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**USE OF SPECIFICATIONS FOR  
PHARMACEUTICAL PREPARATIONS**

**Report of a Study Group**

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**WORLD HEALTH ORGANIZATION**

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GENEVA

1957

**STUDY GROUP ON THE USE OF SPECIFICATIONS  
FOR PHARMACEUTICAL PREPARATIONS**

*Geneva, 4-8 December 1956*

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# USE OF SPECIFICATIONS FOR PHARMACEUTICAL PREPARATIONS

## Report of a Study Group

The WHO Study Group on the Use of Specifications for Pharmaceutical Preparations met in Geneva from 4 to 8 December 1956.

### 1. INTRODUCTION

The Director-General of WHO, opening the meeting, stated that it was the first time that a study group had been convened to deal with the methods used for the examination of pharmaceutical preparations in different countries and to study principles which could be of help to national health departments and other authorities dealing with this problem.

At its sixth session, held in New York in 1950, the Expert Committee on the Unification of Pharmacopoeias had drafted a questionnaire for circulation to Member States, which in reply had supplied information on the specifications and methods used for the examination of pharmaceutical specialities. At later sessions, the Committee had noted reports on this subject obtained from members of the Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations and other specialists, and it was on the basis of these and other studies obtained from various sources that the discussions of the meeting were being held and that its provisional agenda had been drafted.

The Executive Board had in 1951 requested the Director-General to continue the study of the advantages of more uniform methods for the control of drugs in the various countries in the interest of health and international commerce.<sup>1</sup>

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<sup>1</sup> Resolution EB7.R79, *Off. Rec. Wld Hlth Org.*, 1951, 32, 33

The Director-General indicated that particular attention should be given at this meeting to the means of obtaining information and of improving laboratory methods of examination, and to the problems connected with the introduction of new pharmaceutical preparations of therapeutic interest. However, the meeting would deal with general principles and would not have to prepare specific recommendations, since these problems had to be studied, planned and organized in a great variety of ways by national or other authorities, depending on their own circumstances, stages of industrial development, traditions, and regulations, and on their facilities in personnel and equipment.

## 2. INTERNATIONAL PROGRAMMES

The Study Group noted with interest that the Pan American Sanitary Organization had, as early as 1945, undertaken the study of ways and means for improving food, drug and cosmetic services in the Americas. At the Twelfth Pan American Sanitary Conference, in 1947, the wish had been expressed to have data collected, published and distributed by the Pan American Sanitary Organization on new pharmaceutical preparations, and to include techniques of identification and evaluation.

The particular problem of the registration of pharmaceutical preparations in the different countries of the Americas had also been studied by the Fourth General Assembly of the Pan American Medical Federation in 1955. At that time, it was moved that the Executive Committee of the Federation should hold a meeting at which the possibility of obtaining more uniformity in this field in collaboration with the Organization would be discussed.

While it was found advisable to proceed carefully in this important field, the suggestion was also made at this assembly that a number of steps should be taken as early as possible, and in particular that arrangements should be made to assess the nature and the extent of the problems in the different countries, and to study the possibility of later establishing co-operative food and drug services. A clearing house would be useful to provide information on food and drug laws, regulations and practices of American countries, and to publish information and data on research and procedures on drug registration, and other information of this nature.

Other suggestions were made concerning the establishment of recommended specifications on the basis of those prepared by the World Health Organization in the International Pharmacopoeia, and concerning fellowships and laboratory services.

The Group expressed its appreciation for these suggestions, as well as for the studies already made at the Pan American Sanitary Organization and the WHO Regional Office for the Americas, and expressed the wish that, since these suggestions and studies pertained to the same subjects and corresponded to similar work to be undertaken in other parts of the world, full collaboration should be maintained on these matters between the Pan American Sanitary Organization and the World Health Organization.

The Group noted that work was also being undertaken in this field by the International Pharmaceutical Federation, particularly through the meetings of directors of laboratories for the control of medicaments, which had taken place annually since 1947 and at which laboratory assay methods for the examination of pharmaceutical preparations, as well as procedures and administrative arrangements, were discussed. The Group hoped that this important means of collaboration between laboratories would be extended as much as possible within the Federation and among groups of countries, in conjunction with similar activities undertaken by WHO. The Group also noted the work of the Federation on the registration of pharmaceutical preparations through its Section of Industrial Pharmacists, which was studying the information demanded by different countries for the introduction of pharmaceutical preparations and was making suggestions for simpler and more uniform requirements.

The Group was informed of the work of the Pharmaceutical Products Sub-Committee of the Western European Union, which had met regularly for some years and had discussed and reported on many pharmaceutical problems, including a unification of specifications for pharmaceutical preparations in national pharmacopoeias of countries in the Union. Samples of chemicals had been exchanged between experts, and melting-points and limits of impurities had been determined in different laboratories, with a view to standardizing methods. Unification along these lines would obviously assist the exchange of pharmaceutical preparations between the countries concerned. The Sub-Committee had studied their various national regulations with a view to obtaining greater uniformity, particularly in the classification of poisons and in labelling-requirements. The examination of pharmaceutical specialities had also been discussed and had led to an investigation of the possibilities of interchanging certificates of analysis from the official laboratories of the countries in the Union. If certificates from the country of origin could, under certain circumstances, be accepted by the importing countries, much duplication of effort could be prevented. Exceptions could be made for unstable products. It was hoped that much of this work would be made available through WHO to members of the Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations.

This sub-committee had recently decided to compile an English-French glossary to prevent confusion in interpreting the text of its reports. This was not intended to be a technical dictionary of pharmaceutical terms, but would be restricted to words which had raised particular difficulties. A first list of English and French equivalents had been produced, and it had been decided to add German and Italian equivalents. It should be possible to supply copies of this glossary to WHO for circulation to members of the Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations with the request that they submit suggestions and comments. It was suggested that the members of the Group could assist the compiler of the glossary by submitting suitable pharmaceutical terms to the Secretariat of WHO for forwarding to the Western European Union.

The Group noted that the Pharmaceutical Union of the Arab League at its Fifth Conference in 1955 had discussed the examination of pharmaceutical preparations, facilitation of commerce in such preparations within the League, the creation of a pan-Arab pharmacopoeia, and the improvement of pharmaceutical education.

### **3. EXAMINATION OF PHARMACEUTICAL PREPARATIONS AT THE NATIONAL LEVEL AND IN THE PHARMACEUTICAL INDUSTRY**

#### **Review of the situation in certain countries**

The Study Group had received reports from its participants on the general principles governing the examination of pharmaceutical preparations in their own countries by the authorities and in the pharmaceutical industry.

In Canada, such examination is exercised at the federal level in accordance with the Food and Drugs Act and the Proprietary or Patent Medicine Act, which cover all preparations on the market, whether domestic or imported. All pharmaceutical preparations are subject to the Food and Drugs Act, and the Proprietary or Patent Medicine Act contains additional legislation requiring the registration of household remedies whose labels do not provide complete information concerning their composition. The Food and Drugs Act provides for standards, labelling and packaging; puts certain restrictions on advertising; requires licensing of biologicals; allows certain drugs to be sold only under prescription; requires submission of information establishing safety of pharmaceutical

preparations; and establishes a list of official publications containing specifications for drugs.

In Egypt, there is a Pharmaceutical Section in the Ministry of Public Health, under the direction of a pharmacist. When a pharmaceutical preparation is imported into the country, the manufacturer or importer sends samples thereof to the Pharmaceutical Section. All the samples are sent, with information on the composition and methods of analysis, as well as pharmacological and clinical data, to a controlling committee which checks the labels and advertising and forwards the samples to a central laboratory for analysis. If the analysis is in conformity with the labelling, the preparation may be distributed to pharmacies; otherwise, modifications must be made before release. Following release, samples may be taken from the market for further analysis. This applies to pharmacopoeial drugs as well as to specialities, except that specialities have to be registered, if accepted, and pharmacopoeial drugs have only to conform to pharmacopoeial specifications.

In France, pharmaceutical preparations are covered by a Pharmacy Law and must satisfy the requirements of the French Pharmacopoeia, when described therein. For pharmaceutical specialities the composition must be given, as well as the method of manufacture and analysis, and pharmacological and clinical data. A technical committee studies the information submitted and, on the basis of novelty, therapeutic interest and safety, decides whether the preparation may be introduced or whether further information is needed. It should be noted that the responsibility for the quality of production of pharmaceutical preparations is borne by pharmacists at all stages of manufacture. Advertisement to the general public is subject to certain restrictions, and publicity over the radio or television is not permitted.

In India, control over pharmaceutical preparations is exercised by the Federal and State Governments. The Federal Government is responsible for the importation of pharmaceutical preparations, which is limited to certain ports and is under the authority of the Drugs Controller. The Federal Government is also responsible for the establishment and maintenance of a control drug laboratory, a technical advisory board on drugs and a consultative committee on drugs, which advise the Federal and State Government with a view to obtaining uniformity of administration. The States are responsible for control over manufacture, sale and distribution. All premises where drugs are produced or sold are licensed. Advertisement of pharmaceutical preparations comes under a separate law. The introduction of new pharmaceutical preparations is controlled.

In Japan, the examination of pharmaceutical preparations is the responsibility of the pharmaceutical department of the Ministry of Welfare, and the

laboratory examination is carried out by the National Hygienic Laboratory, except in the case of antibiotics and biological preparations, which are examined in the National Institute of Health. Preparations described in the pharmacopoeia and other official works have to meet their specifications. Non-official preparations, especially new ones, must be approved by the Ministry of Welfare, and analytical methods as well as pharmacological and clinical data must be submitted prior to their introduction. For household remedies, indications, dosage and method of use must be approved.

In Sweden, when a speciality is introduced, the manufacturer, or, in the case of imports, the manufacturer's representative, must notify the Royal Medical Board, send a sample and provide full details on its composition, as well as relevant chemical, clinical and biological information. This information and the samples are forwarded to the pharmaceutical laboratory for investigation. Under certain circumstances the preparation may be sold pending completion of the investigation. When the chemical or biological investigation is finished, the results are sent back to the Royal Medical Board. The results are presented to a special committee which includes representatives of industry. When the speciality is accepted, it is registered and may then be marketed in accordance with the regulations.

In the United Kingdom, control of pharmaceutical preparations is based on the Food and Drugs Act, the Pharmacy and Medicines Act and the drug-testing scheme within the framework of the National Health Service. A specific law exists only for the control of biological preparations.

In the United States of America, basic specifications are contained in the Pharmacopoeia of the United States and in the National Formulary, and specifications for certain antibiotics are promulgated by the Food and Drug Administration in consultation with industry. New drugs as defined in the federal Food, Drug and Cosmetics Act cannot be marketed until their safety has been ascertained by the Food and Drug Administration. The data submitted by the manufacturer must include a statement of the identity of the drug as well as analytical methods to permit quantitative examination. Biologicals such as vaccines are regulated by means of licences under a separate law, administered by the US Public Health Service.

In the pharmaceutical industry, control is essential not only to safeguard the consumer, but to protect the manufacturer. Supervision and control of routine productions are necessary at various stages of manufacture, beginning with raw materials, and no lot of any product should

be allowed to leave the factory without being checked and released by the control units. In addition to the routine control, samples from stock should be checked.

Difficulties may be encountered in establishing the specifications and analytical methods for a new pharmaceutical preparation, and very close co-operation of different groups such as pharmacological, pharmaceutical and analytical departments is essential. Ultimately, when its margin of safety has been shown to be satisfactory, it should be subjected to clinical trials to establish the optimal dose.

### **Discussion**

The Group was interested to note that the various reports and statements on this subject, as well as the information given above, revealed many similarities as well as significant differences in the methods employed. It was noted that biological products, such as sera, vaccines, antitoxins, and certain antibiotics, are generally manufactured and sold under licence. In the case of new pharmaceutical preparations, many countries require detailed data from the manufacturers before they may be introduced on the market.

It was noted that in most of these countries national pharmacopoeias or other books of reference supply specifications for official pharmaceutical preparations, while some of them require registration of all pharmaceutical preparations.

The Group noted with satisfaction that excellent methods of examination are in effect in many pharmaceutical manufacturing companies.

From the above, and from other information available to the Group (see Annex, page 28), it is apparent that most countries exert some degree of control over pharmaceutical preparations manufactured or introduced within their boundaries. Some countries require that all pharmaceutical specialities be registered prior to sale, others merely demand that they conform to labelled claims as to composition and that they be not falsely advertised. Considering the very large number of pharmaceutical specialities available and actually offered for sale, it would be useful from the standpoint of public health if government control agencies could be informed of all pharmaceutical specialities sold in the country in question. In a number of countries such information is not available.

While most of the systems of examination described above may be considered as essentially sound, the Group noted that the means for putting them into effect is often insufficient in view of the rapidly growing complexity of the task.

#### 4. ACTION BY WHO AND MEMBER STATES

The Study Group noted that WHO had already made valuable contributions in this field by providing specifications to be used in the examination of a number of pharmaceutical preparations. The publication of Volume I of the first edition of the *Pharmacopoea Internationalis*, with monographs and appendices giving suggested specifications for purity and potency, for assay methods and for posology, for some 200 important pharmaceutical preparations in international commerce, and of Volume II completing the first edition with 210 additional monographs, is a matter of great interest and practical assistance to those countries not having a national pharmacopoeia as well as to other countries in the preparation of their national specifications. The preparation of a supplement to the first edition is now under way, and the preparation of a second edition has been started. Lists of proposed international non-proprietary names for important pharmaceutical preparations<sup>1</sup> are also being issued from time to time, and contribute actively to preventing confusion arising from a multiplicity of common names for the same preparation.

It was agreed that the Group would examine what further contribution would be most useful in these fields, with the collaboration of national, international and commercial institutions, in order to protect public health and facilitate international commerce in pharmaceutical preparations.

The Group noted that twenty years ago the pharmacopoeias were still dominant in the establishment of specifications for the examination of pharmaceutical preparations. Today the situation is different. It has been estimated that a few hundred new medicinal substances are being introduced into the *materia medica* every year. This large number of new substances presents a certain hazard to public health, especially as a relatively short time may now elapse between the production of a new substance and its use in therapeutics. Twenty years ago this interval could be as much as five to ten years, and today it may be as short as six months. Side-reactions and toxicity cannot possibly be well determined during such a short time. New preparations may be very widely used shortly after introduction, and it is important to have means for their immediate supervision. The Group noted that keen competition forced the manufacturers to produce new pharmaceutical specialities at frequent intervals. For the protection of the users it is necessary that arrangements should be made to obtain as early as possible sufficient knowledge of

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<sup>1</sup> See *Off. Rec. Wld Hlth Org.*, 1955, 60, 55.

the toxicity, pharmacological and clinical action, and side-effects of these preparations.

#### **Examination of pharmaceutical preparations**

This is a very difficult problem involving precise knowledge of many thousands of compounds. This large number of substances makes it almost impossible for any organization to be familiar with the whole subject. National pharmacopoeias usually describe a number of basic drugs. However, the preparation of a pharmacopoeia is a difficult task requiring much time and the assistance of many groups of scientists such as pharmacists, physicians, bacteriologists, serologists, etc. It is not unusual for twenty to one hundred such persons to spend several years in preparing material for a pharmacopoeia, and these official books cannot be easily or quickly revised. It is recognized that in practice it is impossible to include all substances of therapeutic interest in the current editions of a pharmacopoeia. In many cases the specifications can only be made available in the form necessary for publication in a national pharmacopoeia at a time when the actual use of the preparation is already diminishing or has even practically disappeared.

While recognizing that scientific publications are of great importance in supplying a large part of the necessary information, the Group realized that the amount of literature and the diversity of the sciences involved make it difficult or impossible for those responsible for the control of pharmaceutical preparations to keep abreast of the flood of information or data being issued. A further obstacle is the fact that publications in several languages covering a variety of sciences such as chemistry, pharmacology, bacteriology and medicine must be studied to find the most recent relevant developments.

The specifications contained in national codices, formularies, etc., may provide an additional source of information and can be made official. However, even with these additions, it is not possible to make available to the control laboratories all the necessary information for the examination of the growing number of pharmaceutical preparations.

#### **Possible future action by WHO**

The Group faced with these facts discussed a suggestion to have a service within WHO which would obtain, examine, collate and distribute reference data concerning new pharmaceutical preparations. As this information would best serve its purpose if it were available early, the Group believed it advisable to obtain the collaboration of the pharmaceutical industry, either directly or through the members of the Expert

Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations and other specialists, as well as through pharmacopoeia commissions, health administrations or other authorities, as in the case of non-proprietary names. On the basis of the information thus obtained, and information from other sources, WHO would compile information sheets.

These information sheets would contain, for instance, particulars concerning the quantitative composition of a new preparation, its active ingredients, its contents, the field of indications and dosage, clinical and toxicological findings, analytical data and references to published literature on the subject. It could also include melting-points, boiling-points, data on solubility, refractive indices, infra-red and ultra-violet spectra, melting-points of derivatives, and assay methods for the pure substance as well as for the pharmaceutical preparations manufactured from the substance. Even if all these data were not available, part of this information would already be of help and would be valuable to Member States.

It was pointed out that, no matter how careful manufacturers and control officials may be, it is not possible, in advance of distribution, to have sufficient knowledge of possible side-effects of new pharmaceutical preparations, as no preliminary tests can be devised which would accurately reproduce the conditions of use by millions of people. It is thought advisable, therefore, that data concerning side-effects of pharmaceutical preparations should be included when possible in the information sheets to be obtained and distributed by the Organization. If all such information is not available when a new substance is introduced, the Group suggests that it should be distributed later as an amendment.

After an information sheet had been received, examined, completed and arranged by the Organization, it would be distributed to Member States, to members of the Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations, and to other specialists and control laboratories. The Group suggested this as a means of helping countries to keep abreast of current developments in connexion with the supervision which they have to exercise in this field. It was noted, however, that it would be extremely difficult to keep the information sheets up to date, and some means of solving this problem should be sought. It may be expected on the other hand that studies would be undertaken by the authorities, laboratories and persons receiving this information and that they would forward their results, comments, and suggestions, which would be of assistance in revising the specifications.

It was also pointed out and accepted that in some specific instances it would be impossible for a manufacturer to supply complete data, as in so doing he might place himself in an unfavourable position in relation

to his competitors. It was further thought that these information sheets would probably contribute towards a speeding-up of registration procedure in countries which had this system, and would therefore be of assistance to the manufacturers of pharmaceutical preparations.

The Group pointed out that the data collected by means of information sheets could very well serve as a basis for future revisions of the International Pharmacopoeia. This would be a particularly good method of revision, since it would be based on actual and recent experience with the proposed methods.

## 5. CENTRE FOR AUTHENTIC CHEMICAL SUBSTANCES

The Study Group noted that a centre for authentic chemical substances was being opened at the Apotekens Kontrollaboratorium in Stockholm, in accordance with an agreement between Apotekarsocieteten and WHO, following a recommendation of the Expert Committee on Biological Standardization, and under the aegis of the Expert Committee on the International Pharmacopoeia. It should start operation within the next few months. The centre will keep, control and distribute a restricted number of pure chemicals to be used for reference purposes by control laboratories of governments or other authorities.

The centre will keep the following substances to start with : vitamin A acetate, digitoxin, ergometrine maleate, oestrone, progesterone, tubocurarine, melarsen. Some of these substances have been received from the Medical Research Council, London, which kept and distributed them in the past as International Biological Standards and Reference Preparations. It had been decided that they should now become part of the Centre's collection of authentic chemical substances since they could be defined by physico-chemical methods. The other substances were acquired in collaboration with the United States Pharmacopoeia Reference Standards Office in New York or purchased by the centre from various manufacturing concerns.

These substances will be placed at the disposal of government control laboratories, which may order them from the centre and may prepare from them reference substances for use by other laboratories in their own countries. The centre will operate for some time on an experimental basis and it is therefore not expected to increase the list of substances appreciably until sufficient information is available on its usefulness. It will also be limited to substances used in the laboratory control of medicaments and for pure research. The difficulty in ascertaining the

exact composition of some of the substances would be a reason for keeping their number to a level which can be operated successfully.

The Group expressed appreciation of the work undertaken and thought that it would prove of value for control purposes since it was sometimes difficult to obtain substances of a definite composition.

## 6. DEFINITIONS

The study of national regulations pertaining to pharmaceutical preparations in the different countries is complicated by the variety of terms used to designate pharmaceutical preparations, and by the fact that identical terms may have a different meaning in different countries or under different conditions. The Study Group stressed the difficulties involved in interpreting pharmaceutical regulations of a given country and translating specific terms into another language.

Differences arise also from the fact that, while certain of the terms used in pharmaceutical regulations are defined, others are not, and when difficulties exist the meaning of these terms must be decided in court on the basis of expert evidence. Moreover, certain concepts have been modified owing to new scientific developments in this field.

The definitions given in various countries are not rigid. In certain legislations the meaning of a term, although defined in a principal law, may be further defined by a regulation.

The members of the Group reviewed the systems used in their respective countries for the supervision of pharmaceutical preparations and considered many definitions. They noted that the terms "drug" and "pharmaceutical preparation" are often used synonymously. The following were mentioned as examples of definitions broad enough to include the different types of pharmaceutical preparation and pharmaceutical speciality:

(1) A drug (or pharmaceutical preparation) is any substance or mixture of substances manufactured, sold, offered for sale or represented for use in:

- (a) the diagnosis, treatment, mitigation or prevention of disease, abnormal physical state or the symptoms thereof in man or animal;
- (b) restoring, correcting or modifying organic functions in man or animal.

(2) A pharmaceutical speciality is a simple or compound drug ready for use and placed on the market under a special name or in a characteristic form.

The Group expressed the view that the above definition of a pharmaceutical preparation is better than one which defines a drug as a substance named in an official list. Although the latter definition may be easy to apply, it is weak in at least one important aspect—namely, that a manufacturer can avoid having to submit a preparation to government control by making it slightly different in its chemical composition from other preparations of the same class which may be included in the list, or, in the case of a vegetable drug, by using a drug from a closely related plant.

## 7. INTRODUCTION OF A PHARMACEUTICAL PREPARATION

### Essential requirements

It was agreed that a most important responsibility of officials who deal with the control of pharmaceutical specialities is that of ensuring that these substances are safe for their intended use.

Regulations for this purpose differ widely from country to country. In some countries, special requirements have been imposed for new preparations not generally recognized by medical experts as safe. Such preparations are referred to in the US Food, Drug and Cosmetics Act as "new drugs" and cannot be marketed until their safety has been approved by the Food and Drug Administration. Other countries have adopted a similar procedure, and in such cases the new drug may be sent under certain conditions to experts who test it to determine safety for the intended purposes. The manufacturer supplies the following information: (a) a report of *all* the investigations that have been made to show safety of the drug in use; (b) a complete disclosure of the components of the drug; (c) a statement of the composition of the therapeutically active components of the drug; (d) a detailed description of the methods used in the manufacture, processing and packing of the drug (if the person submitting the application does not himself perform all the manufacturing, processing and packing operations, he must state the name of the person responsible for them); (e) full information concerning the analytical and other controls employed to ensure the identity, strength, quality and purity of the drug, including data of batch and other control numbers and their significance; (f) data showing whether or not a date of expiry is necessary; (g) specimens of the drug with its labels and a statement whether or not the article is to be sold only on the prescription of a physician.

In reviewing the requirements existing in various countries, the Group thought that the following information might be useful to the authorities responsible for public health and welfare:

- (a) the qualitative and quantitative composition declared in the commonly accepted nomenclature ;
- (b) details of analytical methods and possibly certain useful indications on the method of preparation ;
- (c) physico-chemical constants if not already known ;
- (d) the therapeutic indications and dosage ;
- (e) the recommended method of selling (prescription, etc.) ;
- (f) samples in sufficient quantity for analysis ;
- (g) information concerning label, package and publicity (advertising).

If a speciality contains substances, or combinations thereof, the action of which is not generally known, additional information may be required such as :

- (h) publications or documents regarding the pharmacological action of the substance and its toxicity, clinical reports on its therapeutic efficacy and side-effects.

Internationally, clinical results from the various countries may in certain cases be accepted on a reciprocal basis.

National requirements for the introduction of pharmaceutical preparations may cover the following points : chemical composition, biological properties, pharmaceutical form, stability, indications of use, posology, precautions, toxicity, therapeutic advantages, novelty, bibliography, authority or power of attorney for imported specialities, samples, details of facilities of maker, publicity and leaflet details, specimen labels, indication whether on sale elsewhere, analytical data, trademark details, name of responsible pharmacist, details of ingredients or raw materials, statement that local manufacture is impossible.

The Group noted that no country requires information about every one of the items listed, some of which concern protective legislation and commercial interests rather than public health. The Group felt that there is need for continued study of the legislation in different countries concerning pharmaceutical preparations and that a meeting should be called later to consider this legislation and determine how it could be simplified and made more uniform in order to reduce obstacles to international commerce to a minimum and still provide ample protection to public health.

#### **Principles of labelling**

The Group deems it advisable that the labels for pharmaceutical preparations should bear certain basic information, and recognizes that

different types of preparation will require additional statements. In all cases the label should bear the name of the speciality, the composition, the batch number and the name and address of the manufacturer. In certain cases, the route of administration should be given. Special indications might be required for posology, physiological incompatibilities, conditions for sale on prescription or otherwise, special conditions for storage, etc. It is important that the composition should be given in terms normally employed or officially defined.

It would be an advantage if agreement could be obtained between the different countries on the information to be included on the label and how it should be expressed (e.g., units of measurement), in order to facilitate international trade and for the general protection of physicians, pharmacists and consumers. In addition to the trade-name, an approved non-proprietary name is demanded in many countries, and in such cases this should be given on the label in a conspicuous manner. In this connexion, the Group noted the work of WHO in successfully providing proposed international non-proprietary names for many new drugs, thus helping to prevent confusion arising from the use of several names for the same preparation.

The Group noted that in certain countries a preparation may not be supplied unless it is labelled with (1) adequate directions for use, and (2) adequate warnings against (a) use by children, (b) use in those pathological conditions where it may be dangerous, and (c) unsafe dosages or duration of administration or application, in such form or manner as is necessary for the protection of the users. Where any requirement of clause (1) as applied to any preparation is not necessary for the protection of public health, the authority dealing with the examination of new pharmaceutical preparations shall issue regulations exempting the preparation from such requirement.

The Group felt that statements or other information required to appear on the labels should be sufficiently conspicuous so as to be clearly legible and likely to be read and understood by the user. The danger presented by pharmaceutical preparations to children was stressed. Upon hearing many distressing cases of poisoning by drugs, the Group felt it its duty to draw attention to this great danger, which could be prevented by care in the storage and handling of medicaments in the home. All pharmaceutical preparations should be kept out of the reach of children.

*Date of manufacture.* The Group noted that it may be misleading to mention this date specifically on the label, since this may lead the purchaser to believe that the drug is too old when in fact it is very stable and perfectly suitable for use.

*Batch number.* A batch or lot number should be given on the labels of many pharmaceutical preparations, particularly those recommended for internal use. Such a number should permit the controlling authorities to trace the batch through manufacturing procedures and to identify it on the market.

*Expiry date.* This date should be given for certain drugs. It is desirable that the date given by the manufacturer agree with the known facts about the stability of the preparation under specified storage conditions, and be acceptable to the controlling authorities when supported by evidence as to its validity. As more information becomes available, it may be necessary to modify the expiry period.

Special stress must be laid upon conditions which are peculiar to certain areas of the world, such as tropical climate and long-distance transport under unfavourable conditions. High temperature and high humidity are serious problems in relation to the stability of drugs. The expiry date of a preparation should take into account the climatic conditions of the proposed market. It is also desirable that the manufacturer should indicate to prospective purchasers the best conditions of storage for the preparation. Furthermore, it was considered that a manufacturer should refuse to consign his preparations to climates particularly liable to destroy their potency unless special precautions are taken to preserve them.

It is the responsibility of the purchasing country both to store imported drugs and to transport them in its territory under satisfactory conditions. The Group is aware of the excellent storage facilities in some of the central medical stores and hospital pharmaceutical departments of certain tropical countries. The members are of the opinion that, whenever needed, governments should provide every facility to the responsible authorities for the best possible use of cold storage warehouses, rail and air transport, etc., in keeping with climatic requirements.

#### **Principles for classification of pharmaceutical preparations to be dispensed on prescription and otherwise**

For many years, most countries restricted certain groups of drugs—e.g., barbiturates, amidopyrine, and other dangerous preparations—to medical prescription. The advent of the sulfonamides twenty years ago created a new problem. Here was active medication, not to be classified as poison in the general sense, which merited restriction to prescription. During the past two decades, many new drugs have appeared and have merited the same restriction, e.g., certain antibiotics, anti-histamines, cortisone and derivatives, amphetamines and other stimulants.

This development has changed the situation and older systems of classification may no longer be suitable. It is therefore advisable that information be collected on systems of classification operating in different countries, and that further studies be made on this subject in order to obtain a certain uniformity in the principles of classification in the different countries, particularly concerning inclusions in the list of preparations which have to be restricted to medical prescription.

**Information on analytical, physico-chemical, microbiological, pharmacological and other methods**

It is important to have available, whenever possible, certain physical constants of the constituent substances, such as melting-point, refractive index, rotatory power, solubility to various solvents, etc. Information for the identification and assay of the individual constituent should also be supplied to the authorities, as well as the method of identifying and assaying the constituents in the finished product. Separation of components creates difficult problems, and the assay methods for the finished product will often be different from those used for the determination of the substances in their natural state. This information regarding the methods of studying the finished product may be important, as these methods are often difficult to establish. This concerns new preparations. For preparations described in the pharmacopoeias or other books of specifications, the expert is, in many countries, obliged to use the method described. The problem of pharmaceutical specialities is different. Each speciality represents a fresh problem to be solved by the analyst. The difficulties are essentially due to the presence of several active substances and to the excipient. The technique adopted for one speciality can rarely be used for another without modification. It may be that in certain cases the method proposed by the manufacturer is not yet sufficiently perfected, and in such cases the manufacturer and the control laboratory should co-operate. However, the Group is of the opinion that the control laboratory should make the final decision and adopt the method which it considers the best.

The work of the International Pharmaceutical Federation should be taken into consideration, especially the work of the directors of control laboratories who meet every year. Collaboration in these matters is advisable between all concerned.

**Evaluation**

One of the most difficult problems in the examination of new pharmaceutical preparations is the evaluation of pharmacological and clinical reports.

These reports are usually favourable during the first period of the life of a new preparation. It may take some time until the side-effects are noticed. Instances could be quoted where a drug was used for one or two years with favourable reports, after which serious side-effects were noted and reported. The Group felt it extremely desirable that the Organization consider the possibility of further study of this question.

In the introduction of a new pharmaceutical preparation, clinical tests to establish the safety of the preparation must be performed on material of the same composition and in the same medical form as will subsequently be manufactured and offered in the market. The preparation marketed by the manufacturer must have the same composition and properties as the sample submitted to clinical tests.

#### **Acceptance of pharmaceutical preparations in different countries**

It is advisable that imported specialities be subject to the same specifications as those manufactured within the country. Each country should adopt an objective attitude with regard to imported specialities, and may admit without formalities medicaments which have been accepted for introduction in another country, provided the methods of examination in the exporting country are satisfactory.

In countries where most of the preparations are imported, the services for examination of pharmaceutical preparations may not yet be fully equipped and staffed.

If the importing country has established or adopted specifications of its own, it is normal that it require important medicaments to comply with these specifications. Otherwise, they should conform to the specifications of the exporting country or any other specifications demanded. It should be noted in this connexion that governments can make official in their territories any specifications that meet their needs.

If the importing country is not yet equipped with adequate assay laboratories, it could, in order to check the quality of the product, designate a laboratory to examine the imported preparation. Groups of countries may find it satisfactory to establish a common official laboratory for this purpose.

The problem is somewhat different in the case of specialities not described in official books. On what should the quality of such specialities be based? If the exporting country has introduced the speciality in question, it will be possible to evaluate to a certain degree the quality of the product, knowing the standard of the examination in the country of origin. A temporary solution may be to request the importer to supply a certificate of analysis from the exporting country. However, while

this suggestion may have some merit, it does not solve the problem since the appropriate control officials in some of the important exporting countries have no authority to issue such certificates, and moreover such certificates might be found to be unacceptable in some of the importing countries.

These are, in the opinion of the Group, difficult problems which would require further study. On the other hand, it may happen that a number of countries will undertake to make arrangements to accept each other's certificates.

## **8. ORGANIZATION OF A NATIONAL CONTROL AUTHORITY**

### **Administration**

The administration dealing with the application of specifications for pharmaceutical preparations is in most cases the responsibility of a government. In some countries this responsibility has been delegated by the government in part to statutory or recognized professional groups such as national pharmaceutical associations.

The government administration may be carried out entirely by a central agency or, when a federal system exists, much of the enforcement may be left to the states, provinces, republics or other units forming the federation. Choice of the method depends on constitutional requirements, tradition or considerations of efficiency.

The administrative staff includes the senior officers in charge of the work, legal advisers, the advisory boards and committees necessary to assist the administrator, and clerical personnel.

The size of the organization and whether or not it is entirely centralized will depend on many factors, including the population and territorial size of a country and other geographical considerations.

The government administration may have laboratory examinations as well as the other work carried out entirely in government laboratories, or may delegate the analytical or other work to university departments or to scientific institutes designated for the purpose. In the latter case it is advisable that the administrator be solely responsible for the work of the designated organization in order that the most efficient use of its facilities be made. The responsibilities of all such organizations should be clearly defined and the channels of authority and communication definitely specified.

There must be central co-ordination so that all branches work together to accomplish the desired objective with the least expenditure of effort and money. For example, inspectors must not collect samples for analysis without sufficient reason.

Savings in personnel, equipment and other charges may be obtained by having the administration and laboratory services located in one centre ; this plan may be found to be particularly useful in countries which are not large geographically. In countries with large territories, it will usually be necessary, for reasons of time and convenience, to establish regional laboratories in the large urban centres.

In connexion with many administrative decisions, it is advisable to consult with non-governmental authorities, not only to eliminate sources of criticism which may be directed at the administration and possibly the operation of the laboratory, but also to obtain a fresh viewpoint on the problems in question. Such consultants, who could be formed into special commissions, may include professors of pharmacy, pharmacology and medicine, and also scientific and technical officers from pharmaceutical and chemical manufacturing firms.

### **Inspection services**

The inspectors employed by the authority dealing with the examination of pharmaceutical preparations should be professionally qualified and well trained. These individuals are in daily contact with the industry and the pharmaceutical profession and, in addition to their scientific knowledge, they should have a considerable knowledge of manufacturing procedures, record controls and laboratory examinations of raw materials and finished products.

Since inspectors act as public relations officers as well as intelligence officers of the control agency, they must be able to answer many kinds of questions about specifications, methods of tests and sampling, and good control procedures, and, in general, inspire confidence and respect. A number of countries are issuing manuals to assist them in this task.

### **Collection of samples for assay**

The reliability of the results of a batch analysis depends on the kind of sample selected, and the sample should accurately represent the batch involved. Sampling presents complex problems which vary with the product, e.g., its homogeneity or otherwise. The principles of modern statistics, including sequential analysis, should be utilized in planning sampling schedules.

### Scientific services

In the past, specifications for pharmaceuticals have been largely based on the use of physical and chemical tests such as melting-point, specific rotation and qualitative reactions. With the increasing introduction into pharmacy of closely related compounds, it became strikingly evident that these tests, particularly for products isolated from natural sources, were not reliable. In the last few years, new techniques have become available for the identification of chemical substances and the estimation of their purity. X-ray diffraction techniques, the determination of crystallographic characteristics, and infra-red absorption spectra have been found to be extremely good means of identifying many substances. Absorption and chromatographic separation, ion-exchange resins and counter-current extraction techniques have been applied to the separation of many closely related compounds, and paper chromatography has been used for the separation and identification of components of mixtures, and for the detection of contaminants. In some cases, it has been possible to develop this technique to lend itself to quantitative application. Ultra-violet and infra-red absorption spectroscopy and non-aqueous titrations have been found to be particularly valuable for the final estimation of substances previously purified by the techniques mentioned above.

### Equipment of a pharmaceutical control laboratory (chemistry and physical chemistry department)

As far as equipment is concerned, it is necessary to consider the apparatus used by each individual worker (beakers, burettes, pipettes, test-tubes, flasks, gas-burners, etc.) as well as the more expensive and complicated equipment for general use. The extent of such general equipment will vary according to the size of the laboratory, but ideally it should be available even in a small laboratory employing a limited number of analysts. The following list may serve as a first rough estimate for a laboratory in its first stage of development :

(1) *For a team of up to 4 or 5 chemists*

- 1 sensitive analytical balance
- 1 small precision balance
- 1 torsion balance
- 1 ordinary balance
- 1 electrophotocolorimeter
- 1 pH-meter
- 1 set of Parr bombs
- 4 or 5 burettes
- 1 water-bath with several holes ; 4 circular water-baths for flasks

1 electric or gas oven  
 4 electric heating jackets, with regulations  
 1 small gas—or preferably electric—ignition furnace with electric thermocouple and millivoltmeter  
 Standard flasks ; standard pipettes  
 Kjeldahl flasks  
 1 set of thermometers  
 Extraction apparatus  
 1 steam distillation apparatus  
 Mechanical and magnetic stirrers  
 1 shaker  
 1 centrifuge  
 1 platinum crucible  
 1 platinum evaporating basin  
 10 ordinary Bunsen burners  
 5 small burners  
 2 Meker burners  
 Various supports ; bosses, clamps, etc.

(2) *Equipment for a team of up to 10 chemists (over and above (1) )*

1 potentiometric titration apparatus with a platinum electrode for oxidimetric titrations and a silver electrode for argentometric titrations  
 1 Fischer apparatus for determination of the water  
 1 Kofler bench : 1 apparatus for determination of melting-point (capillary tube method)  
 1 muffle furnace, with electric thermocouple  
 1 water-bath with thermostat (accurate to 0.1°C)  
 1 tablet disintegration machine

(3) *For general use, in laboratories of all sizes*

1 spectrophotometer (ultra-violet and visible light)  
 1 spectrograph for metal emission spectra with micrometric device for locating the lines  
 1 sensitive polarimeter  
 1 viscosimeter  
 1 refractometer  
 1 flame photometer  
 1 polarograph  
 1 vacuum pump  
 Chromatographic equipment (column paper, and electrochromatographic apparatus)  
 Simple installation for glass working  
 Small workshop

*Possibly :*

Infra-red spectrophotometer  
 Vapour-phase chromatographic apparatus  
 X-ray diffraction technique apparatus

(4) *Individual equipment may differ, but the following list gives an idea of what are basic requirements :*

Ordinary glassware ; beakers, Erlenmeyer flasks, round flasks, test-tubes, pipettes, burettes, small standard flasks, etc. ; porcelain, silica and nickel evaporating dishes ; crucibles for ignition, etc. ; funnels ; various crucible tongs, etc.

**Personnel of a pharmaceutical control laboratory (chemical and physical chemistry department)**

The chief of the service in the chemistry and physical chemistry department should be thoroughly grounded in inorganic and organic chemistry. As a chemist or pharmacist, he should be acquainted with the many fields of analytical chemistry and should also have adequate knowledge of current physico-chemical methods such as polarimetry, potentiometry and spectrophotometry. He must be a specialist in pharmaceutical chemistry and his knowledge should be completed by a good understanding of pharmacology and physiology.

The training of the analyst should be adequate and he should be proficient in the analysis of preparations which are described in the pharmacopoeia or other official books, i.e., medicaments for which assay methods have been established. He may have to work for several months in the pharmaceutical control laboratory before he can be of service and regularly obtain reliable results. After this training, he will be entrusted with the analysis of certain medicaments. Under the direction of the chief of the service, he will then learn to work out methods for separating constituents and choose the best way of assaying. After a number of months of this regular work and training, he should be able to solve by himself problems connected with the analysis of the more complex mixtures of drugs in their various pharmaceutical forms.

Administrative officers responsible for the organization of assay laboratories should understand the difficulties which the analyst may have to meet and remember that in many cases immediate results cannot be obtained. The analysis of a speciality often requires the development of a new method, and too much haste may lead to unsatisfactory situations. Moreover, analysts should be selected not only for their basic knowledge, but also for their ability to handle instruments.

The above description applies to qualified chemists or pharmacists. Laboratory technicians could also be employed under close supervision, and carry out certain operations such as distillations, extractions, assay in series, etc. They will not, however, be able to work out new techniques themselves as they will not have the necessary general scientific background. These laboratory technicians would make it possible for the qualified analyst to give more time to this work and also to undertake some research, which in the opinion of the Group is an excellent means of creating interest in his task and of producing satisfactory results.

It may be mentioned also that each member of the staff should have adequate pay, at least equal to that offered by the chemical and pharmaceutical industries, as otherwise the best elements may be absorbed by these industries.

**Fellowships**

Although in many countries the administration of food and drug control laboratories is under the same direction, it was pointed out that it is difficult for the same person to acquire within a limited period of time sufficient training in both the laboratory methods used in the control of pharmaceutical preparations and those used in the control of food. Fellows should in general devote their time to one of these branches of study, depending on their qualifications, experience and major responsibility in their future work. For instance, when a country is starting to establish a control laboratory, the person responsible may have to deal with both subjects, and therefore may have to study the most essential techniques in both; another instance is when the candidate is administratively responsible for both subjects, the actual technical work being carried out by separate personnel.

Fellows who are expected later on to carry out laboratory techniques should be given the opportunity to fit into the everyday routine work in the institute which they visit as fellows, and they should stay there for a number of months. Fellows who are interested mainly in the administrative and organizational side could limit their visits to these laboratories to a few days or weeks, and this applies also to experienced persons who would only wish, for instance, to learn or discuss differences of techniques or acquire a special technique in addition to the ones they have already mastered. The fellows should of course be sufficiently familiar with the language of the country visited.

**Control of pharmaceutical preparations at the time of manufacture**

It is realized that there are now so many pharmaceutical preparations offered for sale in most countries that the analytical staff of an official control laboratory cannot examine all of them within any reasonable period of time, e.g., one year. It is not anticipated that sufficient personnel will ever be available in even the most advanced countries to provide an adequate service for the analysis of every batch of every preparation sold. It is estimated, for instance, that in Canada there are 26 000 pharmaceutical preparations offered for sale. If only two batches of these are manufactured annually, 52 000 analyses, some of them very complicated, would have, in theory, to be performed each year by the government control authority. It is thus obviously impossible for complete laboratory control to be exercised by the official laboratories. The Group is of the opinion that under the circumstances, in addition to the work done at these laboratories, it is important to ascertain whether each pharmaceutical manufacturer is able to exercise an adequate control

over every batch of all preparations he offers for sale, in order that the public and the medical and pharmaceutical professions have adequate protection in respect of the safety and usefulness of the products offered to them.

It is therefore one of the most important functions of the authorities dealing with the examination of pharmaceutical preparations to arrange for the inspection of pharmaceutical manufacturing plants, with a view to ensuring that they have proper systems of control over their preparations, beginning with the raw materials, through the production stage and into the final pharmaceutical form. Control of the labelling, which may be considered as important as the analytical control at the laboratory, should be included.

There may be different methods of approach to the pharmaceutical manufacturer, and it is suggested that, following a survey of the manufacturing establishments in any particular country for the purpose of determining the extent of the problem, an educational approach should first be used to urge those manufacturers not having suitable control systems to install them as quickly as possible. Education may require detailed advice to the manufacturer as to what a suitable control programme should be. Repeat visits by the inspectors should then be made to ascertain to what extent the advice has been followed, and the necessary arrangements should be made in order to obtain the desired results.

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## Annex

## LIST OF SUPPORTING DOCUMENTS

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- Melnitchenko, A. & Senov, P. L. The use of chemical methods of analysis in the practical work of pharmacies in the USSR (WHO/Pharm/306)
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