was paid to methods for the examination and analysis of pharmaceutical preparations; particular points receiving study were official methods, analytical methods used by the manufacturer, need for standardization of methods, modern physico-chemical methods of control, biological and bacteriological methods of control, and the need for new methods of quality control. Supplementary requirements such as labelling, inspection and the organization of services for official pharmaceutical quality control were dealt with.

As recently as November, 1968 a further conference on quality control of pharmaceutical preparations organized by the World Health Organization was held, the report of which is so far not published. Among those attending were representatives of the Commission for the European Communities the Council of Europe, the European Free Trade Association and the International Pharmaceutical Federation.

In January, 1968 a very detailed report by the Director General on the control of the quality of medicaments was published under reference EB41/38. This covers requirements of an administrative nature dealing with manufacture, export and import of pharmaceuticals, and certification.

In an annexe it contains detailed recommendations concerning control, such as specification of the final product and raw material and intermediates, control of production and detailed rules on good manufacturing practice. These detailed rules on good manufacturing practice illustrate an aspect of control which is receiving increasing attention, and the subject has been studied also by other international bodies. Good manufacturing practice is also incorporated in the United States legislation, but possibly this World Health Organization report is one of the most comprehensive documents so far available on the subject.

In 1967 the Scientific Group of the World Health Organization in Technical Report Series No. 403 made recommendations, including one that local research committees should review the purpose and design of clinical trials, and procedures should be designed to protect the patient and investigator better than existing laws. It was also considered that better reporting on adverse reactions should be sought. The World Health Organization also has a Scientific Monitoring Group on Monitoring of Adverse Drug Reactions, together with a procedure for notification to member Governments.

The World Health Organization also publishes quarterly in English and French the International Digest of Health Legislation, which deals not only with quality control but covers the whole field of laws and regulations affecting the manufacture, distribution and sale of pharmaceutical products. From time to time comparative reviews are made which are invaluable, an illustration being Volume 19, No. 3, 1968, which has an article on comparative health legislation, including advertising.

SECTION 2 (b)

WORK DONE BY OTHER INTERNATIONAL ORGANIZATIONS

INTRODUCTION

Although the World Health Organization is the most important of the international organizations working on the subject of quality control and has probably gone deeper into the specific question of analytical and quality controls, a number of other Governmental and quasi official bodies have studied the question, some with emphasis on the administrative aspects. In any system of control involving quality and efficacy an adequate and well designed administrative structure is necessary.

These organizations dealing with the question include the Organization for Economic Co-operation and Development, the European Economic Community, the International Pharmaceutical Federation, and the Pharmaceutical Industries' Association in EFTA. Set out below is a summary of the work and main recommendations made by these bodies on the question of registration of pharmaceutical specialities. The emphasis on specialities is due to the fact that National Pharmacopoeias, the International Pharmacopoeia, and shortly the European Pharmacopoeia, set standards which are considered as adequate for generic drugs, and in respect of these the main requirement is for adequate analytical and control procedures. Recommendations on such procedures will be set out later in Section 4.

ORGANIZATION FOR ECONOMIC CO-OPERATION AND DEVELOPMENT (O.E.C.D.)

The Council of O.E.C.D. set up an ad hoc Pharmaceuticals Committee to deal with the question of product registration and the labelling of pharmaceuticals, principally from the point of view of standardising procedures based on the best and regarded as internationally desirable, and with a view to diminishing any restrictions on the free passage of pharmaceutical products between member countries.

In their document CP/WP(62)2 dated 2nd August, 1962, the following recommendations were adopted for consideration by member countries.

All applications for registration of a pharmaceutical speciality should be accompanied by documents containing the following information, which is to be regarded as necessary and adequate.

1. Name and address of the manufacturer or responsible importer.
2. Name of the speciality.
3. Description of the pharmaceutical presentation.
4. Information concerning labelling and packaging.
5. Declaration of the qualitative and quantitative composition of all ingredients.
6. Statement of qualitative and quantitative testing methods to be employed.
7. Statement of stability.
8. Therapeutic indications, contra-indications, side-effects and dosage.
9. Results of pharmaceutical, physiological and clinical tests of any origin of adequate reliability, showing in particular that:
   (a) the therapeutic indications are based on medical facts,
   (b) the product has no harmful effects exceeding what is acceptable in the present state of medical knowledge.

It is of no use having adequate controls if a system of supervision is not exercised, and one of the most commonly used methods of supervision is a clear declaration on labelling. The labelling should give required information to Government Authorities, doctors, pharmacists and others concerned, thus facilitating a check on the product as well as providing necessary details. O.E.C.D. in Annex III to CP/WP(62)2, set out their criteria for the labelling of pharmaceutical specialities.

The following list gives the maximum information which, from the public health point of view, should have to be shown by law on the outside of a package containing a pharmaceutical speciality or on the container (bottle, tube, etc.) containing the speciality.

This list should not be considered to preclude the insertion on labels of other information (such as price data) which national regulations require to be shown, insofar as this additional data is called for on grounds other than those of public health.

It is recognised that the information to be included on ampoules and other small containers must be left to the discretion of the Authorities.

1. Name of the speciality;
2. Composition (formula)

   (a) qualitative
   (b) quantitative
   } of active principles;

3. Reference number for identifying production (batch number);
4. The number of the marketing authorisation
5. Name and address of

   (a) Manufacturer

   or (b) Responsible vendor;

6. Restricted distribution, where applicable;
7. Pharmaceutical form and contents;

   This information should only be shown on the outside of the package. It should be noted that, under the Norwegian regulations, the pharmaceutical form and contents should be indicated on bottles, tubes, etc., unless the container is very small.

8. Methods of use;

9. Date of expiry (if necessary);

10. Special conservation precautions (if necessary);

11. Special distinctive marks under legislation relating to poisons and narcotics.

Note:

The information required under Items 8, 9 and 10 should be given in the language or languages of the country in which the pharmaceutical speciality is being sold.

It will be noted that the recommendation on language is restricted to Items 8, 9 and 10, and it may well be a matter of debate whether a firm recommendation on language or languages should not be made in respect of some of the other items.

O.E.C.D. in addition to setting out requirements in respect of documentation for registration and requirements for labelling also established criteria for registration, and these were set out in document C(61)106(Final) dated 27th September, 1962. The criteria are:

Definition

A pharmaceutical speciality is any medicine with a specific composition, prepared in advance and offered for supply to the public in a distinctive packing and under a trade name.

1. Documentation for registration

An application for registration should be accompanied by documents showing among others that the product has no harmful effects in normal conditions of use.

2. Duration of registration procedures

Time limits should be fixed by the competent authorities in the various Member countries for dealing with registration applications so

that administrative delays may be avoided in the interests of public health. The time limits adopted by the various Member countries should be standardized and should be as short as possible (for instance, 60 days).

3. Rejection of an application for registration

An application for registration should only be rejected for reasons of public health and not for economic reasons.

Furthermore, an application should not be rejected on the following grounds:

(a) lack of medical need,

(b) the fact that the product is not registered in other countries.

Any rejection of an application for registration of a pharmaceutical speciality should be justified. There should be provision for an appeal in the event of rejection.

4. Suspension, withdrawal and duration of registration

Registration of a speciality with a view to distribution may be suspended or withdrawn if the Authorities find that the original supporting documents presented do not correspond with the facts concerning the product or if the product no longer corresponds with these documents or if the product, although used as directed, is subsequently found to be harmful to public health as a result of scientific or therapeutical knowledge or if misleading publicity continues to be conducted after warnings have been given.

Excepting any untoward circumstances, there should preferably be no time limit for the period of registration.

5. Naming of a speciality

The naming of a pharmaceutical speciality, and especially the free choice of a trade name, subject to international conventions, should be

vested in the manufacturer but no name which is likely to be misleading should be chosen.

EUROPEAN ECONOMIC COMMUNITY (E.E.C.)

E.E.C. is the Common Market and must, under the Treaty of Rome, harmonize its legislation where possible, and one of the subjects which received earlier attention was that of pharmaceutical products, and particularly the registration of them, so that adequate controls can be exercised. It should be noted that although the primary purpose of the work was harmonisation, nevertheless each of the member countries concerned was anxious to ensure that any directive should give adequate protection from the public health point of view to their nationals.

The Journal Officiel des Communautes Europeennes No. 369/65 of 9th February, 1965 contained the Council directive on registration, No. 65/65/CEE. A free translation of the directive is as follows:

Article 1 (Articles 1 and 2 deal only with introduction and definitions)

No speciality should be placed on the market by a member State without an authorization having been previously obtained from the competent Authority of the member State.

Article 4

The person responsible for introducing the product on the market should make a request to the competent Authority, submitting the following documentation:

1. Name and registered address of the responsible person, or where applicable the manufacturer.
2. Name of the speciality (brand name or generic name associated with the trade mark or name of the manufacturer, or a

scientific name associated with the trade mark or name of the manufacturer).

3. Qualitative and quantitative composition of all ingredients of the speciality in usual terms excluding complicated chemical formulae and with the international common name recommended by the W.H.O. where such name exists.
4. Summary description of the method of preparation.
5. Therapeutic indications, contra-indications and secondary effects.
6. Dosage, pharmaceutical form, method and route of administration, and stability, if this latter is less than three years.
7. Methods of control used by the manufacturer (analysis and estimation of the ingredients of finished product, special tests, for example, sterility tests, pyrogen tests and determination of heavy metals, stability trials, biological and toxicity trials).
8. Results of the following trials:

   physico-chemical, biological or micro-biological
   pharmacological and toxicological
   clinical

In addition, bibliographical documentation relative to the pharmacological, toxicological and clinical trials, presenting results as follows:

i) In respect of a speciality already exploited and having been tried sufficiently for the effect on man, including all effects secondary, and appearing in papers and journals,

ii) For a new speciality, also the composition and active principles when they are identical to specialities already known and exploited,

iii) In the case of a new speciality, including ingredients used for the first time, already associated in proportion comparable with medicaments already sufficiently tried and exploited.

(b) In respect of a new speciality containing known ingredients but those which have not already been used for therapeutic purposes, complete documentation on the trials concerning these new ingredients.

9. One or more samples or mock-ups of the sales pack of the pharmaceutical speciality and any printed matter it is proposed to include with it.

10. A document which states that the manufacturer is authorized in his own country to produce pharmaceutical specialities.

11. An authorisation for sale obtained for this pharmaceutical speciality in another member State or in a third country where such authorization exists.

Articles 5 - 12 inclusive are merely on administrative office procedures.

Article 13

Containers and outside packages of pharmaceutical specialities should carry the following indications:

1. Name of the speciality, whether it be a trade mark or a scientific name associated with the trade mark or name of the manufacturer.
2. Immediately after the name of the speciality the qualitative and quantitative composition of the active principles stated either by content or percentage.
   International common names recommended by the W.H.O. should be used where these exist.
3. A reference number to identify production (lot or batch number).
4. The registration number authorising sale.
5. Name and registered address of the responsible person or where applicable the manufacturer.
6. Method of administration.
7. Expiry date for specialities where stability is less than three years life.
8. Storage precautions where these are applicable.

The pharmaceutical form and the content in weight or volume or in units can be shown on the outside package only.

Article 14

When it is a question of ampoules, the indications set out in Article 13 may be placed on the outside package. The containers need only carry the following:

the name of the speciality,

the quantity of active principles,

the method of administration,

the expiry date.

Article 15

In the case of small containers other than ampoules containing only one dose and on which it is impossible to set out all the requirements of Article 14, the requirements of Article 13 are applicable only to the outside container.

COUNCIL OF EUROPE

The Council of Europe, which comprises the six Common Market countries with Switzerland and the United Kingdom, has ratified the Partial Agreement on Pharmaceuticals. Of particular interest is the collaborative revision by the European Pharmacopoeia Commission of pharmacopoeial standards. These will become the official standards in each of the participating countries and will replace the existing monographs in their respective national pharmacopoeias. The first volume of the European Pharmacopoeia is now in the press.

INTERNATIONAL PHARMACEUTICAL FEDERATION (F.I.P.)

The Industrial Pharmacists Section of F.I.P. was among the first of the international bodies to study registration and controls in detail and worked closely on the subject with the F.I.P. Speciality Control Commission and the Section of F.I.P. composed of Directors of Control Laboratories and Directors of Pharmacopoeias. A world survey was made in 1958 covering procedures and controls throughout most of the countries then having legislation and arising from the work and studies a document was submitted to the General Assembly of F.I.P. in September, 1958 and a resolution adopted recommending the governing bodies of pharmacy to consider sympathetically the views put forward. As a matter of interest, the report produced by the F.I.P. was used at the meetings of O.E.C.D. and

E.E.C. on the subject of control of pharmaceutical specialities, and many of the recommendations adopted. The recommendations in respect of applications for specialities are:

1. The qualitative and quantitative composition declared in commonly accepted nomenclature, including all the ingredients (active principles and excipients). Solubilizing and emulsifying agents, etc. should be declared to the Drug Controller in order to help him to check the product in question analytically, but no declaration of these should be required on the label, apart from those considered necessary by the control service. It is for the protection of public health that no ingredient should be permissible which has not been declared to the Drug Controller, but as this is valuable manufacturing know-how this information should be treated as confidential.

2. The field of indications and dosage.

3. Contents of each package size.

4. The recommended method of publicity by the manufacturer (to the public or restricted to the practitioner).

5. A sample of the speciality, together with the raw materials (active principle, and excipients if necessary), in a quantity sufficient for the purpose of analysis.

6. The draft of the package, label and leaflet. When advertising is planned, the draft of the publicity text.

Although the labelling of specialities is strictly outside the remit of the Sub-Committee, it is thought this matter should be studied either by the Sub-Committee or that the remit of the Sub-Committee on uniformity of labelling of poisons should be extended. They consider that a label should show, from the registration point of view, the following points:

(a) The manufacturer's name.

(b) For imported products, the name of the agent.

(c) The mention that the speciality has been officially registered.

(d) A number or reference allowing one to trace the history of manufacture.

7. A certificate of origin and acceptability issued by the appropriate Government Department of the country of manufacture.

8. If a speciality contains substances or combinations thereof, the action of which is not known, it is required to furnish in addition:

(a) Publications or works regarding the pharmacological action of the substances and their toxicity, clinical reports on their therapeutic efficacy, as well as their side-effects. (It is desirable that experimental and clinical publications of real scientific value should be accepted internationally on a reciprocal basis.)

(b) If the substances or combinations in question are new, the physico-chemical constants.

9. Methods of analysis of the product and if necessary of the active principles and excipients.

10. Statement of responsible person in the territory (for imported products only).

It was noted that much of the information which will be presented by a manufacturer could be set out in one suitable document, and they suggested that a standard information document or data sheet or scientific memorandum be accepted by all countries, and that it should contain the following in the order given:

1. Qualitative and quantitative composition.

2. Methods of analysis.

3. Physico-chemical constants (for new substances).

4. The field of indications and dosage.

5. Details of toxicity.

6. Contents of each package size.

7. The type of publicity proposed.

The F.I.P. has also studied regulations referring to good manufacturing practice, including control of quality. Their views and recommendations are in line with those of the W.H.O. mentioned in Section 2(a) and are also in line with those of the Pharmaceutical Industries' Association mentioned below.

PHARMACEUTICAL INDUSTRIES' ASSOCIATION IN EFTA (P.I.A.)

The Pharmaceutical Industries' Association, which is a Federation of the national associations of manufacturers from the member countries of EFTA, together with the associated country Finland, have prepared basic rules on pharmaceutical legislation, including registration. Their recommendations are:

1) The registration of pharmaceutical specialities in a public register may be useful for the supervision of their sale.

2) If the registration of a pharmaceutical speciality is legally necessary, it should not be subject to examination of medical or economic need.

3) An application for registration should be accompanied by valid documents showing among others that the pharmaceutical speciality, when used as prescribed, has no harmful effects exceeding the limits which are acceptable in accordance with existing medical knowledge. Registration should not be refused because of any special conditions associated with an individual case.

4) The introduction to the market of a pharmaceutical speciality should not be delayed by the registration procedure. Every application for registration should be examined within a period of 30 days. If the authorities have reasonable cause to question the validity of the documents submitted with the application, they should be at liberty to exceed the prescribed time-limit up to a maximum of 60 days to allow for completion of the documentation.

If, however, no conclusive objections are raised within the period of 30 days, then the pharmaceutical speciality may be placed on the market after the expiry of the said period.

5) Every rejection of an application for registration of a pharmaceutical speciality should be adequately justified. If the applicant considers that the reasons given for rejection are invalid, there should be a right of appeal.

6) The registration of a pharmaceutical speciality should not be made contingent upon a similar registration having been effected in another country.

7) The period of validity of registration of a pharmaceutical speciality and thus the right to sell such pharmaceutical speciality should not be subject to any time limit.
The State should, however, be entitled to prohibit the sale of a pharmaceutical speciality already registered if it is established that:

a) the documents submitted in connection with the procedure for registration do not correspond with the facts,

b) or a speciality already on sale does not correspond, or no longer corresponds, with the documents submitted at the time of application,

c) or the speciality, when used as prescribed, has given rise to harmful effects exceeding the justifiable limits,

d) or misleading information or advertising is being conducted after warnings have been given,

e) or for non-payment of fees.

8) In the testing of substances, those analytical or other methods laid down in a recognized pharmacopoeia should always be accepted. Furthermore, the applicant should be free to cite any other testing method available. If a testing method for the substance in question is not given in a recognised pharmacopoeia, or cannot be used for the pharmaceutical speciality submitted, the applicant must indicate a testing method.

9) The naming of a pharmaceutical speciality, especially the free choice of a trade mark, should be left entirely to the manufacturer but such a name should in no sense be misleading.

It is becoming increasingly recognised that proper control of quality is best effected from the first stages in the manufacture, and that the aim should be to obviate any possibility of error or lack of quality early in the manufacturing stage rather than exercise a testing procedure after a product has reached the doctor, hospital or pharmacy. It is for this reason that organisations such as W.H.O., F.I.P. and P.I.A. are paying more and more attention to standards of good manufacturing practice and why such standards are beginning to feature in national legislation. P.I.A. in its Plenary Meeting in Stockholm in June, 1968, adopted standards as follows. These standards, irrespective of any legislative control, have been accepted by all member firms of the national association belonging to P.I.A.

BASIC STANDARDS OF MANUFACTURING PRACTICE IN PHARMACEUTICAL MANUFACTURING ESTABLISHMENTS IN E.F.T.A.

1. APPLICATION

The Basic Standards of Manufacturing Practice shall apply to the manufacture of all pharmaceutical preparations intended for human use.

2. SPECIFICATIONS FOR PREPARATIONS

Preparations shall comply with the specifications established by regulation or which are accepted by the appropriate Authority in the country of manufacture.

Products manufactured for export shall comply with any additional specifications which may be required by the importing country.

3. PERSONNEL

3.1 Each establishment shall employ sufficient personnel possessing adequate educational, technical and practical attainments to ensure, and maintain, the identity, safety, purity and quality of the products manufactured.

3.2 Key personnel shall hold such qualifications as are recognised by the law of the country for the supervision of manufacture and control of the pharmaceutical products manufactured in the establishment.

3.3 Key personnel shall have specific responsibilities and adequate authority to discharge those responsibilities.

3.4 Decisions concerning approval or rejection of materials must rest with the person responsible for quality control.

4. PREMISES AND FACILITIES

4.1 Buildings shall be of suitable construction and be maintained in a hygienic state.

4.2 Premises shall be of sufficient size and adequate facilities provided to ensure:-

4.2.1 the clear differentiation of raw materials, bulk products, labels, packaging materials and finished goods both in storage and during processing;

4.2.2 that cross-contamination of products does not occur in manufacture and packaging;

4.2.3 the control of air humidity, or other atmospheric conditions, where this is necessary;

4.2.4 that appropriate procedures are observed when aseptic techniques form part of the manufacturing process.

4.3 Hygienic garments shall be worn by all staff in processing and packaging areas.

4.4 Handwashing facilities shall be provided in all areas.

4.5 Other sanitary and toilet facilities, and eating places, shall not form part of areas in which manufacturing processes are carried out.

4.6 Quality control shall be provided through a functionally independent analytical laboratory provided with sufficient equipment to carry out all necessary assays and tests.

4.7 If, in exceptional circumstances, the services of an independent laboratory are employed, the testing shall be comparable with that which would have been undertaken by the manufacturer.

5. EQUIPMENT

5.1 Equipment shall be maintained in a hygienic condition; it shall be non-reactive in respect of materials being handled and constructed so as to be capable of easy and efficient cleaning.

5.2 Weighing and measuring equipment shall be of appropriate accuracy in relation to the work being carried out and shall be subject to periodic testing.

5.3 The arrangement of equipment for finishing and packaging shall incorporate adequate safeguards to avoid intermixing of different products.

6. PROCEDURES

6.1 Systematic procedures shall be established to control at all appropriate stages of manufacture, the identity and quality of each product and its raw materials and other components.

6.2 These procedures shall incorporate sufficient independent checks or mechanical safeguards to eliminate dependence upon a single individual at all critical stages in the handling of raw materials, packaging materials, materials undergoing processing, and finished products.

6.3 Each product, its raw materials and other components, shall be clearly identifiable and securely labelled at all stages of manufacture, storage and transportation.

6.4 Each product shall have a master formula safeguarded by a person of responsibility.

Copies of the master formula required for working purposes shall be prepared in a manner, e.g. photocopying, which will eliminate any possibility of trahscription errors.

6.5 Batch records shall be maintained from which, together with other records, it shall be readily possible to ascertain in respect of any batch of any product:-

the date of manufacture

full manufacturing details

the origin of all raw materials and

other components.

6.6 All relevant records shall be retained for the period required by law, or other agreed period, in the country of manufacture.

6.7 Stocks of incoming raw materials shall be differentiated from those raw materials approved for issue.

6.8 All raw materials shall be kept separate from materials undergoing processing.

6.9 Records shall be kept of the use of the raw materials; such records shall make provision for the signature of the person responsible for weighing and issue.

6.10 Representative samples of all raw materials shall be retained for the period required by law, or other agreed period, in the country of manufacture.

6.11 Batches of products shall not be split, or combined, during manufacture unless the person responsible for quality control is satisfied that records of such operations exist for future reference.

6.12 Records of all operations on materials shall be signed by the person(s) carrying out the operation(s).

6.13 An adequate number of samples shall be examined during, and after, manufacture to ensure, in respect of each product:-

Uniformity of composition

Correct proportions of ingredients

Uniformity of dosage (in unit dosage preparations).

6.14 Yields of products shall be carefully compared with the input of raw materials and any abnormal discrepancy thoroughly investigated and accounted for.

6.15 Representative samples from finished products shall be retained for the period required by law, or other agreed period, in the country of manufacture.

6.16 The department responsible for the issue of labels shall be kept under adequate security and all issues therefrom shall be made by a responsible person.

6.17 A procedure shall be established for the issue of labels to ensure that labels issued correspond with the product being packed.

6.18 A procedure shall be established to safeguard against issued labels becoming intermixed before and during use.

6.18.1 Labels of final containers, or the final containers themselves, shall bear a distinguishing mark to enable the history of the contents to be readily ascertained by reference to batch records.

6.18.2 Such distinguishing marks must be sufficient to identify a particular batch if it is necessary to withdraw that batch from open sale.

6.18.3 Safeguards shall be operated to ensure that the correct batch number is applied to labels or final containers.

6.19 Procedures shall be established to ensure that packaging lines, tables and equipment are free from materials used in previous operations.

6.20 Procedures shall be established to ensure that the contents of filled containers are correctly identified.

6.21 The number of final packages shall be carefully compared with the number of units which the batch was designed to produce. Any abnormal discrepancy shall be investigated and satisfactorily accounted for.

6.22 Finished packages shall be differentiated from packages passed for sale until approval has been given by the person responsible for quality control.

6.23 The procedure for stock-keeping shall be such as to prevent preparations of unduly old manufacture being released for distribution.

6.24 Where necessary, products ready for distribution shall be periodically inspected and tested to ensure that deterioration has not taken place during shelf storage whilst awaiting release for sale.

SECTION 3

REVIEW OF THE THREE MAIN SYSTEMS OF REGULATORY STATUTES NOW IN FORCE

INTRODUCTION

Control is exercised over pharmaceutical preparations by three major methods, being a) new drug submissions; b) product registration; c) the visa system. The fundamental aim of all three systems is the same, i.e. to ensure that pharmaceutical products made available to the professions and the public satisfy definite criteria as to quality, efficacy and safety, and the variations in procedure have grown from the different types of national legislation and the type of pharmacy and pharmaceutical industry found within the territories. A detailed survey illustrative of these types of control is set out in the following pages.

For the most part control is exercised only over pharmaceutical products intended for sale, but in a few countries, notably the United States and United Kingdom, approval is also needed to take a product to clinical trial. Although the information required for approval for clinical trial is less than that required for approval for sale, there is a tendency to complicate what is a necessary step in the development of pharmaceutical products and a step which is closely supervised by trained observers undertaking what is really a research project.

The U.S. procedure for approval for clinical trial or for "investigational drugs" as they are referred to in the Act, is set out on pp. 44 - 47. It is suggested that developing countries should accept new drugs (and only new drugs should be subject to clinical trial control) for clinical trial provided i) that the new drug has been accepted already for clinical trial in a country exercising control over trials; ii) or, that the applicant has submitted evidence on analytical controls and toxicity; iii) and that the trials will be carried out by registered practitioners or in approved hospitals.

Details of the three main systems follow and it will be seen that the "new drug" procedure is not sufficiently wide for a developing country because of its restriction to new drugs and the difficulty of defining such in the context of a pharmaceutical industry in development; also for some time there may possibly be considerable imports of finished products. The visa system is unsatisfactory mainly because of its reliance on listed experts rather than on the responsibility of the manufacturer, which should be the main consideration. Furthermore, it is doubtful if a sufficient number of experts would be available.

The author considers that a developing country should rely, for the protection of the public, on a sensible and realistic procedure for the registration of pharmaceutical products and the recommendations in Section 4 are designed to that end.

SECTION 3 (a)

NEW DRUG SUBMISSIONS

The control of pharmaceuticals by approval of new drugs is found essentially in common law countries, e.g. the United States, Canada, the United Kingdom, Australia and India. The United States was the first country to set up a procedure for approval of new drugs, and in the following pages the detailed system of control is set out. The control of quality of known drugs, for example, products in the pharmacopoeia or generic named drugs, is exercised by food and drug legislation on quality control, similar in many ways to the early food and drugs laws of the United States and United Kingdom. It was the organic chemical revolution after the first War which set up a need to investigate more closely the complex new drugs coming on to the market. The United States has extended the scope of its legislation to cover not only new drugs, but new uses for drugs already known, and this has happened in other countries also. Essentially the system relies on adequate documentation, a knowledge of the company submitting the application, and where feasible inspection of the premises, and an expert assessment of the evidence submitted. In the United States, samples and analysis are not part of the control system, and such procedures would only arise in the case of suspected breach of the law. No particular legal forms, such as legalisation, stamped paper, affidavits, etc. are necessary, although the application must be in a specified manner, making use of the appropriate forms when necessary.

Federal legislation in the United States is subject to the doctrine of State sovereignty, and therefore control of drugs at the Federal level can only deal with inter-state traffic. Intra state control of drugs

rests with the State legislators, but most States have enacted similar legislation to the Federal Food, Drugs and Cosmetics Act. Inter-state means not only between the various States of the Union, but also export out of the Union and import into the national territory. Therefore, products imported must comply with the requirements of the drugs control, and products manufactured in the United States, even if destined for overseas countries with different controls, must, because they are inter-state, satisfy the requirements. There is a tendency to consider the implementation of a system of approval or registration of all products, new or already known drugs, and, in fact, the "grandfather" clauses of the Drugs Amendment Act do provide for the eventual assessment and clearance of all pharmaceutical products already on the market.

Canada, whose original Food and Drugs Act was a combination of the United States and United Kingdom, now has new drug legislation similar to that of the United States. In fact, many United States companies trading in Canada use their U.S. new drug submission as the basis of their Canadian application. It is only in minor matters and form that there are differences. The Provincial Constitution of Canada is different from the States Constitution of the U.S.A. and Federal legislation can be made to apply throughout the country. Therefore, Canadian Federal drug control is not limited to inter-state traffic.

The United Kingdom, after the thalidomide tragedy, introduced a voluntary control system by a Committee under the Chairmanship of Sir Derrick Dunlop, and therefore the system is known as Dunlop Committee clearance. This is essentially a new drug procedure, and although the requirements appear similar to those necessary to satisfy the United States Authorities, there are differences.

The Dunlop procedure is less bureaucratic than the Federal Drug Authority (F.D.A.) and a product is approved for sale more quickly. In the case of approval for clinical trial, a positive acceptance is required from the Dunlop Committee which takes about three months, whereas under the F.D.A. procedure trials may start immediately after submission but can be stopped by order at any time if the F.D.A. have queries on the documentation.

However, following successful clinical trials, the Dunlop procedure is much simpler as material submitted for approval for clinical trial is taken into consideration in approval for sale, and clearance for sale normally takes only three months. The F.D.A. should clear for sale in 180 days but in practice constantly raise queries and as they require a completely new submission for approval for sale, all of which must be closely examined, clearance usually takes about two years.

The F.D.A. also require individual case records, a requirement which is criticised in detail in Section 4, p. 93, and demand as secondary evidence, in addition to U.S. work, bibliography and clinical trial results on the product wherever used. Furthermore, although there is nothing governing it in the regulations, the F.D.A. in practice require for many drugs toxicity data on work carried out for a period of two years as compared with the Dunlop period of three to six months.

Although the Dunlop Committee procedure works well, it is not suitable for transfer in its entirety to developing countries. Suitable portions of the procedure are contained in the recommendations on documentation in Section 4.

Under the new Medicines Act, 1968, which will come into force soon in the United Kingdom, clearance of new drugs will be replaced by

a licensing or registration system requiring all pharmaceutical products to be cleared and entered upon a register. For a transitional period all products currently on sale at that time will be accepted, but the Authorities reserve the right to call for submission of data later and may then review their status.

Federal Australia has a new drug procedure similar to that of the U.K. Dunlop Committee, and although there are variations in form and sometimes supplementary information will be requested, an applicant who can satisfy Dunlop can usually meet the requirements of Australia. The Australian Federal Constitution is similar to that of the United States, and the States have rights of their own. In this respect many of the States have a registration system for veterinary drugs, and the State of Victoria has a registration system for drugs intended for human use.

India is similar to the United Kingdom but is one of the few new drug countries that requires samples and sometimes analyses them. They are also very particular about printed matter and closely regulate advertising and promotion.

CONTROL OF TRADE IN PHARMACEUTICAL PRODUCTS IN U.S.A.

There are three laws which regulate trade in pharmaceutical products at the Federal level, namely:-

i) The Federal Food, Drug and Cosmetic Act

ii) The Federal Trade Commission Act

iii) The Public Health Service Act

Of these, the most important is the Food, Drug and Cosmetic Act, and this will be treated in some detail as far as it affects new drugs, but first the other Acts should be mentioned in passing.

The Federal Trade Commission Act prohibits the dissemination of false advertisements (other than labelling) of drugs in inter-state commerce and it is administered by the Trade Commission. The F.D.A. also regulate advertisements and labelling under the authority of the Food, Drug and Cosmetic Act.

The Public Health Service Act controls biological drugs (serums, toxins, vaccines, viruses, etc.) intended for use in man. Under this Act, the Division of Biological Standards of the Public Health Service administer a licensing system.

In addition, certain narcotics are subject to the Federal Narcotics Drug Act, which is enforced by the Bureau of Narcotics of the U.S. Treasury Department.

Finally, at the state level, there are Acts which follow the provision of the Federal Food, Drug and Cosmetic Act to a varying extent. There is, in fact, a "model" Act, uniform with the Federal Act, which has been adopted by most of the States.

The Federal Food, Drug and Cosmetic Act 1938 is, in the words of Congress, "An act to prohibit the movement in inter-state commerce of adulterated and misbranded food, drugs, devices and cosmetics and for other purposes".

Under Section 501, a drug is deemed to be adulterated:

(a)(1) If it consists in whole or in part of any filthy, putrid, or decomposed substance; or (2) (A) if it has been prepared, packed, or held under insanitary conditions whereby it may have been contaminated with filth, or whereby it may have been rendered injurious to health; or (B) if the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirements of this Act as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess; or (3) if its container is composed, in whole or in part, of any poisonous or deleterious substance which may render the contents injurious to health; or (4) if (A) it bears or contains, for purposes of colouring only, a colour additive which is unsafe within the meaning of section 706 (a), or (B) it is a colour additive the intended use of which in or on drugs is for purposes of colouring only and is unsafe within the meaning of section 706 (a).

(b) If it purports to be or is represented as a drug the name of which is recognised in an official compendium, and its strength differs from, or its quality or purity falls below, the standard set forth in such compendium. No drug defined in an official compendium shall be deemed to be adulterated under this paragraph because it differs from the standard of strength, quality, or purity set out in such compendium if its differences from such standards are plainly stated on its label.

(c) If it is not subject to the provisions of paragraph (b) of this section and its strength differs from, or its purity or quality falls below, that which it purports or is represented to possess.

(d) If it is a drug and any substance has been (1) mixed or packed therewith so as to reduce its quality or strength or (2) substituted wholly or in part therefor.

Under Section 502, a drug is deemed to be misbranded:

(a) If its labelling is false or misleading in any particular.

(b) If in a package form unless it bears a label containing (1) the name and place of business of the manufacturer, packer, or distributor; and (2) an accurate statement of the quantity of the contents in terms of weight, measure, or numerical count : Provided, That under clause (2) of this paragraph reasonable variations shall be permitted, and exemptions as to small packages shall be established, by regulations prescribed by the Secretary.

(c) If any word, statement, or other information required by or under authority of this Act to appear on the label or labelling is not prominently placed thereon with such conspicuousness (as compared with other words, statements, designs, or devices, in the labelling) and in such terms as to render it likely to be read and understood by the ordinary individual under customary conditions of purchase and use.

(d) If it is for use by man and contains any quantity of the narcotic or hypnotic substance alpha-eucaine, barbituric acid, beta-eucaine, bromal, cannabis, carbromal, chloral, coca, cocaine, codeine, heroin, marihuana, morphine, opium, paraldehyde, peyote, or sulfonmethane; or any chemical derivative of such substance, which derivative has been by the Secretary, after investigation, found to be, and by regulations designated as, habit forming; unless its label bears the name, and quantity or proportion of such substance or derivative and in juxtaposition therewith the statement "Warning - May be habit forming".

(e) If it is a drug, unless its label bears, to the exclusion of any other non-proprietary name (except the applicable systematic chemical name or the chemical formula), (i) the established name (as defined in sub-paragraph (2)) of the drug, if such there be, and (ii) in case it is fabricated from two or more ingredients, the established name and quantity of each active ingredient.

(f) Unless its labelling bears (1) adequate directions for use; and (2) such adequate warnings against use in those pathological conditions or by children where its use may be dangerous to health, or against unsafe dosage or methods or duration of administration or application, in such manner and form, as are necessary for the protection of users.

(g) If it purports to be a drug the name of which is recognised in an official compendium, unless it is packaged and labelled as prescribed therein.

(h) If it has been found by the Secretary to be a drug liable to deterioration, unless it is packaged in such form and manner, and its label bears a statement of such precautions, as the Secretary shall by regulations require as necessary for the protection of the public health.

(i) (1) If it is a drug and its container is so made, formed, or filled as to be misleading; or (2) if it is an imitation of another drug; or (3) if it is offered for sale under the name of another drug.

(j) If it is dangerous to health when used in the dosage, or with the frequency or duration prescribed, recommended, or suggested in the labelling thereof.

(k) If it is, or purports to be, or is represented as a drug composed wholly or partly of insulin, unless (1) it is from a batch with respect to which a certificate or release has been issued pursuant to

section 506, and (2) such certificate or release is in effect with respect to such drug.

(l) If it is, or purports to be, or is represented as a drug composed wholly or partly of any kind of penicillin, streptomycin, chlortetracycline, chloramphenicol, bacitracin, or any other antibiotic drug, or any derivative thereof, unless (1) it is from a batch with respect to which a certificate or release has been issued pursuant to section 507, and (2) such certificate or release is in effect with respect to such drug.

(m) If it is a colour additive the intended use of which in or on drugs is for the purpose of colouring only, unless its packaging and labelling are in conformity with such packaging and labelling requirements applicable to such colour additive, as may be contained in regulations issued under section 706.

(n) In the case of any prescription drug distributed or offered for sale in any State, unless the manufacturer, packer, or distributor thereof includes in all advertisements and other descriptive printed matter issued or caused to be issued by the manufacturer, packer, or distributor with respect to that drug a true statement of (1) the established name as defined in section 502(e), printed prominently and in type at least half as large as that used for any trade or brand name thereof, (2) the formula showing quantitatively each ingredient of such drug to the extent required for labels under section 502(e), and (3) such other information in brief summary relating to side effects, contraindications, and effectiveness as shall be required in regulations.

(o) If it is a drug and was manufactured, prepared, propagated, compounded, or processed in an establishment in any State not duly registered under section 510.

NEW DRUGS

The Act prohibits the introduction of new drugs into inter-state commerce unless they have been approved by the Food and Drug Administration. A "new drug" is defined as one, the composition of which is not generally recognized as safe and effective for use under the conditions recommended or suggested in the labelling, or one that as a result of investigations to determine its safety and effectiveness for use has become recognized as safe and effective, but which has not otherwise than in such investigations been used to a material extent. A drug which may be regarded as safe and effective in other countries and which may have enjoyed extensive use in such countries but which has not been marketed in the United States is usually regarded as a "new drug" under U.S. law. Indeed, arising out of the time taken to obtain drug approval, it is not uncommon for new drugs not only from foreign sources, but also of U.S. origin, to be marketed in other countries before being marketed in the U.S.A.

In addition, clearance of a new drug in favour of an application from a particular applicant does not mean that this particular drug is cleared generally for sale. For example, a drug already approved and on sale in the U.S.A. by Company "A" must go through the whole procedure again if it is to be sold by Company "B". In respect of the submission of data by Company "B", data previously submitted by Company "A" can only be taken into account if Company "A" gives its permission.

In order to have a new drug "approved", applications have to be filed with the Food and Drug Administration (F.D.A.) in a prescribed form and complete translations of any material not written in English have to be appended to the original. The application has to be signed by the applicant or by an authorized attorney, agent or official. If the applicant or representative does not reside or have a place of business

within the United States, the applicant must also furnish the name and post office address of, and must be countersigned by an authorized attorney, agent or official, residing or maintaining a place of business within the United States. The prescribed form varies somewhat according as to whether the drug is for human use, veterinary use or for medicated feeds use, but the same basic information is required in all cases, that is, assurance of safety and effectiveness for the purpose recommended. The form for drugs for human use comprises:-

1) Table of contents
2) A summary
3) An evaluation of safety and effectiveness
4) Copies of the label and all other labelling to be used for the drug
5) A statement as to whether the drug is to be limited to use under the professional supervision of a practitioner licensed by law to administer it.
6) A full list of the articles used as components of the drug
7) A full statement of the composition of the drug
8) A full description of the methods used in and the facilities and controls used for, the manufacture, processing and packing of the drug.
9) Samples of the drug and articles used as components
10) Full reports of preclinical investigations that have been made to show whether or not the drug is safe for use and effective in use.
11) The names and addresses of all investigators
12) Full reports of clinical investigations that have been made to show whether or not the drug is safe for use and effective in use.

Applicants are permitted (and encouraged) to submit a more detailed summary and evaluation according to specified guidelines in place of the normal summary and evaluation laid down. Such "expanded summaries" are said to facilitate the evaluation of the application.

An application may be amended at any time during its examination, but the "filing date" is adjusted accordingly. If it is found that additional evidence is necessary to assure the safety and effectiveness of the drug, the application may be withdrawn without prejudice to a future filing, whilst the necessary data is obtained. Upon resubmission, the time limitation runs from the date the resubmission is received by the F.D.A. A decision on the application must be given within 180 days after the filing date, unless an additional period be agreed between the applicant and the F.D.A., or the application be declared "incomplete". Both these contingencies commonly arise and most new drug applications take considerably more than the stipulated 180 days before approval is given.

Following approval of a new drug, any changes in manufacture, control or labelling must be notified to the F.D.A. as a supplemental new drug application and a decision regarding the acceptance must be given within 180 days. It is necessary to maintain records and reports concerning experience on drugs for which approval is in effect, and all adverse drug experiences must be reported to the F.D.A., who have the authority to suspend any N.D.A. previously granted.

INVESTIGATIONAL DRUGS

Regulations are in effect exempting from the New Drug requirements drugs intended solely for investigational use. In such cases the drug must be labelled "Caution : New Drug - Limited by Federal (or U.S.) Law to investigational use", and a "Notice of claimed investigational

exemption for a new drug" (I.N.D.) must be filed with the F.D.A. by a "sponsor" who maintains control over all aspects of the investigational study. If the investigational drug is imported, the importer must act as the agent of the foreign exporter and sponsor the clinical investigation to assure compliance with the conditions prescribed. In certain cases it is possible for a foreign exporter to avoid the use of an agent by shipping the drug directly to a recognized and approved scientific institution which acts as the sponsor.

The I.N.D. must be submitted in the prescribed form and must include :

1) The best available descriptive name of the drug.
2) Complete list of components of the drug, including any reasonable alternates for inactive components.
3) Complete statement of quantitative composition of drug, including reasonable variations that may be expected during the investigation.
4) Description of source and preparation of any components.
5) A statement of the methods, facilities and controls used for the manufacturing, processing and packing of the new drug to establish and maintain appropriate standards of identity, strength, quality and purity as needed for safety and to give significance to clinical investigations made with the drug.
6) A statement covering all information available to the sponsor derived from preclinical investigations and any clinical studies.
7) Copies of all informational material, including label and labelling which is to be supplied to each investigator.

8) The scientific training and experience considered appropriate by the sponsor to qualify the investigators as suitable experts to investigate the drug;

9) The names and a summary of the training and experience of each investigator, and of the individuals charged with monitoring the progress of the investigation.

10) an outline of the planned investigations.

The investigation is considered to operate in three phases. Phase one starts when the new drug is first introduced into man with the purpose of determining the clinical pharmacology of the drug; phase two covers the initial trials on a limited number of patients for specific disease control or prophylaxis purposes; phase three covers full scale clinical trials in which the drug's safety is assessed and the optimum dosage schedules are determined.

11) A statement that the sponsor will notify the F.D.A. if the investigation is discontinued.

12) A statement that the sponsor will notify each investigator if a new drug application is approved, or if the investigation is discontinued.

The sponsor is required to maintain records setting out details of each shipment of drug to each investigator, and he is required to monitor the progress of the investigations throughout. The sponsor is required to notify the F.D.A. and all the investigators of any findings suggesting significant hazards, contraindications, side effects and precautions pertaining to the safety of the drug, and if the finding is alarming it shall be reported immediately and the clinical investigation discontinued until a decision is reached as to whether it is safe for the trial to

continue. The sponsor is required to discontinue deliveries of the new drug to any investigator who repeatedly fails to maintain or make available his records or reports of his investigations.

INSULIN AND ANTIBIOTICS

Any drug intended for human use that contains an antibiotic or insulin and certain specified antibiotics for veterinary use, may not enter inter-state commerce or be imported to the U.S. unless it is from a batch which has been tested and certified by the F.D.A. The manufacturer must first provide full details of the manufacturing, processing and packing operations and control exercised at all stages of the manufacture and despatch of the finished drug. Any foreign manufacturer must agree to permit an authorised official to inspect the manufacturing facilities concerned with the production of such drugs. Once the F.D.A. are satisfied on these points each batch of antibiotic or insulin is tested for certification on request and on payment of a fee.

REGISTRATION AND INSPECTION OF PRODUCERS OF DRUGS

Each U.S. drug manufacturing establishment is required to be registered annually and must be inspected by F.D.A. officials at least once every two years. The authority to inspect such establishments embraces access to all things which have a bearing on violation of the law with respect to such drugs (records, files, papers, process, controls and facilities). The only exceptions are financial data, sales data, pricing data and research data.

Regulations applicable to manufacturing establishments in foreign countries are still to be promulgated, but they are permitted to register under the domestic arrangements on condition that they comply with all the

requirements which have to be met by U.S. manufacturers. They must thus be open to inspection. Drugs emanating from foreign establishments which are not registered must be examined by the F.D.A. to determine whether such drugs are admissible.

The criteria applied in determining whether the methods used in or the facilities and controls used for the manufacture, processing, packing or holding of a drug conform to the necessary standards are set out in the Good Manufacturing Practice Regulations. These Regulations cover such things as buildings, equipment, personnel, components, master formulae and batch production records, production and control procedures, product containers, packaging and labelling, laboratory controls, distribution records, stability data and complaint files.

SECTION 3 (b)

PRODUCT REGISTRATION

Product registration is the commonest system of control of pharmaceutical products. Countries which have a control system dealing only with new drugs tend to develop these controls and extend their application to preparations made from known drugs, firstly by controlling new combinations or new uses of human drugs and later all products, thus moving toward a registration or licensing of all products. The basic principle is that every pre-packed product commercially sold, whether for the doctor, hospital, or over the counter, must be registered with the Authorities, and before registration there must be a submission of documentation and samples. It may arise from the national characteristics, but whereas legal form and samples play little part in the new drug systems, they appear to be important with many registration Authorities. This is especially so in Latin America and Asia, where documentation frequently has to be prepared on fiscally stamped paper. Much documentation and the certificates submitted by overseas countries must be verified by the Foreign Office in the country of origin, notarialised and legalised by the appropriate Consul. There seems to be little value in this legal form, and one would expect that a simple certificate from the authorised officials of the Company or appropriate Government department of the exporting country should suffice.

Registration in Sweden is set out in detail in the following pages as an example of the system found throughout the Nordic countries. It is particularly designed for sophisticated countries where samples can be analysed and a rigid state control set up. Its disadvantage is that it strays into the economic area, for example, limiting the number of brand names in Denmark, favouring manufacture by district pharmacies in comparison with industry in Sweden, and a price control in Norway.

Nevertheless, it is honestly and well operated. Detailed procedure for Venezuela is set out as typical of Latin America. Although there are minor variations, an applicant can assume that if he is able to provide documentation to obtain approval in Venezuela, he will have sufficient information and documentation for application anywhere else in Latin American. About 76 countries enforce product registration, and although the procedures vary, all require submission of data for all pharmaceutical products intended for sale. The products when approved are entered on a register maintained by the authorities. Renewal periods vary from one to ten years and some continue indefinitely. Holland and Germany set up systems shortly after the formation of the Common Market, and so far harmonization between the member countries has not yet been achieved. The Dutch and German systems are fair and do not insist on unnecessary legal form, but are very searching in the requirements for clinical trial proof and tend to favour trials carried out in the registering country. Austria is an example of particular requirements in that one must submit samples not only of the product but of the active ingredients and even known excipients. Thousands of samples are stored in the Health Ministry and apart from deterioration, it is difficult to see what value these are as references, particularly in the case of known constituents.

In Eastern countries where registration occurs, there is a tendency to insist on a great deal of printed material and multi-lingual packs are common as well as allowed in, for example, Thailand. In the case of Taiwan, large numbers of mock-ups (24 for each product) are required, and this must create difficulty of storage and handling in a developing country. A study of the procedures in some of the small European and developing Asiatic and African countries shows a need to study the question more closely with a view to simplifying the procedures,

abolishing unnecessary paper work, and yet exercising a closer supervision. Where sophisticated analysis is not possible because the resources are not available, there should be a requirement for better supporting material and a closer assessment of it.

CONTROL OF TRADE IN PHARMACEUTICAL PRODUCTS IN SWEDEN

The manufacture, importation, labelling, distribution, control and inspection of medicines in Sweden is governed by the Decree No. 701 of the 14th December, 1962 and by regulations issued under the authority of this Decree. The Decree became effective on the 1st January, 1964 and replaced the original Act (No. 300 of the 14th November, 1913) and proclamations made under that Act.

Administration under the Decree is chiefly under the National Board of Health (which is under the Ministry for Social Affairs). Certain functions are under the control of the State Pharmaceutical Laboratory (S.P.L.), which also work in conjunction, where appropriate, with the State Bacteriological Laboratory and the National Institute of Public Health. The S.P.L. is divided into four main Divisions, namely:

Chemistry Division

Biology Division

Pharmacotherapeutic Division

Pharmacy Inspectors Division

Authorization to manufacture pharmaceutical products is granted by the Board of Health and Social Welfare. The manufacturing license may be issued for a certain period or until further notice, and may relate to one or more specified products or to pharmaceutical products in general.

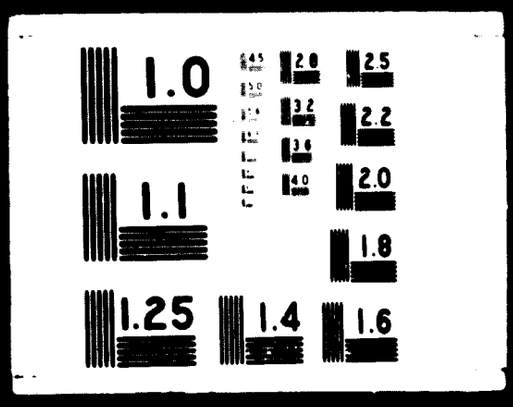
Manufacture of pharmaceutical products on premises other than a pharmacy must be carried out under a manager approved by the National Board of Health; in larger factories, different managers may be approved for the various departments. A person may be approved as a manager only if, in respect to the nature and extent of production, he possesses the requisite theoretical knowledge and adequate practical experience and is considered in other respects to be suitable. The manager is responsible

4. 4. 72

2 OF 2

DO

0260



for the technical quality of the manufacture and also for the compliance with the pharmaceutical regulations.

Authorization to manufacture pharmaceutical products may be revoked in whole or in part by the National Board of Health if the manufacturer fails to comply with the pharmaceutical regulations; or if the manager is absent or fails to exercise proper supervision over the manufacture; or is clearly incapable of exercising proper supervision; or if in the course of manufacture a serious mistake, or repeated mistakes are made; or if the manufacture is otherwise carried out under conditions which are clearly unsatisfactory. Before the authorisation is revoked, the National Board of Health must, unless there are special reasons to the contrary, give the manufacturer an opportunity to provide an explanation and take any corrective measures which might be necessary.

Pharmaceutical products may only be imported into Sweden by:

1) a person who is authorised to manufacture or carry on trade in pharmaceutical products.
2) certain research institutes for use in research.
3) a person who has permission to import a pharmaceutical product or products into the country.
4) travellers who may bring into the country a product for their own personal use.

Certain bacteriological preparations may be imported into Sweden only by the Principal of the National Bacteriological Laboratory.

Wholesale trade in pharmaceutical products may be carried on only by the person who lawfully has manufactured the products in Sweden, by the manager of a pharmacy, or by a licensed wholesaler. A licence to wholesale pharmaceutical products is granted in a similar way to

manufacturing licences and similar conditions apply to the approval and conduct of the approved manager.

Apart from exceptions relating to the supply by wholesalers to certain establishments, and the supply of bacteriological preparations to doctors and veterinarians, retail trade in pharmaceutical products may only be carried on by the manager of a pharmacy.

Clinical trials with unregistered pharmaceutical preparations may only be undertaken after a notification in the prescribed form has been lodged by the physician with the S.P.L.

The responsibility for the experimental laboratory testing of a new pharmaceutical preparation lies with the manufacturer. When the manufacturer considers that sufficient evidence exists to justify clinical trials, he must come to an agreement on this subject with a clinician, who then becomes responsible for such trials (possibly together with another physician in a responsible position). The physician must then make the notification to the S.P.L. at least two weeks before the trials are begun.

Trials are classified as Type A or Type B according to their character. Type A trials are limited trials to determine the clinical pharmacology, etc. and the initial therapeutic effects of the drug. Type B trials involve extensive investigations into the therapeutic value of the drug.

The notification must be accompanied (irrespect of the type of trial proposed) by a detailed report on the pharmacological and toxicological investigations carried out, including inter alia experimental data on the uptake, metabolism and excretion of the drug in animals. The chemical structure of the preparation, if known, must be given. The purpose of the trials, composition of the patient material and the approximate number of patients, together with the principles underlying the proposed procedure must also be given in full detail.

In the case of Type B trials, any recent results of importance (e.g. data from supplementary toxicity tests) must also be given.

As a rule, clinical trials may only take place in hospitals or institutions with similar resources. The physician responsible for the trials must keep a record book for the patients involved in the trial; he must report immediately both to the S.P.L. and to the manufacturer or his agent, all serious side-effects which appear during the trials; he must also, in collaboration with the manufacturer or his agent, report to the S.P.L. any major changes in the plans for the trial.

In addition to the above procedure, the National Board of Health, on special application being made, may authorize the sale of non-registered specialities for testing by clinicians or for the treatment of certain individuals. The application must be accompanied by the data as needed for clinical trials as described above and the control of the sale is generally similar as to clinical trials.

With the exception of specialities which are manufactured in a Swedish pharmacy which comply with standards for such preparations in the current edition of the Nordic Pharmacopoeia, and also specialities with special authorizations for sale as described in the preceding paragraph, all pharmaceutical specialities must be registered before they may be sold.

An application for the registration of a speciality is lodged with the National Board of Health with the data as described below. The data is first studied by the S.P.L. - the Chemical Division of the S.P.L. considers the chemical and pharmaceutical data, the Biological Division considers the animal experimental data, and the Pharmacotherapeutic Division considers the clinical data. The S.P.L. often collaborates with outside agencies during the study of the application, e.g. the State Bacteriological Laboratory, the National Institute of Public Health

and outside specialist consultants. During their examination the S.P.L. will often contact the manufacturer and ask for supplementary data or suggest further clinical testing.

When the application has been investigated by the S.P.L., the application and the report of the S.P.L. are considered by an independent Committee, the members of which have been appointed by the Government. Its meetings are attended (in an advisory capacity only) by the S.P.L. and the Board of Health departmental heads who have dealt with the application. The Committee will recommend whether or not to approve registration or it may postpone its decision pending further studies or the submission of further data.

The final decision on approval or rejection is taken by the National Board of Health. An approved speciality is entered in the registry of pharmaceutical specialities and is given a registration number. The registration is valid indefinitely (subject to the payment of annual fees) unless it is surrendered by the manufacturer or struck off by order of the Board.

If an application is refused, the reason for refusal must be stated.

The following must be supplied when an application is made for the registration of a pharmaceutical speciality:-

1. <u>Name and Address of Applicant</u>

Applications must be made by the manufacturer of the speciality. Where the drug is manufactured outside Sweden, the manufacturer must have an agent resident in Sweden to represent the manufacturer in all matters concerning the speciality. The agent should hold a power of attorney authorizing him as representative, and his name and address should be stated in the application.

2. The Name of the Speciality

The name of the speciality consists of the trade or generic name under which it will be designated, the pharmaceutical form and, where applicable, the strength.

The name of the speciality must not be misleading or designed to be mistaken for another preparation. Specialities not containing similar active substances may not be given the same name; different forms or strengths of the same active ingredients must bear the same name when made by the same manufacturer. However, specialities intended solely for veterinary use must be distinguished from specialities for use in human medicine either by the use of entirely different names or by the inclusion of, for example, the word "vet" in the name.

A speciality's pharmaceutical form should, where possible, follow the nomenclature of the Nordic Pharmacopoeia or other nomenclature approved by the Nordic Pharmacopoeia Commission.

In the application it should be stated if the trade name is a registered trade mark.

3. Composition, Pharmaceutical Form and Stability

All constituents of the speciality must be described fully. If the constituent is described in the Nordic Pharmacopoeia or another Pharmacopoeia or well-known collection of monographs, this is normally all that need be stated. A constituent which is not unequivocally described as a pharmacopoeial product or the like, should be described by giving details of the analytical control employed by the manufacturer set out in the same way as a pharmacopoeial monograph.

In the case of a new therapeutically active constituent, the monograph must be accompanied by the fullest data possible on the structural formula, molecular weight and appearance, together with physical data

such as solubility, melting or boiling point, spectrophotometric properties (together with copies of standard spectra) and optical rotation. A description should be given of the methods of synthesis, manufacture and scientific proof of the composition.

The preparation of the finished speciality must be described and details of the specification and analytical controls which are exercised must be given. In the case of a speciality which is manufactured aseptically or is sterilised, information should be given on the procedures adopted to ensure freedom from microbiological contamination. For delayed release formulations, full details must be given of how this is achieved and the reasons for the choice of certain particle sizes or crystalline forms.

The application must contain details of the packaging materials and evidence presented for their suitability of use, for example, details of the quality of glass in containers and the action of aerosol packs described. The composition of non-standardised materials such as plastics should be declared if they come into contact with the pharmaceutical preparation in such a way that the latter could be affected.

The applicant must state what the estimated life of the speciality is when stored under the recommended storage conditions. If the life is estimated to be more than five years, the precise life need not be stated.

Details of the stability tests carried out should be presented. These should demonstrate physical and chemical decomposition. As a rule, reports are expected on several manufacturing batches, which are examined quantitively at the time of manufacture and at suitable times during the storage period. Previous experience on similar preparations, together with the results of accelerated experiments, provisionally can

be accepted as a basis for registration (although further data should be presented after registration until testing, as described above, has been carried out for five years).

4. Pharmacological, Toxicological and Clinical Data

Full details must be given of the pharmacological, toxicological and therapeutic properties of the speciality, together with the indications, contra-indications, side effects and dosage.

The documentation should be presented in the form of articles or manuscripts for articles in well known scientific journals, or as properly written reports from specified institutions or clinics. Undocumented statements and testimonials or unprocessed data are not normally acceptable. The documentation should be available in Swedish, Danish, Norwegian, English, German or French. If applications are made for several specialities with the same active agent, reference may be made to one of the applications with regard to this documentation.

Data and documentation requirements vary with the character and properties of the drug but the following describes the general requirements in respect of a new drug:-

a) Pharmacological properties

Data is required on the general pharmacological effect of the drug on different organic systems (e.g. circulatory, respiratory, nervous systems, etc.) and on individual organs; detailed information is required on the pharmacological effects which are correlated to the clinical uses of the speciality.

Documentation should be supplied on the absorption, distribution, metabolism and excretion of the drug unless there are special reasons why data on one or more of these properties is not available. As far as possible, full data on at least one animal species should be presented and the work correlated with the action in humans.

In the case of veterinary drugs, investigations into the above metabolic processes and also the tissue residues which might be expected to be found in slaughtered animals and in foods such as milk and eggs should be described.

b) Toxicity Studies

The studies are expected to be related to the proposed use of the drug and follow the general recommendations given in the guidelines issued by the Biological Department of the Swedish State Pharmaceutical Laboratory and also the recommendations published by the European Toxicological Society.

Data on acute toxicity tests should generally be given for at least two animal species and the LD_{50} (and preferably also the LD_5 and LD_{95}) calculated for different methods of application. The animals used should be described (by age, sex, weight, breed, diet used, etc.) and as a rule results should be given after an observation period of 24 hours and, in some cases, after 7 days or more.

Data on prolonged toxicity tests must be supplied for all new drugs. The tests should be carried out on at least two species, one of which should not be a rodent. The drug should be given by the same route of administration as will be used by humans. A control group and at least two dosage groups should be used; the highest dose level should be sufficient to induce one of several toxic effects and the lowest level should more or less correspond to the highest clinical dose in humans (in the rat an intermediate dose level should usually also be chosen).

The duration of the test and the number of animals chosen should depend upon the clinical usage of the drug. For drugs intended to be administered clinically as a single dose, the prolonged toxicity test should be of two to four weeks duration and for drugs intended for prolonged administration three months testing would generally be considered

desirable. The examinations and observations carried out should be chosen in relation to the test employed and the usage envisaged for the drug, and would usually include weight-gain checks, appearance and behaviour, mortability, haematology, urine biochemistry, renal and liver function studies, autopsy observations, organ weights and detailed histopathological examination.

Results of tests for teratogenic effects must be presented for most new drugs. These tests should normally be carried out in at least two animal species and with at least two dosage levels. Where applicable, information on dead foetuses and on foetal absorption should also be supplied.

For certain drugs the effects of dermal application should be ascertained and, for example, data on absorption and on sensitivity reactions may be required.

Only in exceptional cases would information be demanded on mutagenic effects, carcinogenicity or effects on fertility.

c) Therapeutic Effects

For new preparations, well-presented, systematic investigations into therapeutic effects and side effects must be provided. Although in some cases a study involving only a small number of patients may be acceptable, as a rule extensive clinical testing carried out at different clinical centres over a sufficiently long period is required (usually involving over one hundred patients). Studies involving different dosage levels and using control groups, and in certain cases involving double blind techniques, are normally necessary. The trials should be sufficiently extensive with regard to number of patients and time of usage so as to indicate the possible side effects and their frequency.

Details must be stated on how side effects and their frequency have been investigated. Laboratory tests carried out for the purpose of indicating side effects should be described, (for example, haematological investigations, liver and kidney function tests).

In the case of veterinary preparations, clinical testing should be concerned chiefly with the species of animals for which the preparation is mainly intended. For other species where the indications are similar but in which the preparation is expected to be of lesser importance, smaller scale studies may be accepted.

The indications and dosage which the manufacturer intends to recommend must be stated, together with the contra-indications, side effects and symptoms and treatment of acute overdosage. This information must be included in information literature and advertising concerning the speciality and accordingly a note on how this will be presented must be given, and if possible samples of the planned advertising presented.

In the case of combination preparations, in addition to supplying information on the individual active agents, the applicant should, as a rule, present details of investigations to illustrate the pharmacological and toxicological properties of the combination in question. Results of clinical investigations should be presented to support the contention that the combination is therapeutically desirable and does not cause any special side effects. In a combination preparation, all constituents must be chosen for valid reasons. If claims are made for a therapeutic effect which is in addition to the total effect expected from a combination of known drugs, clinical documentation must be of the same character and extent as for a new drug.

5. <u>Packages and Price, etc.</u>

The different sizes and types of pack must be stated, together with the prices to be charged to pharmacies.

Two sample packs of the speciality (usually the smallest size of pack) must be submitted. Where the speciality has active agents which are new drugs, samples of such active ingredients should be submitted, together with samples of standard reference materials (with details of potency) if needed during the examination of the speciality.

Samples of the proposed Swedish labelling must be submitted with the application, possibly in the form of proofs or manuscripts. The labelling should be in Swedish or Latin (although any directions for use or warnings should be in Swedish). Any special storage conditions must be stated on the label, together with an expiry date (where the product is stable for less than three years). As a general rule, the dosage of the drug should not be stated on the label, although directions for use (e.g. diluting before use, swallowing a tablet whole) should be included. The batch number of the drug should be included on all labels.

The prescribed application fee must be sent at the time of lodging an application.

If the speciality has been registered, or applications submitted, in Denmark, Finland or Norway, details should be supplied.

A pharmaceutical speciality may not be granted registration unless it is suitable for the purpose for which it is designed and:-

1) it is of a perfectly satisfactory quality and, when put to normal use, it does not produce injurious effects which are at variance with the effect intended.

2) it is labelled with a complete declaration of its composition and the proportion of ingredients unless the National Board of Health has directed otherwise.

3) the name of the speciality is not misleading in relation to its composition, its effects or general properties, nor is the name designed to be mistaken for another pharmaceutical product.

4) the price of the speciality is reasonable.

Registration may be cancelled if the circumstances on which registration was based no longer prevail. Cancellation may also take place if any conditions laid down regarding the supply of the speciality are disregarded or if it becomes the subject of advertising which contains untrue, greatly exaggerated or misleading information about the effect or properties of the speciality.

The control of registered specialities is carried out by a system based upon random checking. Samples of the speciality are obtained (usually from a pharmacy) and subjected by the S.P.L. to a full examination - this includes chemical analysis and checking the labelling and advertising. Generally speaking, the same criteria of assessment are applied in the post registration control as in the original examination.

If any change in the composition or labelling of the speciality is proposed, this must be referred to the National Board of Health for consideration, similarly fundamental changes to the packs must receive prior approval by the Board. When a change of more than 10% in the quantity of the active agent content, or a change in pharmaceutical form, is proposed, normally a new registration application is necessary.

Any new clinical findings of importance affecting a registered speciality must be reported to the National Board of Health and to the S.P.L.; this applies especially to side effects and contra-indications, and if these may materially affect the use of a speciality, clinicians must be notified simultaneously to the notification to the Authorities. No new indication may be claimed without the prior consent of the National Board of Health.

CONTROL OF TRADE OF PHARMACEUTICAL PRODUCTS IN VENEZUELA

The Ministry of Health and Social Welfare (Ministerio de Sanidad y Asistencia Social) is the body responsible for the control of the practice of pharmacy in Venezuela, and has powers to license pharmaceutical products for sale and supply.

Pharmaceutical preparations are divided into four classes for the purposes of such control :

(1) Chemical products which are sold under their scientific names;

(2) Pharmacopoeial products where the preparation is sold under the pharmacopoeial name;

(3) Biological products;

(4) Pharmaceutical specialities. These preparations must conform to the following conditions:

(a) Their formulae must not appear in any pharmacopoeia.

(b) Their formulae cannot be changed.

(c) They must have some definite pharmacological merits due to their form, mode of action, novelty or composition.

(d) Their names must be acceptable and ethical in accordance with scientific principles and must not suggest exaggerated claims or denote their therapeutic indications.

(e) Their labelling must show the name and the quantity of each of the active agents present in each dosage unit.

The sale and supply of national and foreign pharmaceutical specialities is prohibited unless authorised by the Ministry of Health

and Social Welfare. (This stipulation is also applicable to certain other products including injectable products, medicinal wines, hair dyes, depilatories and preparations for the purification of water.)

To obtain authorization for the sale and supply of a pharmaceutical product, the following procedure should be fulfilled:

An application must be made by a pharmacist with a Venezuelan Diploma, on national stamped paper; applications must be made separately for each pharmaceutical form and for each concentration or strength of the product. (It is only necessary to notify the Ministry of the varying proposed pack sizes.) An authentic power of attorney (in Spanish) must be presented to the Ministry by the sponsoring pharmacist, and in the case of a foreign product this document must have been legalised by the Venezuelan Consul in the foreign country.

For foreign products it is also necessary to send a certificate of approval and free sale in the country of origin made out by the competent Health Authority, and legalised by the Venezuelan Consul.

The application must be accompanied by a summary statement giving the quantitative and qualitative formula, the expiry dates of biological products, and copies of the labelling and package leaflet which will be used for the product. In addition, details of the active ingredients of the preparation must be given specifying why the preparation may be regarded as a pharmaceutical speciality, and giving an account of its biological or pharmacological advantages.

In addition to the above, in the case of products which contain new unofficial drugs, or whose composition, therapeutic use, indications or tolerance are not generally known, the applicant must provide the following information:

(1) Generic name, chemical name and structural formula.

(2) Physical and chemical properties.

(3) Details of the experimental work (pharmacological and toxicological) which has been carried out during the development of the drug. (If the drug is of foreign origin, a considerable part of this work must have been carried out in the country of origin.)
Teratogenic studies must have been carried out in at least three species of animal (one of which must not be a rodent), and must have been carried out during the whole of the gestation period, using graduated doses. The numbers of animals involved in such studies must be declared and the number must have been sufficiently large to justify the corresponding statistical evaluation.

(4) Details of the clinical trials which have been carried out; papers submitted should have been published and where they are in a foreign language, they must be accompanied by a Spanish translation.

Samples of the product must be submitted to the Ministry for analysis; the labels and package leaflets must have been signed and dated by the sponsoring pharmacist and must bear the name and address of the manufacturer. The sample packs, with the exception of those which are hermetically sealed, must be provided with a "band" or "seal" which ensure their inviolability. In the case of ampoules the name of the product must be printed on the ampoule indelibly; if this is not done, an undertaking that this will be done when registration has been completed, will suffice. (Ampoules packed individually in outer containers are exempt from this requirement.)

Where it is intended that a product shall be manufactured in Venezuela, samples prepared elsewhere may not be submitted for registration purposes.

If the product is an antibiotic, the manufacturing date and expiry date must be shown on the label, the month and year being specified in each case.

The samples submitted for registration must be accompanied by the chemical, biological or microbiological methods of assay. In the case of mixtures, the analytical details must be applicable to the pharmaceutical form and must not refer to the determination of each ingredient as if it were in isolation.

Where necessary, a sufficient quantity of the analytical reference sample must be provided, and where the analysis requires special reagents, apparatus, or instruments, these must be provided by the applicant.

If the Minister is satisfied that the various conditions have been fulfilled, he will instruct the appropriate Chemical or Bacteriological Laboratory to carry out the analysis of the preparation. The results of this analysis are studied by a Committee, which includes the Head of the Division for the Inspection of Pharmacy and Medical Professions, two physicians and two pharmacists appointed by the Minister.

If the Committee finds that the results of the analysis are satisfactory, and that the product offers some advantages in the treatment or prophylaxis of disease, and that the labelling, leaflets and publicity material are ethical in character, not making exaggerated claims, the Minister will grant the product a licence for sale, specifying whether the product may be sold freely or by prescription only.

The labelling of pharmaceutical specialities must bear the following details on the inner and outer containers:

(a) Name and quantity of product.

(b) Name and address of the manufacturer.

(c) The formula expressed in the metric system.

(d) The dates of manufacture and expiry, giving details of the month and year, in appropriate cases.

(e) Name of sponsoring pharmacist.

(f) Batch number.

(g) The phrase "Autorizado por el Ministerio de Sanidad y Asistencia Social bajo el numero .....", and a phrase indicating whether the product may be sold freely or by prescription only

(h) Instructions concerning the use and storage of the product.

(i) Special wording as appropriate, e.g. "Uso Externo".

(j) Ampoules must be printed indelibly with the name of the product, except in cases where the ampoules are packed singly in outer containers.

All packaging components (labels, leaflets, etc.) must be in the Spanish language, but may, however, bear other languages, provided that they do not give the false impression that a product manufactured in Venezuela is of foreign origin.

The licence granted to a pharmaceutical product remains in force permanently, but the Minister may from time to time order investigations to be carried out to ensure that the product still satisfies the conditions under which the licence was granted. If it is found that variations have taken place, the licence may be revoked. Approval of the Ministry is, therefore, essential before any changes in

title, nomenclature, composition, strength or recommendations, etc. may be made.

SECTION 3 (c)

THE VISA SYSTEM

THE CONTROL OF SALE OF PHARMACEUTICAL PRODUCTS IN FRANCE

Prior to 1941, control of pharmaceutical products in France was exercised by a law against fraud and adulteration, and a requirement that those products listed in the French Codex should meet the standards of that book. In 1941 it was decided that more modern legislation was necessary adequately to protect the public, and it has been stated that the reasons were that there had been overwhelming criticism of the current system and i) it was possible to exploit any type of pharmaceutical formulation without having produced proof of its efficacy and even its freedom from harm; ii) it was permissible on account of the principle of the non-patentability of medicaments resulting from the law of 5th August, 1844 to imitate without limit original medicaments already available.

It was further said that as a result of this, the country found itself in the presence of a situation which was prejudicial to the interest of the public health and at the same time to the inventors of new methods of therapy. Furthermore, the great variety of pharmaceutical specialities available for use gave rise to unfavourable reaction from retail pharmacists.

The basis of the 1941 visa law is referred to in this way because each product approved was granted a visa as follows:

(i) No speciality should be placed on the market unless it had previously obtained an administrative authorisation granted under the form of a Ministerial Visa.

(ii) A visa was granted to a speciality when it had been proved that it possessed character of novelty and also therapeutic efficacy, and that it showed no danger to the moral or physical health of the public.

(iii) For six years from the date of grant of the visa the holder of the visa found himself protected against all imitations.

As a result of harm arising from the use of products which had received a visa, the system was revised by laws and regulations of 1959/1960, and at that time attained its particular characteristic in the use of "Experts Agrées" (listed experts), which is typical of the French system and not found elsewhere. At the present time, however, the Common Market in discussing their harmonisation are considering whether the system of experts should be common throughout the six countries. The experts are leading men in their own field, clinicians, toxicologists, pharmacologists, analysts, biologists, etc. of a neutral character, being neither Government employees nor engaged in industry. It is their function to carry out tests on all products submitted for a visa, and to prepare a dossier for submission to the Government. The Government has to accept the experts' views, and if they can show adequate control, efficacy and freedom from toxicity, the product is granted a visa. Responsibility rests with the experts. The visa system is applied to all pre-packed pharmaceutical products on sale in France, with the exception of those prepared by a retail pharmacist for sale within his own pharmacy.

The visa is only granted to a speciality when the manufacturer can justify:

(1) that he has shown proof of the harmlessness of his product under normal conditions of use, its therapeutic efficacy, as well as adequate quantitative and qualitative analytical control.

(2) that he can demonstrate the methods of manufacture and notably control procedures of the nature to guarantee the product manufactured by his methods.

The law states further that contrary to regulations in force before 4th February, 1959, the proof that the manufacturer can provide as to guarantee of manufacture and control of the speciality is insufficient. His techniques and his results must, in accordance with Article L.605-2, be themselves verified by experts chosen by the manufacturer from the List of Experts accepted by the Ministry.

The conditions of manufacture to be justified by the manufacturer are as follows:

He must provide a description of the method of manufacture, which should be sufficiently detailed, and in particular set out special manipulations so that checks can be exercised. He should also give adequate details of the control. If there is lack of information on technical material or the absence of precautions considered indispensable by the Ministry, his application can be rejected.

In spite of the work to be done by the experts, the manufacturer himself must proceed to establish control techniques for the speciality, also for the raw materials used. Pharmacological and clinical trials are confined to the experts carrying out the work on the product. The law lays down requirements for control of raw materials and the finished product as follows:

1. <u>CONTROL OF RAW MATERIALS</u>

(a) In the case of materials covered by the Pharmacopoeia, the manufacturer must show a reference to the book, and also adhere to the analytical methods and standards which are indicated therein. He is allowed to show supplementary specifications. Having indicated the Pharmacopoeial reference, he should then carry out complete trials on his material and provide documentation covering these.

(b) Raw materials not covered by the Pharmacopoeia. The manufacturer must himself suggest control techniques suitable for the manufacture and eventual use of the product. He should set out details of the raw materials, giving methods of identification, tests for purity and dosage techniques. Here again he must prepare documentation on the actual controls. In the case of materials covered by a foreign Pharmacopoeia, the manufacturer should include a photocopy of the appropriate pages of the book citing the references, and carry out trials, together with documentation, as set out under (a) above.

2. CONTROL OF FINISHED PRODUCTS

The following points are necessary in the case of control of the finished product.

(a) Manufacturing standards must be established, e.g. average weight of tablets and tolerance limits, volume of ampoules, disintegration time for tablets and dragees and organoleptic examination.

(b) Verification of general characteristics, e.g. density, pH, refractive index.

(c) Identification of dosage and active principles.

Most detailed information must be given by the manufacturer, and he should suggest acceptable limits. A complete analytical document must be submitted, and tests should be carried out on several batches of raw materials and finished products so that a batch can be traced right through and a complete picture built up of raw materials and finished products. The batch numbers should be shown on all documents referring to analysis and to analytical, pharmacological and clinical trials carried out on particular batches. Furthermore, the manufacturer must, in all cases, himself make an initial study of the stability of the product using techniques of accelerated storage.

When the manufacturer has carried out his own tests as shown above, the experts then proceed to their examination, and the law states that they can only carry out trials in the three disciplines for which they are accepted on the Ministry list, i.e. analysis, pharmacology and toxicology, and clinical work. The experts must work as follows:

1. Analytical Trials

The expert must carry out himself qualitative and quantitative analysis of the medicament, and having verified the validity of the technique submitted by the manufacturer, must himself proceed to verification of the conformity of the product to the stated formula. Concerning the quantitative and qualitative analysis, the expert's report should set out a detailed protocol of the technique used by the manufacturer, and then give the results obtained by the expert, limits of tolerance, interpretation of the results and conclusions arrived at; in particular his statement whether or not a protocol can be prepared providing a satisfactory control. The expert is not required to carry out procedures on products inscribed in the Pharmacopoeia, but when reference is made to raw materials inscribed in the Pharmacopoeia the expert must himself carry out full analytical trials in his own laboratory. It is also the duty of the expert to recommend acceptable tolerances for all stages of the control.

2. Toxicological and Biological Trials

These trials have as their aim an estimation of the toxicity of the product in animals and a verification of its pharmacological properties according to the recommended method of use in humans with suggestions for margins of tolerance. The trials must be carried out by one or more experts accepted in the List of "Pharmacologists-Toxicologists". In

particular, toxicity studies must cover (a) study of acute toxicity; (b) study of sub-acute, chronic or medium term toxicity; (c) study of long term toxicity; (d) study of local tolerance. It is not necessary to delay clinical trials until the end of a chronic toxicity study, as this may last one or more years.

Biological trials have as their aim experimental verification of the properties of the medicament, and they can be carried out in different disciplines, e.g. micro-biological, biological chemistry, animal physiology. They are intended to guide the work of the clinician so that he can know a certain amount in extent of the effect the medicament will have on the patients to whom he administers it. Analytical and toxicological experts should combine together to reach conclusions on the stability of the medicament, and to make recommendations on what complementary trials may be necessary.

3. Clinical Trials

These trials have as their aim the verification of the therapeutic efficacy of the medicine, and must be carried out in accordance with detailed instructions given by the Minister of Public Health in a document dated 9th December, 1960, ref. DO 3780.

When all the information has been assembled by the manufacturer, being his own and that obtained from the experts, it is set out in approved form and submitted directly to the Central Pharmaceutical Service of the Ministry of Health. When it refers to a new product hereto unknown in France, it must be accompanied by suitable documentation asking for the grant of a common name, and this common name is usually cleared also by the French Pharmacopoeial Commission with the World Health Organisation. Subsequent to grant of the visa, the manufacturer can then

apply for permission to sell, and in the case of France must satisfy certain requirements as to advertising, price description, etc.

SECTION 4

MAJOR ITEMS TO BE TAKEN INTO CONSIDERATION WHEN FORMING REGULATORY STATUTES FOR DEVELOPING COUNTRIES TO COVER CONTROL OF QUALITY AND EFFICACY

INTRODUCTION

In Section 1 the need for regulations and a brief historical review was given, and outlined in Section 2 was work done in this field by various International organizations. Section 3 set out in some detail actual regulatory statutes currently in use of three different types, being new drug, product registration, and the visa system. It is worthy of note that the visa system has found no favour in countries outside France, except those developing nations which were originally part of the French Union. In the countries which work a new drug system, the tendency is to change over to complete product registration and, in fact, the second interim report of the task force set up by the United States Department of Health, Education and Welfare, said in respect of prescription drugs that it recommended the development of a registration system for all drug products inter-states to cover quality control standards. In the United Kingdom, where the voluntary system under Dunlop, being the Committee on the Safety of Drugs, was set up to deal with new drugs, the Medicines Act 1968 provides for the licensing (or registration) of all medicinal products available.

For developing countries the obvious system is that of product registration, because in the early stages of developing their own pharmaceutical industry, there may well be more imported drugs or known products made under licence rather than new drugs discovered within the territory. Furthermore, in order that their systems may develop towards a sophisticated control, in the public interest it is advisable that all medicines be satisfactory for quality and efficacy, whether new or old and whether indigenous or imported.

The question of uniformity is worth mentioning at this stage. As the registration procedures in developed countries become more comprehensive, and one sees the introduction of registration procedures in the developing countries, it is becoming increasingly time-consuming for the pharmaceutical manufacturer to provide the differing sets of data required by the various Authorities. For example, the results of teratogenicity tests are required by many different Authorities, but often the animals in which such tests must be carried out vary from country to country, e.g. Country A, for instance, may ask for teratogenicity tests in mice and rabbits, Country B in rats and rabbits. In framing legislation, it would be beneficial for all concerned if the legislating country paid great attention to existing procedures, and in this respect this present Working Group of U.N.I.D.O. might well bear harmonisation in mind when making its recommendations.

It is intended in the following pages to deal generally with the requirements of a national system of drug control, and then conclude by setting out recommendations as to the documentation which should be submitted. Basically, the controls applied should be satisfied by all products, local or imported, but in respect of imported products certain additional safeguards or documentation will be necessary in order that the Health Department of the importing country is satisfied as to origin of the medicine and status of the manufacturer.

Controls are often related to the stage of development of pharmacy and the pharmaceutical sciences in the country concerned, thus countries with little or no pharmaceutical manufacture, and consequently dependent on importation, will tend to concentrate attention on checking the quality of bulk imports before distribution. Conversely, in many countries where there is a well established pharmaceutical industry, one

finds a great deal of responsibility for quality placed on individual manufacturers. State controls may also vary according to the stage of development of the drug concerned, and according to its nature. Control may be exercised at various stages, and the vigour with which it is applied will depend on the importance assigned to the subject by the community.

POTENTIAL SCOPE OF CONTROL SYSTEMS

Any national system should be based on the following:

(1) approval of quality standards for products;

(2) approval of methods, premises and personnel for manufacture;

(3) testing of samples;

(4) satisfactory evidence as to efficacy and safety;

(5) administrative requirements.

1. APPROVAL OF STANDARDS

This should be based on the submission of technical information, in confidence, by the manufacturer, normally comprising a brief specification on the lines of a pharmacopoeial monograph. Whether the statements made are checked in a State laboratory or in the laboratories of consultant analysts depends on the stage of advancement of the country concerned. It must eventually be the aim of all developing countries to set up at least such laboratories as will allow of a check in case of doubt, but a system of acceptance on a reciprocal basis of one Government's analytical checks by another is worth consideration. In the early stages the Authorities may have to rely on the documentation alone, combined with proof of status and responsibility of the manufacturer. In many cases standards submitted by licensed and known manufacturers do not require time-consuming and expensive checks. Frequently after a product has been available for a number of years, standards appear in official

books or pharmacopoeias, and these standards should be acceptable both to the manufacturer and the Authorities, and at this stage have usually been subject to independent laboratory checks.

2. APPROVAL OF PREMISES

An increasing number of countries require that premises used for manufacture, processing or packing of drugs be licensed and registered. The nature and frequency of inspection and the minimum standards of cleanliness, etc. of factories and the requirements in respect of qualifications of staff vary between countries according to the general levels prevailing at the time. The detail will be a matter for the country in which the drug is to be sold when it is manufactured locally.

The inspection can range from a short visit to an examination lasting possibly several weeks and involving a detailed study of all records and processes. One important general requirement is that all procedures should be recorded in detail as written instructions or manuals and be available to the Authorities. Manufacturing instructions should indicate everything that is done to avoid error, and indicate also who is the responsible person at each stage of manufacture or processing. There must be clear directives to workers on hygiene and cleanliness to avoid contamination. Quality control methods must be defined, and must include stage of testing, for example, raw materials, process control, finished products, methods of sampling, analytical techniques and retention of records.

It is possibly a difficult matter for developing countries without some guidance to decide on what provides suitable inspection. However, as outlined in Section 2, certain organizations, particularly

the World Health Organization and the Pharmaceutical Industries' Association, have published documents entitled 'Rules of Good Manufacturing Practice". These publications provide all that is necessary for a developing country on which to base an inspection procedure, and in particular that formulated by the Pharmaceutical Industries' Association in EFTA is simple, effective and satisfactory.

In the case of imported drugs, whether imported in bulk or the finished state, it is not practicable to inspect the factory of the exporting manufacturer. However, it is essential that the developing country has some guarantee, and it is recommended that in such cases, provided the premises and personnel of the manufacturer are subject to licensing in his own country, an authorized certificate from the Department of Health in the manufacturer's country should suffice. In those few cases where licensing in the manufacturing country does not exist, a syetem of inspection either by the developing importing country or under a national body, such as the World Health Organisation, will have to be arranged. It is unfair to a developing country that they should accept drugs from unknown and uncontrolled sources.

3. SAMPLING

Some Health Authorities require to examine samples at the time of application for registration, but it is more usual to withdraw random samples at intervals, either from a factory, wholesale, or retail. In the case of developing countries where the expenditure on State or other laboratories to carry out sampling and analysis of all products before registration would be a heavy financial burden, it is recommended that random sampling after registration take place and that samples be withdrawn within the country from normal sources of distribution.

(a) The Modern Concept of Quality

Having stated that approval of quality standards for products is the prime essential, it is well to set out a modern concept of quality. Before the present era of sophisticated formulations, 'quality' was synonymous with 'purity' or 'strength'. It now embraces many other features, most of which are amenable to some degree of laboratory control and to documentary and practical evidence. They should, therefore, feature in the data submitted for registration to the Health Authorities. The most important aspects are:

i. drug purity

ii. purity and safety of additives

iii. precision of dosage

iv. stability

v. physiological availability.

i. Drug Purity

In the case of new drugs, or those made under patents, this was of prime importance to the manufacturer and to the Health Authorities, but of less importance to the pharmaceutical profession or the industry at large because the drug itself may not be an article of commerce, being available in a formulated state. The data in such cases concentrates principally on standards for formulated products and less on the active drug. On the other hand, drugs which are freely available are amenable to sampling and testing by external analysts, and in such cases standards are nearly always available and widely applied. An interesting trend in the control of drug purity is towards more specific assay processes and to greater reliance on detection of possible impurities and breakdown products.

ii. Additives

Synthetic excipients are now almost as common as synthetic drugs, and may require as much detail, particularly in respect of toxicity, and especially when administered systemically in relatively large doses. Some excipients and particularly artificial colours are used in foods, and in a number of countries legislative control in respect of food for these products is more advanced than that in the case of drugs. It should be emphasised, however, that although food standards provide a guide, they are not entirely satisfactory because excipients and colours are consumed regularly in foods but given only occasionally and in small doses in drugs. It is better, therefore, to assess excipients individually in relation to (a) the drug with which they will be used; (b) the frequency and route of administration, and (c) the proposed dosage level. It is wrong to assume that a substance which has been used for many years in one way, for example, a skin preparation, is equally safe when used in another, for example, administered by mouth or by injection. Some additives, such as preservatives and stabilisers, are used much more frequently as products become more sophisticated, and therefore require special care in their selection. If no standards are available for excipients, it is essential the applicant submit full information on quality and standards with the documentation.

iii. Precision of Dosage

As new drugs tend towards increased potency and as a result lower dosage levels, precision of dosage becomes more important. For this reason alone, unit dose forms, such as tablets and capsules, are preferred to other oral forms, for which the dose must be measured by the patient. Until recently, methods used for control of accuracy of tablets presupposed that the drug was uniformly distributed, control being based on uniformity of gross weight. In some cases, however, the

dose of active ingredient may be less than a milligram, and the proportion of drug to total weight of tablet falls to below 1%. In such cases, the efficiency of mixing becomes an important factor, and the fact that a group of twenty tablets contains the correct dose on average does not mean that each one is satisfactory. In special dosage cases, therefore, it might be essential to devise particular checks.

iv. Stability

Stability under modern conditions is an important aspect of quality. Synthetic drugs, unrelated to natural products, may be distinctly reactive in the chemical sense and susceptible to oxidation, hydrolysis and other forms of chemical breakdown. Decomposition may take place during pharmaceutical processing and subsequent storage, leading to loss of potency and even possibly development of toxic breakdown products. A number of manufactured products, especially those which are exported, must cater for a shelf life of several years to meet the normal system of storage and distribution, and, therefore, in this respect alone the question of stability is of major importance in developing countries. It is essential for the manufacturer to carry out tests and submit proof which show a reasonably accurate estimate of the rate at which a preparation will decompose under normal storage. Modern conditions allow accelerated tests to be done, and these should be accepted by the Authorities, provided a check is kept on newly registered products to see if the estimated stability is supported over a period by actual fact.

4. EFFICACY AND FREEDOM FROM TOXICITY

Data on these is required for newly discovered substances, but only rarely is it required in the case of new preparations which are new

formulations of existing drugs. There have, in the past, occasionally been medicinal products which, although not harmful, were not particularly valuable, and in the days before the modern "drug revolution" it was said that although the bulk of the products available were safe and did not do much harm, neither did they do much good. It would be wrong for any developing country to accept a new drug that did not have proved efficacy, and therefore it is necessary for the manufacturer to submit details of clinical work carried out on the products to show that they have a therapeutic value. A developing country should not insist on clinical trials being carried out within its own territory, provided the applicant for registration of a new drug can give full documentation of trials carried out in reputable hospitals and medical centres by duly qualified, recognised practitioners. The registering country is entitled, however, to insist that where the medicinal product is intended for treatment of diseases having a purely local character or endemic only in certain parts of the world, the trials be carried out under conditions normally found in these countries and preferably in those countries themselves.

It has been stated several times already that modern drugs are highly efficient and potent, and that dosage tends to fail. In addition to high potency and accurate dosage, there is sometimes a possibility of toxicity or unpleasant side effects, and therefore the manufacturer must carry out sufficient tests for the safety of the proposed use to be assessed, or in the case of those medicinal products intended for grave conditions, that the risk from the disease being treated is greater than the risk of toxicity or unwanted side effects, and that the balance lies in the use of the drug under the recommended conditions.

Normally teratogenic tests should be carried out on two species of animal. When submitting documentation on toxicity studies, the manufacturer should provide full information of the number of animals,

stock characteristics, diet, methods of statistical analysis and autopsy findings. In the case of standard procedures, details of which can be fully identified by name, it should be sufficient to give the name and reference.

5. ADMINISTRATIVE REQUIREMENTS

In addition to the technical matter previously outlined, there are certain administrative requirements which the Authorities will need in order adequately to exercise control and assess whether the product should be registered or not. The following are the more important:

(a) Nomenclature : The manufacturer should state his brand name and also any statements made on qualitative and quantitative composition should be in an accepted nomenclature. Any pharmacopoeial references should be given.

(b) The proposed method of distribution, including an indication as to the contents of each package size, and if a novel form of container is used a statement as to the type of container with proof as to its suitability.

(c) Therapeutic indications given by the manufacturer for the product.

(d) A sample of the new product in the form in which it will be made available to the profession, a mock-up being acceptable. If the registering country has the facilities for analysis itself, there should also be a sample of the active principle and any new excipients in quantities sufficient for the purpose of analysis.

(e) A preliminary draft of the label and leaflet when the latter is enclosed in the package of the product, solely as a general indication of the final wording.

(f) In the case of an imported product, it has already been stated that the manufacturer must submit a certificate as to his licensing by his own Authorities. When applicable, with the application there should be the name of the responsible distributer or agent within the territory and with whom the Authorities can deal should any questions arise.

(g) Free Sale Certificate : In addition to proof that the manufacturer is a licensed pharmaceutical manufacturer within his own country, some Authorities like also to have a Free Sale Certificate. This is a document issued by the country of origin showing that the product has already been accepted in the country of origin and is available for sale there. Until such time as a developing country which imports a large number of pharmaceutical products can set up a full control organisation, the Free Sale Certificate provides a useful guarantee from the Authorities of the country of origin that valueless medicines are not being imported. There will, however, be some drugs which have little or no medical use in the country of origin but are required in certain areas overseas, such as the tropics. In such cases, it may be difficult to provide a Certificate stating that the product is on free sale in the country of origin, and any other suitable documentary evidence from the Authorities of the exporting country should be accepted.

However, when a developing country has set up an efficient control system demanding proof as to the manufacturer's status, whether he be indigenous or overseas, proof as to the efficacy and safety of the product, and sufficient information to enable

quality control to be exercised, then the developing country can rely on its own control and procedures, and a Free Sale Certificate has neither place nor value in the registration system.

DOCUMENTATION

Before setting out the actual documentation, it must be noted that in order for a registration procedure to work satisfactorily, it is necessary to have the full co-operation of the registration authority with the industry. There is no point in specifying a detailed list of data required if the authority concerned does not have the funds, people or facilities necessary to evaluate that data promptly. Developing countries must fix their requirements according to their resources. For example, in one highly developed country it is quite clear that the facilities made available to the State Pharmaceutical Laboratory are not sufficient to enable them to carry out their proper task in a satisfactory period of time. Applicants are now advised that it will take at least two years, and one may expect this period of time to increase for a new application for registration of a product to be considered. These delays all result in an erosion of available industrial property, and also more important still, in valuable preparations being withheld from the population of the country concerned.

It is recommended that the following documentation be used in submitting an application for the registration of a pharmaceutical product. This documentation in the main is necessary whether the product be locally manufactured, locally packed or processed, or imported in the sales pack. The amount of practical analysis and checking of materials will depend upon the resources in the case of a developing country, and certain certificates will be required in the case of imported products. Any variations are

indicated against the items listed.

(1) The name and address of the manufacturer, and in the case of an imported product, the name of the local processor or distributor, so that the Authorities can discuss matters locally and also know where to place responsibility should any query arise.

(2) A local manufacturer should state the licence number of his premises, and in the case of imported products a certificate should be submitted from the Authorities in the country of origin, stating that the manufacturer is duly licensed in that country. In the case of those few exporting countries where no licensing exists, inspection of the premises will be necessary, either by the importing country, or if this is not feasible, by an international organization, such as the World Health Organization.

(3) If it is intended to sell the product under a trade mark, the proprietary name should be given. The free name of the product, being either in the form of internationally approved nomenclature, such as W.H.O. free names or the approved names of any recognised pharmacopoeia. In the event that such name is not available, a chemical name according to any recognised international nomenclature.

(4) In the case of new substances, a description of the physical form, structural formula, molecular formula and molecular weight.

(5) A statement should be given of the intended route of administration and how the drug is to be marketed, i.e. for popular sale or only through the professions.

(6) For new substances, a chemical and pharmaceutical scientific memorandum containing the following information about the active ingredients, either sold in their existing form or more likely in formulations:

(a) Method of manufacture, including a flow-sheet diagram, and an explanation of each stage of a synthetic route, including final purification.

(b) Evidence of molecular structure and distinguishing characteristics of the compound, e.g. isomers, etc.

(c) Standards for identity, purity and potency, together with analytical methods employed.

(d) Chemical and physical stability data.

(7) A chemical and scientific memorandum containing information about formulation forms:

(a) A complete formula, declared quantitatively per dose or percentage composition.
Constituents should be described by approved names, or where this is not possible, accepted chemical names.
In the case of quantities of excipients where there are variations in manufacturing technique, e.g. for tablets, a suitable range should be stated and any overages included in the formulation should also be stated.
Where any colourings, flavourings or perfume compounds are used, details should be given, together with some means of identification, i.e. the colour index number related to any known system.

(b) Method of manufacture of formulated product.

(c) In order to ensure quality control, a specification of each constituent, together with a specification of the finished product. Where the constituents or the finished product are contained in a pharmacopoeia, a pharmacopoeial reference will suffice. If a constituent is not already accepted for pharmaceutical use, evidence as to its safety must be given.

(d) Analytical control procedures for constituents for control during processing and on the finished product.

(e) Chemical and physical stability data in the same way as for the active ingredients.

(f) Proposed labelling, including a statement where appropriate as to suggested shelf life (which may be included on the labelling in code) and any cautionary notices necessary for storage.

(5) In the case of new substances, a pharmacological and toxicity memorandum setting out the following:

(a) The names, addresses and qualifications of the persons investigating toxicity.

(b) Details of experimental studies and the observations on which statistical calculations are based to be shown in detail. Full information should be given of the number of animals, stock characteristics, diet, autopsy findings and any other particulars involved in assessing the results.

It is recommended that unless there are special reasons, teratogenicity tests should be carried out on at least two

species of animal, including, if possible, rabbits.

(9) A clinical trial dossier giving full reports on clinical trials carried out on the drug, re-prints or photocopies of scientific papers should be submitted, clearly identified, and it is essential that where the drug is mentioned it can be identified with the product being submitted. Individual case records should not be required, as a demand for such has several ill effects, e.g.:

a) it encourages people to cheat rather than the reverse;

b) it tends to move the onus of responsibility for deciding about the effectiveness and possible danger of the product from the clinician and the manufacturer, to whom they rightly belong, on to the legislative authority;

c) it is often difficult to obtain good case records from clinicians.

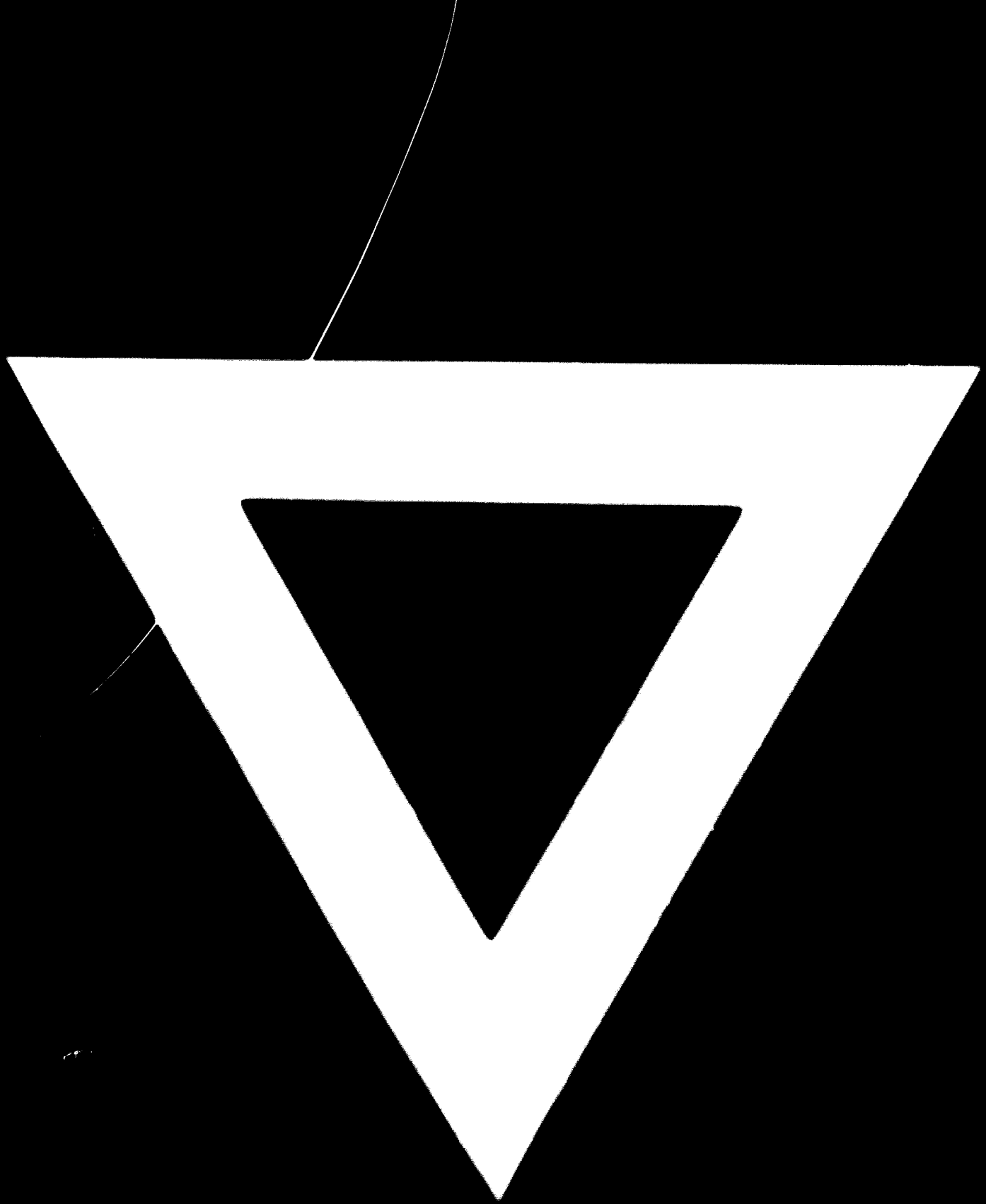
Papers in the major languages (e.g. those used in the U.N.) should be permissible in the original, but in the case of developing countries it may well be that they must insist on either translations or summaries of the papers containing the important points in the language of the country concerned.

Where trials have been carried out, either in hospitals or in private practice, and the work not published, full details should be submitted, including a comprehensive list of names and addresses of the doctors carrying out the trials.

(10) Details should be given of the dosage and any cautionary notices to be included in labels and/or inserts; the dosage should be that for both adults and children, and if intended only for one or the other, this should be clearly stated.

(11) Details of the proposed sales pack should be submitted, and in cases of doubt where a country had adequate analytical facilities, either Governmental or under contact to the Government, actual specimens of the product, together with any unusual excipients, should also be submitted.

(12) In the case of developing countries without adequate control facilities, as a safeguard for the public, the applicant in the case of an imported product should submit a Free Sale Certificate denoting that the product is acceptable and could be on free sale in the country of origin.



4. 4. 72