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# THE QUALITY CONTROL OF PHARMACEUTICAL PREPARATIONS

## Report on a European Technical Meeting

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WORLD HEALTH ORGANIZATION

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# THE QUALITY CONTROL OF PHARMACEUTICAL PREPARATIONS

## Report on a European Technical Meeting

### INTRODUCTION

The European Technical Meeting on the Quality Control of Pharmaceutical Preparations opened in Warsaw on 29 May 1961. After an address of welcome by the Deputy Minister of Health of Poland, Dr F. Widy-Wirski, the meeting heard a statement by Dr Bukowski, Director of the Pharmaceutical Department, Ministry of Health and Welfare, Poland. On behalf of the Director of the WHO Regional Office for Europe, the Deputy Director, Dr J. D. Cottrell, then addressed the participants and gave a short outline of the work of WHO and the purpose of the meeting.

The meeting was called to discuss the application, under the conditions prevailing in different countries of the European Region, of the principles for quality control of pharmaceutical preparations drawn up by the Study Group on the Use of Specifications for Pharmaceutical Preparations held at WHO Headquarters in December 1956.<sup>1</sup> Its terms of reference were: to review briefly the general situation as regards quality control of pharmaceutical preparations in European countries; to examine and define the distribution of responsibilities for quality control; to study requirements for quality control; and to discuss the organization of services responsible for quality control and the training of the personnel required.

Dr S. Bukowski was elected Honorary Chairman, Dr H. Davis, Chairman, Professor W. Rusiecki and Professor L. Domange, Vice-Chairmen, and Mr A. Declerck, Rapporteur.

### 1. REVIEW OF THE GENERAL SITUATION REGARDING QUALITY CONTROL OF PHARMACEUTICAL PREPARATIONS IN DIFFERENT COUNTRIES OF EUROPE

Well over one hundred new pharmaceutical substances are placed on the market every year. In the past such substances have had an average life of two to five years, but the financial resources and considerable efforts.

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<sup>1</sup> *Wld Hlth Org. techn. Rep. Ser.*, 1957, 138.

devoted to research and the close competition between the various pharmaceutical firms and laboratories are tending to reduce this period. Most of the new substances employed in the composition of pharmaceutical specialities used throughout the world have been developed by a small number of countries. If the information on quality control and the introduction of new substances supplied by those countries could be co-ordinated by WHO, it should be possible to draw up general methods and specifications that can be used directly for quality control of pharmaceutical preparations.

The number of pharmaceutical preparations and specialities available to physicians and to the public varies greatly according to country, owing to a number of factors: the resources available, various types of restriction imposed by the authorities, currency difficulties, etc. Thus, in Belgium and in Switzerland there are over 15 000 different specialities on the market, whereas in Denmark and in Poland the figure is well under 2000.

### 1.1 Definition of "pharmaceutical preparation"

The meeting recommended the general use of the term "pharmaceutical preparation" in order to facilitate translation and interpretation and also to avoid confusion with addiction-producing drugs under United Nations control. The WHO Study Group on the Use of Specifications for Pharmaceutical Preparations<sup>1</sup> has given the following definitions:

"(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 Study Group believed that the above definition of a pharmaceutical preparation was better than one defining a drug as a substance named in an official list.

### 1.2 The problem of controlling new pharmaceutical preparations

National authorities responsible for the introduction and quality control of pharmaceutical preparations need adequate specifications for that

<sup>1</sup> *Wld Hlth Org. techn. Rep. Ser.*, 1957, 138, 14.

purpose. Some decades ago the problem of specifications could still be easily solved in most countries. Pharmacopoeias or similar handbooks gave official standards for most preparations sold, and there were relatively few additions to be made from year to year. Classical analytical methods requiring fairly simple equipment were officially accepted so that in most European countries pharmacists were able to analyse nearly all the pharmaceutical preparations on the market and were, indeed, able themselves to prepare many of the drugs given in the pharmacopoeias. Specialities were still very few and those that did exist were not often exported. Moreover, there was sufficient time for the specifications developed to be included in national pharmacopoeias.

Originally there had been no intention to restrict the contents of the national pharmacopoeias or to make them selective. The purpose of the definitions and specifications they contained was to make it possible to control the quality of the pharmaceutical substances and other preparations on the market. According to a WHO enquiry among various pharmacopoeia commissions, in the course of time the idea grew in some countries that drugs included in the pharmacopoeia were preferable to those that were not. The situation is at present dominated by the introduction of a large number of new substances, and of preparations and specialities containing several active ingredients, the quality control of which is a matter of considerable difficulty, calling in many cases for the use of new methods and equipment before these have even been described in official handbooks. Further, in preparations containing only one active substance the addition of inactive ingredients, dyes, stabilizers, etc., often makes analysis extremely difficult.

Obviously, therefore, specifications, monographs and annexes to national pharmacopoeias and other official handbooks are not adequate for complete control of the quality of pharmaceutical preparations on the market in a given country. As to the new substances and specialities offered to doctors or on sale in pharmacies, the quality control authorities are compelled in the first place to ask the manufacturers for specifications and methods of analysis. Moreover, in many countries the dispensing pharmacist very rarely controls the specialities he sells, and he would find it technically very difficult to do so.

As some pharmaceutical preparations are used for a short time only, it is often impossible to prepare specifications in time for the next issue of the national pharmacopoeia or corresponding handbook. It might therefore be an advantage if manufacturers, pharmacopoeia commissions or other authorities in charge of the quality control of pharmaceutical products could supply the necessary specifications to a co-ordinating agency, such as WHO, which would pass them on to the national authorities or professional organizations controlling the quality of these preparations as they are introduced for therapeutic purposes into different coun-

tries. The WHO Study Group on the Use of Specifications for Pharmaceutical Preparations, already referred to, proposed that "information sheets", giving the specifications received by the co-ordinating agency, might be distributed to various laboratories which would submit them to trial, the results to be discussed by correspondence and at technical meetings with a view to improving and facilitating quality control.<sup>1</sup>

### 1.3 International and industrial collaboration for quality control

Such a programme could only be effective with the support of the national authorities in charge of quality control, while the collaboration of all manufacturers would be essential, since they are the first to launch new pharmaceutical substances or preparations on the market. Useful work is being undertaken in this field by the International Pharmaceutical Federation, which organizes annual meetings of experts from a number of countries on the quality control of pharmaceutical preparations.

Whatever might be done to secure satisfactory quality control in official laboratories and in pharmacies, it is not possible to submit all batches manufactured to such control, except for some antibiotics in certain countries, and preparations such as insulin. Consequently, manufacturers must themselves carry out adequate quality control of all batches for sale to the public and to hospitals, and of all samples delivered to physicians. Means of ensuring control at the time of manufacture vary from one country to another. It was suggested to the meeting that certain general principles could be applied within the framework of present-day legislation, in order to introduce a certain degree of uniformity between countries as regards labelling, the use of international non-proprietary names and the classification of pharmaceutical preparations. The resolution adopted by the Seventeenth General Assembly of the International Pharmaceutical Federation in Brussels in 1958 is of interest in this connexion:

"Whereas there are, in different countries, wide divergences in the regulations governing poisons intended for therapeutic use—divergences which tend to cause serious complications in the supply of medicaments to the public;

"Whereas the World Health Organization is already engaged in preparing and establishing useful specifications, such as those of the International Pharmacopoeia, for the purpose of facilitating on the international plane the examination, analysis and the dispensing of medicaments;

"1. The International Pharmaceutical Federation expresses the wish that the WHO will be able, as suggested by a study group of WHO set

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<sup>1</sup> *Wld Hlth Org. techn. Rep. Ser.*, 1957, 138, 12.

up to examine the use of specifications for pharmaceutical preparations, to undertake a study with the object of obtaining uniformity in the principles of classification of toxic substances used in therapeutics in the different countries.

“ In particular, it would be advantageous to study the possibility of establishing a list of toxic substances used in therapeutics in respect of which proposals on labelling and supply to the public might be made to the Governments of the different countries.

“ 2. The International Pharmaceutical Federation offers to collaborate in these tasks and to make available its experience of questions concerning the supply of pharmaceutical preparations.”

#### **1.4 National control authorities**

The meeting also discussed problems connected with the introduction of pharmaceutical preparations, the setting up of a national control authority, and the training of qualified personnel for pharmaceutical control.

Some participants described the pharmaceutical control systems in their countries. In France, new legislation has been passed introducing the licensing of drugs and setting up a council, the members of which are selected from a list of State-designated advisers, to examine the new preparations and assess their “ therapeutic value ” and safety before they are placed on the market. In Belgium a recently-established board also investigates the therapeutic value of drugs already on the market or about to be marketed. In the USSR the control of pharmaceutical preparations takes place in three stages : (1) control at the time of manufacture ; (2) control on sale ; (3) control by special State institute. Each plant is responsible for the quality of its products, and in every plant there is a fully autonomous control unit with adequate laboratories and qualified staff. Control unit laboratories analyse every batch of raw material (active ingredients and excipients) and every batch of finished products to make sure they are up to the standards of the USSR Pharmacopoeia or other official specifications. The control unit supervises the manufacturing process by carrying out inspections in the various factory departments.

## **2. RESPONSIBILITY OF PHARMACEUTICAL MANUFACTURERS**

The meeting accepted the principle that pharmaceutical manufacturers must take the main responsibility for the quality of the preparations they produce since they are in the best position to do so. It was further agreed that laboratory analyses and other forms of control by governments or

their recognized agencies are also necessary to reveal any mistakes that might have occurred and as an additional safeguard in preventing unsatisfactory or dangerous products from reaching the physician or being used by the public.

It was pointed out that it is a difficult or even impossible task for a government control laboratory to examine and analyse completely every batch of every pharmaceutical preparation on the market. The number of pharmaceutical preparations in one country might run into thousands and include combinations of two or more active ingredients, sometimes presenting difficult analytical problems. There are other factors that affect the safety and effectiveness of pharmaceutical preparations, such as the pharmaceutical form in which they are presented and their stability. There is also the question of the safety and inertness of the excipients or vehicles.

The pharmaceutical manufacturer is in a position to prevent mistakes by adequate care in the various manufacturing procedures and he has the first opportunity to detect any mistakes that occur by analysis in his own control laboratory. The quality of a pharmaceutical preparation depends on the purity of the materials used in its formulation, the care with which the ingredients are measured, and the precision with which they are mixed. Care must also be taken to ensure that the correct labels are used and that the final container and package are suitable for their purpose.

All these necessary procedures for the production of pharmaceuticals of good quality can be controlled by the manufacturer. He alone is in a position to check the identity and purity of the raw materials purchased and to keep a constant check on every step in the manufacturing and packaging processes for every batch produced.

The most important factors in consistent production of satisfactory pharmaceutical preparations are (1) a good system of control by the manufacturer, implying rationally organized and systematic procedures with strict rules in force at all times, and (2) the employment of adequately trained and experienced quality control supervisors, who are conscientious and alert, as well as thoroughly familiar with manufacturing procedures and aware of the dangers involved in mistakes. In addition to control of the manufacturing processes, the manufacturer must exercise analytical control, when necessary, at the various stages of production. Analytical control of the finished product is, of course, indispensable, and samples should always be taken from products that are ready for distribution.

It should be noted that the director of control should be responsible for all forms of control over raw materials, products in course of production, and finished products. He should not be under the supervision of the production manager, but should be responsible only to the top management of the company.

Another requirement for the satisfactory production of pharmaceutical preparations is the cleanliness and tidiness of the premises in which they are prepared. Well-kept premises, good organization with strictly enforced rules, well-trained and conscientious personnel and the quality control described above, will ensure the production of reliable pharmaceutical preparations.

The manufacturer is also in the most favourable position to assess the stability of his products because of his knowledge of the ingredients and the manufacturing procedures used, and because he can check their stability by laboratory tests on a number of batches under controlled conditions.

No government or external laboratory can exercise such close control over pharmaceutical preparations as the manufacturer. However, periodic inspection by qualified and experienced government inspectors can reveal a great deal about the control facilities and the manufacturing procedures and personnel. Naturally, inspection of manufacturing plants is not always possible if the plant is located in another country. This difficulty could be largely overcome if various governments adopted adequate but not necessarily identical standards of inspection and other control methods. If this were done, pharmaceuticals of foreign manufacture could be treated by government control agencies on the same basis as those manufactured in the country. A suitable pattern of inspection and other controls acceptable to a number of countries would reduce the amount of laboratory work now necessary for the adequate control of imports from those countries.

During the discussion it was noted, in particular, that manufacturers who have the financial resources usually maintain excellent production and analytical controls and that they consider both forms of control to be necessary. Among the smaller manufacturers there are undoubtedly some who cannot afford the cost of proper equipment and personnel to carry out wholly satisfactory control procedures in their own premises. It was pointed out that such manufacturers could engage outside laboratories to perform analyses and other assays on their products.

Imported pharmaceuticals were said to present a particularly difficult problem for government control laboratories because of the lack of knowledge of the manufacturing and analytical control procedures employed by the producers and of the control standards laid down in the country of manufacture.

It was also stated that some manufacturers are attaching increasing importance to manufacturing or processing controls which, it was believed, might have equal or even greater value than analytical controls in ensuring the consistent production of dependable pharmaceutical preparations.

It was noted that some manufacturers might object to the inspection of their plants by government officers, and that inspectors would need to have exceptional qualifications to be able to inspect manufacturers'

control procedures without interfering to any extent with the normal running of the plant being inspected. Inspectors would also need to have sufficient personal ability to win the respect of the technical and scientific personnel in the industry.

### 3. ESTABLISHING THE SAFETY OF NEW PHARMACEUTICAL PREPARATIONS PRIOR TO SALE

#### 3.1 Pharmacological properties

Attention was drawn to differences among the various animal species in their sensitiveness to drugs, and to the great difficulty of extrapolating to man the results found for animals. Moreover, while the pharmacologist generally gives the drug being investigated to a healthy animal, the doctor administers it to a sick person whose internal and excretory organs are often malfunctioning. To offset such difficulties attempts have been made to reproduce diseases experimentally in animals, but as this is not always possible, man has often to take the place of the experimental animal, even though there are many objections to this course.

When commencing pharmacological trials of a new drug it is important to make a thorough study of toxicity. This should include the determination of: (a) acute toxicity; (b) subacute toxicity; (c) chronic toxicity; and (d) local tolerance.

Attention was drawn to the need to achieve agreement between the methods used in industry to establish drug toxicity and those used by government authorities. WHO could play a useful part in proposing and advising on methods that could be applied more generally.

In the Soviet Union all new pharmaceutical preparations have to be submitted to very strict toxicity tests on various animals. Compulsory requirements to which new drugs have to conform are drawn up by the Pharmacological Committee of the Ministry of Health, and the drugs are controlled in government institutes and laboratories.

#### 3.2 Experimental procedures

It was pointed out that while administrators want to establish set patterns of pharmacological procedures in studying new products, pharmacologists have strong reservations as to the value of such compulsory experimental procedures. Drugs, even those belonging to the same pharmacological series, differ too much to comply fully with the same standards. Therefore, the assays should not be made too rigid or standardized, and should be capable of modification or adaptation as circumstances require. With this reservation in mind, it is nonetheless desirable to have standard

assay procedures available to ensure at least some measure of comparability. Such procedures are already being worked out in a number of countries.

### 3.3 Side effects of new pharmaceutical preparations

It was agreed that while drugs are usually given to patients for one specific purpose, nearly all drugs produce more than one effect. From the doctor's point of view, any effect other than the one needed for the treatment of his patient may be regarded as a "side effect"—for example, the drowsiness produced by an antihistamine given to treat an allergic condition. Side reactions are often observed during the animal screening of new drugs. This information should be passed on to the clinician when he is asked to carry out clinical trials.

The problem of undesirable side effects must be given full consideration. Whereas the side effects of a particular drug might be serious enough to make it unwise to use it for the treatment of a trifling illness, it might be permissible, knowing the risk, to prescribe the same drug for a more dangerous disease for which it is known to be a specific remedy.

### 3.4 Safety

It was emphasized by several participants that from country to country there is no uniform procedure for the study of drug safety. It is therefore most important that WHO should take up the problem of establishing internationally acceptable standards of drug safety. WHO should also make recommendations on methods of examination and control of drug toxicity.

The Canadian Food and Drug Regulations<sup>1</sup> define a "new drug" as one that "because of its

- (a) composition,
- (b) method of manufacture,
- (c) dosage, or
- (d) route of administration

is not generally recognized by persons qualified to evaluate the safety of the drug as safe for the use for which it is proposed or recommended . . . " However, for the purpose of implementing legislation on new preparations, no satisfactory answer appears yet to have been given to the question "When does a drug cease to be new?"

It was pointed out that it is difficult to give an adequate definition of "safety" and that this might lead to unwarranted condemnation of manufacturers. The usual definitions are all negative, yet to define "safety"

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<sup>1</sup> Canada, Ministry of National Health and Welfare, Food and Drugs Act, Food and Drugs Regulations section C.01.301, as amended 29 December 1960 (see *The Canada Gazette, Part II*, 1961, 95, 33).

as "absence of toxicity" is as unsatisfactory as to define "health" as "absence of disease".

It was recognized that there is no such thing as a safe drug; and even placebos can give rise to accidents. Everything depends on the dosage and the conditions under which the drug is given, as Claude Bernard showed in his study on "foods, poisons and drugs". Indeed, for some serious diseases, such as cancer, very dangerous drugs have to be used, such as nitrogen mustard, in which cases there can be no question of safety.

In France "safety under normal conditions of use" is specified, but the meeting felt this to be insufficient because abnormal conditions could occur in which the use of a drug was justified—for example, when doses that under normal circumstances would be considered toxic are given in an attempt to save an otherwise hopeless case.

It was agreed that the use of a drug always involves risk. It is the physician's responsibility to be aware of the possibilities, even remote, of danger in the use of a drug in particular cases. That is why it is so necessary that directions for use should include a statement of undesirable side effects, contra-indications and possible dangers.

It was proposed that a later meeting might consider the selection of a more suitable term than "safety" or the addition of some qualifying phrase.

#### 4. METHODS FOR THE EXAMINATION AND ANALYSIS OF PHARMACEUTICAL PREPARATIONS

##### 4.1 Official methods

For products described in the pharmacopoeias, the methods laid down there automatically become official.

In the case of a new substance for which a request for registration or a licence has been filed, if the substance is not described in any handbook of specifications, the method proposed by the manufacturer can be considered as official, provided the state laboratory recognizes its validity.

For ill-defined pharmaceutical preparations—for example, some biological or vegetable preparations—the issue of official methods would seem to be necessary.

In order to carry out their assays efficiently, official laboratories should obtain from manufacturers samples of the various ingredients making up the pharmacological preparation in question.

##### 4.2 Analytical methods used by the manufacturer

Firms producing new pharmaceutical preparations generally make every effort to use starting materials of irreproachable quality and to manu-

facture pharmaceutical specialities of adequate stability. Generally, too, the physicochemical characteristics of new substances introduced into therapeutics have been sufficiently well studied to allow their identification and assay in pharmaceutical preparations, provided that they can be extracted quantitatively.

A manufacturer who has a thorough knowledge of his raw materials and good supervision of his manufacturing processes may be able to use simple non-specific tests on the finished product to prevent gross errors and detect mistakes in manufacturing. However, when analytical control is a legal requirement the producer must attempt to devise accurate analytical methods for his pharmaceutical preparations to ensure their acceptance and to guarantee their quality.

#### 4.3 Need for standardization of methods

In considering the need for uniformity in methods of analysis a number of points ought to be remembered. (1) The methods given in different pharmacopoeias often vary, but even minor modifications in the same method may give significantly different results. (2) It is most important to both manufacturer and control agency to use the same analytical method for any particular product. (3) International standardization of methods is desirable in the interests of international trade, which is expanding greatly through the establishment of economic communities and common markets.

In connexion with the above considerations uniformity of preliminary tests should be given special attention. Standardized methods should be used and precise limits of tolerance laid down, in particular in respect of the following :

(1) Weights of tablets and powders : number of units to be used and permitted tolerances.

(2) Disintegration time of tablets and dragées : composition of the different test media to be used ; precise description of the equipment indicating intervals, if any, between periods of agitation ; time limits.

(3) Clarity of injectable solutions : careful description of how the test is to be performed (black background and/or white background—position of the light source), taking into account possible ocular fatigue on part of operator ; limits of tolerance.

(4) Volume contained by ampoules, with and without taking into account the amount of liquid adhering to the walls ; limits of tolerance for non-viscous and viscous liquids.

(5) Hardness of tablets : description of methods and limits of tolerance.

(6) Melting point of suppositories: exact description of the method to be used.

(7) Number of drops per millilitre for dropping bottles and for droppers enclosed in packings.

In addition, consideration should be given to specifications for sterility tests, tests for pyrogenic and histaminic substances, and determination of acute toxicity.

It has to be remembered that certain products may deteriorate and it is therefore necessary to fix sufficiently broad limits to ensure the effectiveness of the drug within the period of use laid down. Further, uniformity is desirable in the use of additives, such as colouring matter, sweetening agents, preservatives, antiseptics, and oxidizing and reducing agents, permitted by different countries.

In comparison with physical or chemical methods, biological methods are difficult to standardize, but as far as possible, international agreement should be reached on methods for assessing the potency or safety of biological products, vegetable preparations, and other ill-defined substances.

#### 4.4 Modern physicochemical methods of control

Most modern pharmacopoeias include methods available as a result of the more recent scientific and technical developments—for example, paper chromatography, ultra-violet spectrography and the Karl Fischer moisture determination procedure. Official laboratories concerned with the quality control of pharmaceutical preparations are often forced to go further than the requirements of modern national pharmacopoeias since the control laboratories of the pharmaceutical industry are nowadays usually outstandingly well equipped and staffed by well-trained specialists. They have at their disposal physicochemical methods that are appreciably more sensitive than the conventional pharmacopoeia methods and frequently offer the only possibility of determining the identity, purity and composition of a medicinal substance with sufficient accuracy. Where such procedures are used by the manufacturing and pharmaceutical laboratories, they must also be available to the official control laboratories.

The use of highly sensitive physicochemical methods nevertheless involves several problems. Their sensitivity may be so great that impurities are detected in every drug, as happens, for example, in gas chromatography and infra-red spectrography. It is then necessary to define acceptable tolerances for the less demanding requirements of the pharmacopoeia.

Another problem is that of staff. The proper use of complicated technical equipment necessitates special training and qualifications. Pharmaceutical studies are generally all too limited where technical analysis is

concerned and it is therefore difficult to find pharmacists sufficiently well qualified. For an analytical laboratory with modern equipment, the best solution is to employ someone who can also deal with the very important question of the statistical evaluation of analytical results.

The traditional methods of analysis and assay, such as gravimetric, volumetric, titrimetric, alkalimetric, acidimetric, bromometric or iodometric analysis, remain an essential and firm basis for any general analytical laboratory. From these procedures micro- and semimicro-chemical methods have been developed that make it possible to work with only minute amounts of substances, many of which are extremely expensive.

New theories and analytical methods have been worked out. For instance, an extension of Arrhenius' hypothesis on the dissociation of acids and bases has led to the introduction of protometry or titration in a non-aqueous medium, by means of which certain alkaloids can be assayed. Similarly, complexometry and chelatometry have become routine methods in control laboratories.

Chromatographic methods have given a new impetus to qualitative analysis. The various applications of those methods (on plates, columns or paper; ascending, descending or circular chromatography) afford a means of distinguishing between several products in a mixture, and are very valuable for identifying colouring matter, amino-acids, vegetable dyes and products with very closely related physicochemical properties, e.g., the sulfonamides. Using these methods, it is also possible, by means of successive fractionation, followed by elution, to assay several compounds of the same chemical group in a mixture, as well as products resulting from the deterioration of certain organic substances. More recently, vapour-phase chromatography has opened up a completely new field of research in analysis, since it enables essential oils and volatile products to be identified, substances that it was almost impossible to detect in pharmaceutical preparations by the traditional methods.

Physicochemical methods of analysis are being used more and more in the laboratory. Potentiometric titration has been employed for a considerable time, as also have colorimetric and spectrophotometric methods. These have been supplemented by flame spectrophotometry and above all by improved spectrophotometric methods, using instruments with a range extending from short-wave ultraviolet up to infrared rays. Despite the high price of the equipment required for infrared spectrophotometry, this extremely valuable technique is becoming more and more widely used in analytical laboratories, and is prescribed for many substances in the latest edition of the United States Pharmacopoeia.

Dropping-mercury electrode polarography and oscillopolarography, which make it possible for the analyst rapidly to form a general picture in drug analysis, are being applied to an ever-increasing extent in the pharmaceutical industry.

#### 4.5 Biological and bacteriological methods of control

Biological, microbiological and bacteriological methods differ essentially from chemical and physicochemical methods in that they make use of living matter. They often have a wider margin of error than the physicochemical methods but are generally very specific.

Biological methods are employed in the examination of insulin and certain hormones, vitamins, coagulants, anti-coagulants, hypotensives, hypertensives, and cardiotonic glycosides. It is often useful to supplement them by chemical determinations. Bacteriological methods are used for the control of products of bacterial origin, yeasts and lactic ferments, for measuring antiseptic power, and also for checking sterility. Microbiological methods are indispensable for checking the activity of certain vitamins and antibiotics and for some time they have been used for assaying trace elements. Mention must also be made of the assay of enzymes, methods for the control and standardization of which are now being studied more carefully and systematically, and of the measurement of cellular respiration in connexion with products intended to activate such respiration. Other biological tests, such as those for pyrogenic or histaminic substances and the determination of acute toxicity have already been listed as preliminary tests.

Generally speaking, methods of control are becoming more and more sensitive and precise. This may result in more and more stringent requirements that do not correspond to medical necessity. A practical, common-sense approach must therefore be adopted, if only to prevent unnecessary increase in costs.

#### 4.6 The need for new methods of quality control

The new drugs that are constantly appearing on the market are presented in a variety of pharmaceutical forms. These often contain very complex substances, such as solvents, binders, preservatives, colouring matter, etc. Analysis of these new preparations presents many difficulties, especially when the active constituents of the various pharmaceutical forms have to be isolated or their purity, identity, concentration, safety, etc., determined. These difficulties can be overcome, however, if full use is made of modern analytical techniques. Where chemical analysis is no longer adequate for drug examination, spectrographic, chromatographic and electrometric methods are available. There is, in fact, no limit to the range of analytical methods that can be used in drug control.

Again, whereas no real control of the organo-therapeutic products was formerly possible, the animal origin of some of these products can now be detected by serological tests, even when they are included in complex preparations, provided that the cells have not deteriorated. In this way,

adulteration or gross error can be excluded. There is a hope that it may become possible to identify the organ which was used to produce the organo-therapeutic product and this would constitute a new step forward.

Mention must also be made of automation, which is particularly valuable in the routine control of pharmaceutical preparations, for example, the use of recording spectrophotometers and potentiographs for titration in non-aqueous media. In another field, a photoelectric apparatus has been developed for automatic bacteria counts, and for determination of the size of small particles.

The meeting also stressed the need for new methods and improvements in known methods to be published as rapidly as possible in order to avoid useless research in laboratories.

## 5. THE NEED FOR COLLABORATION

It was pointed out that the great number of publications relating to the introduction of new drugs and the quality control of pharmaceutical preparations make it practically impossible, even for the best equipped control laboratories, to be familiar with all the new developments in this field. To help overcome this difficulty, the Specialities Commission of the International Pharmaceutical Federation has been bringing together control-laboratory directors from some countries to enable them to compare their experience.

New drugs are often introduced into several countries simultaneously. The control laboratories in each of those countries should, at the time that the drug is put on the market, be in possession of the suitable analytical method developed by the manufacturer for the preparation.

In some countries a useful liaison is maintained between the control authorities and the pharmaceutical manufacturers, facilitating an interchange of knowledge on scientific and technical matters. A formal arrangement for the interchange of information can be made by establishing joint committees of scientists from industry and the control authorities. A discussion of new methods of analysis is an important function of such committees, so that when new pharmaceutical preparations are introduced the control authority has knowledge of the proper methods for their analysis. Such liaison between industry and the control authorities exists in a number of countries without loss of respect for the control authorities and without prejudice to the manufacturer's legitimate secrets.

It is certainly important to the manufacturers that the control authorities should be well acquainted with the methods of analysis for new preparations, so that they can be speedily analysed when introduced on the market and so that the results obtained by the two groups should be in good agreement.

### 5.1 Information sheets concerning new pharmaceutical preparations

The kind of information to be included on such sheets was described by several participants and reference was made to the report on this subject by the WHO Study Group on the Use of Specifications for Pharmaceutical Preparations.<sup>1</sup>

A number of countries now require by law that a manufacturer submit to the control authorities information similar to what would be required on such information sheets, besides much additional material, before a new pharmaceutical preparation can be put on the market.

The aim of the information sheets would be to avoid official laboratories in various countries having to do complex research to establish the chemical structure or the physical or chemical properties of new pharmaceutical preparations. Whatever the scientific interest of such work might be, it is obviously a waste of time and money for several official laboratories to carry out the same research at the same time on the same substance or the same mixture, particularly when such research has already been carried out by the manufacturer.

The meeting believed that documents already exist giving data similar to those that would be required for the information sheets. Such documents are intended essentially to give confidential data to the health authorities of the various countries where the registration or the acceptance of pharmaceutical preparations is compulsory. They give proof that the new drugs or preparations can be identified and controlled, are of satisfactory quality and have a known pharmacological effect.

Some participants expressed legitimate fears in regard to the dissemination of such information on an international scale. The meeting concluded that documents addressed to administrative bodies with whom a registration request was deposited should be considered as confidential and not be disseminated. On the other hand, information sheets will be of real interest only if they are rapidly disseminated, and to wait for the registration procedure would cause delay. Furthermore, the manufacturer quite rightly does not like to see all the information given made public. The following possible solution was therefore suggested:

As soon as possible (preferably when requesting registration) the manufacturer should send to WHO the maximum information on a new preparation compatible with his own legitimate interests. The information sheets used for this purpose need not be so complete as those sent in to support a registration request.

The official laboratories should also express their views on the contents of the information sheets submitted by the manufacturer—for example, they might suggest standards or control methods proved in their

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<sup>1</sup> *Wld Hlth Org. techn. Rep. Ser.*, 1957, 138, 12.

experience to be satisfactory for a number of commercial products, or they might indicate modifications or improvements in the information supplied by the manufacturer. Such changes ought to be made in agreement with the industrial laboratories.

The sheets should give mainly analytical technical information, with some pharmacological data and information on therapeutic action.

With respect to the technical information it was emphasized that the following aspects should be given particular attention in any study of the problem: (1) qualitative and quantitative composition; (2) method of preparation; (3) physical and chemical properties; (4) methods of identification and assay. With respect to pharmacological and therapeutic information the following aspects should be dealt with: (1) mode of presentation: tables, suppositories, etc.; (2) therapeutic indications and side effects, contra-indications; (3) dosage for adults and children; (4) storage conditions and possible storage limits.

## 6. QUALITY CONTROL OF PHARMACEUTICAL PREPARATIONS AT THE TIME OF DISPENSING TO THE PUBLIC OR DELIVERY IN HOSPITALS

The meeting emphasized that no pharmaceutical preparations, not even those normally considered as analgesics, should be supplied to the public without some supervision.

The question of the dispensing pharmacist's responsibility is open to debate: in some countries he is responsible only for storage and issue, whereas in others he is responsible for the quality of the drug as well.

It is clear that the dispensing pharmacist can act as an effective buffer in controlling the issue of some drugs that might adversely affect the consumer's health. What is important is that, in one form or another, inspection and quality control of a drug should take place at a stage immediately prior to its issue to the patient.

The responsibility of the hospital pharmacist for all medicaments received or prepared in his department was stressed. This responsibility begins with the receipt of the starting materials or prepared medicines and extends throughout manufacture and storage of the preparations until issue. Even beyond that it is clearly the pharmacist's duty to ensure that medicines dispensed are sufficiently stable to last until administered to the patient. This responsibility obviously necessitates a study of the stability of the drugs and of the containers and conditions in which they are stored.

It was agreed that, although the amount of control exercised must depend on the type of hospital and facilities available, there are many simple and inexpensive tests that can provide a minimum of control. Thus, starting materials can be identified by melting point determination and various other simple identity tests. Each unit prepared from a batch should be marked with the batch number, so that its origin can be traced if necessary.

Another point emphasized was the need for adequate checks on procedures throughout manufacture—checking of formulas and weights, recording and supervision of all procedures, supervision of apparatus, etc. Records must be kept to enable the history of the preparation to be retraced right up to the time of its use.

The need for more elaborate chemical and physical tests during manufacture and for control of the finished product must depend on local circumstances.

In general, pharmacological, bacteriological and pyrogen tests are best performed by an independent laboratory. It might not be essential for such tests to be carried out on every batch, but every hospital pharmacy should be able to refer preparations to a laboratory for tests of this kind should the need arise.

Attention was drawn to the control and safety scheme used in Danish pharmacies,<sup>1</sup> a report on which was given by Professor S. A. Schou to the General Assembly of the International Pharmaceutical Federation in 1960. This scheme, which comprises a series of relatively simple and inexpensive tests devised by Reimers, Ilver & Thomsen,<sup>2</sup> was adopted voluntarily, but has since become compulsory. It has now also been adopted in Norway and forms the basis of a similar scheme in Sweden. With such a scheme in use it is considered permissible for the individual pharmacist to limit his control to checking the identity of the substance.

It was stressed that the hospital pharmacist must bear full responsibility for the quality of the preparations issued by his department. In the case of drugs supplied by firms he knows to be reliable, it might not be essential to carry out full analyses. The pharmacist must rely not only on his professional training and experience but also on his common sense, and must not impose so many controls that the supply of drugs to patients is delayed or their cost increased too much.

It was also pointed out that if hospital pharmacists manufacture on a large scale they should carry out controls similar to those undertaken by pharmaceutical manufacturing firms.

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<sup>1</sup> Schou, S. A. (1960) *J. mond. Pharm.*, **3**, 252.

<sup>2</sup> Reimers, Ilver & Thomsen (1959) *Arch. Pharm. Chem.*, **66**, 1183-1214.

It was noted that the Danish scheme for identifying starting materials is so simple and inexpensive that it could well be adopted generally without much increase in the cost of drugs or in the work of hospital pharmacists. It was emphasized that, if the pharmacist purchases ingredients of pharmacopoeial quality for the manufacture of pharmacopoeial preparations, the resulting product can be expected to be of the required strength and quality.

## 7. LABELLING OF PHARMACEUTICAL PREPARATIONS

### 7.1 Purpose and forms of labelling

The meeting considered that the purpose of labelling was essentially to allow identification and, where necessary, re-issue, besides making clear to the consumer the proper way in which the medication should be used. It was pointed out that labelling regulates the distribution and use of products which, although they might relieve and cure, are also liable to be dangerous if they are taken or administered by mistake or in an incorrect manner. Since the distribution of medicinal preparations between certain European countries will shortly be freed from all restrictions, there is an urgent need to consider measures to standardize rules for the labelling of medicinal preparations in the interests of the consumer's safety, at the same time bearing in mind the commercial interests of the manufacturers, in so far as they do not run counter to those of the consumer.

Labelling performs the important function of giving information to the chemist responsible for distributing the drug, to the doctor and his medical assistants who have to supervise its administration, and to the patient himself and his family. It was agreed that the labelling should be adequate and leave no doubt as to the nature of the preparation and its constituents. It must also allow accurate judgement as to the danger of utilizing the product in the absence of any medical prescription.

All participants were firmly of the opinion that labelling must provide appropriate instructions as regards dosage and route of administration, so as to ensure the proper use of the preparation. Attention was drawn, in particular, to the risk of children being poisoned as a result of confusing medicinal preparations with food or sweets and to the need for including on the label a warning such as: "To be kept out of reach of children." It was also noted that the presentation and labelling of medicinal preparations should enable them to be clearly distinguished from household and cleaning products.

A distinction was drawn between industrially manufactured drugs distributed on a large scale, and those individually prepared on medical prescriptions at a dispensing pharmacy or at a hospital. Labelling regulations for the latter differed somewhat from country to country and their international standardization did not offer any advantage. Some participants pointed out that doctors did not always wish their patients to know what kind of drug they were prescribing. Provision should be made for a good deal of flexibility in the regulations for labelling such preparations.

In some countries the label only gave the name of the pharmacist and the number on the dispensary register, which was also entered on the medical prescription. In other countries, the ingredients were shown on the label. The information was sometimes given in Latin.

The participants decided to confine discussion to the labelling of industrially manufactured drugs. They regarded the labelling of pharmaceutical preparations as a special means of conveying information and desired that such information, which was of major concern to public health, should not lose any of its import in the course of distribution and that no shadow of doubt be left at any stage as to the drug's proper use. The rules for presenting the information should be simple in the extreme and exclude any possible ambiguity of interpretation.

Attention was drawn to the danger of labels intended to promote increased consumption of the drug, and acting as a form of commercial advertising. It was also pointed out that some receptacles are difficult to label because of their small size. The label should enable the contents to be identified, and it was agreed that where this difficulty arises, the minimum information given should include the nature of the drug, its concentration and its batch number, so that the exact origin can be traced in case of accident. The dosage could also be given in so far as the size of receptacle allowed.

## **7.2 Use of international non-proprietary names**

Several participants stressed the value of the publication by WHO of proposed international non-proprietary names for pharmaceutical preparations and said that in their countries these names were already being adopted in the pharmacopoeias. In the USSR, a large number of exported drugs have the international non-proprietary name on the label. The increasing international trade in pharmaceutical preparations would appear to make such an indication on the label a necessity. It was pointed out that the use of other non-proprietary names would be liable to give rise to confusion. The use of the international non-proprietary names would also be helpful for medical and pharmaceutical teaching. The meeting therefore agreed that, where a non-proprietary name has been proposed by WHO, it should be indicated on the label in addition to the trade name

of the manufacturer and that the indication should be made in very clear characters.

### **7.3 Composition and route of administration**

The participants favoured inclusion of the quantities of active ingredients on the label. It was recognized that in certain cases the quantity of the excipients should be given when these affect the way in which the drug acts.

The participants believed that the labelling should give the pharmaceutical form and route of administration, especially as in recent years the number of forms and the possible routes of administration had increased.

### **7.4 Storage indications**

The participants were of the opinion that no pharmaceutical preparation could be stored indefinitely and believed that the manufacturer should state the date-limit for use on the label, either in code or openly, according to the circumstances.

### **7.5 Indications as to conditions of sale**

As conditions of sale by the pharmacist might vary, the meeting felt that, for the pharmacist's benefit, it would be best for some indication to be given on the label as to the category to which the preparation belonged. It was pointed out that an indication of that kind, drawing attention to the need for a doctor's prescription or prohibiting renewal, also provided the pharmacist with justification for refusing it to a patient.

### **7.6 Indication of origin**

The meeting considered it essential that the labelling text should include the name and address of the responsible manufacturer as well as the drug licence registration number. Finally, the batch number of the drug is necessary for tracing its origin in case it should be suspected of giving rise to some accident. An indication of this kind would enable inspectors to exercise more effective control and to take any measures necessary for protection of the public health with due regard to the manufacturer's rights.

The indications for use of exported drugs should be given in the language spoken in the area where they are to be sold.

## 8. INSPECTION OF INSTALLATIONS FOR THE MANUFACTURE OF PHARMACEUTICAL PREPARATIONS

It was pointed out that, in general, there are two kinds of control organization: (1) where the inspection departments and control laboratories come under a single government body; (2) where the inspection departments come under the public health service but the control laboratories are independent (the inspector sending the samples he has taken to them). In either case factory inspection can be an important function of the control organization.

The purpose of inspection is to protect the public health against poor quality products due to badly organized manufacture, possibly connected with a lack of qualified staff, poor working methods, or inadequate control within the factory.

### 8.1 The training of inspectors

The inspectors should have a university education, an extensive knowledge of manufacturing processes and of methods of controlling starting materials and finished products, including practical experience in that field, as well as a thorough knowledge of organic synthesis, pharmaceutical techniques and, in particular, of modern physicochemical analytical methods. They must also understand sampling principles and statistical methods of production control. They must have free access to all factory departments.

The inspector must be prepared in certain cases to act not only as controller but also as adviser, and must be in a position to answer questions relating to the fields previously referred to. Above all, he should inspire confidence and respect.

The industry can assist in the further training of inspectors who have had insufficient experience by giving them the opportunity to work in their plants.

### 8.2 Safety controls

It should be noted that even when the manufacturer has done all he can to ensure that production is covered by adequate controls, there is no such thing as absolute safety. All that can be asked of the manufacturer is to take such measures as will ensure the maximum safety. Whatever form the organization of internal controls in the factory takes, one of the best known guarantees of safety lies in the selection and training of the factory staff.

The statistical methods usually employed in the engineering industry cannot always be applied to the pharmaceutical industry. A manufacturer can only be asked to carry out reasonable checks of sufficient flexibility to meet individual cases. A comparative assay of toxicity can, under certain circumstances, provide useful information beyond that obtained from the regular physicochemical assays.

Starting materials ready for use, products in course of manufacture, and completed products can be sampled and any batch considered as suspect by the inspector should be controlled using statistical methods of sampling. The manufacturer should retain a certain number of units from each lot for later control in case of need.

### 8.3 Inspection in different countries

In Italy there are a large number of factories and the problem is to have enough inspectors to maintain regular visits. Regular inspection is, however, particularly necessary in the case of small factories which are unable to provide such satisfactory guarantees as large plants.

In Germany, each manufacturer is responsible for what he produces and new legislation is being considered which would require that a pharmacist or a pharmaceutical chemist should be in charge of control.

In Switzerland, there is no federal legislation on this question, and the cantonal authorities are responsible for inspection.

In Austria, all the inspectors are pharmacists.

In Belgium, there is control of pharmaceutical products, but not of starting materials, unless they are intended for factory processing.

In France, there is an inspectorate attached to the Service de la Pharmacie under the Ministry of Public Health. As elsewhere, there is a shortage of trained staff, and new legislation provides that the Ecole nationale de la Santé, should organize a year's course to give special training to inspectors in the industry.

In Canada, the inspection system has made it possible in many cases to assist manufacturers in improving their standards. Standard forms are used for recording information on different manufacturing plants and this has facilitated the inspector's work. In the case of new preparations, it is particularly important for control procedures to be carried out strictly.

A few well-qualified inspectors are better than a larger staff with inadequate qualifications. To help overcome the difficulty of training a sufficient number of qualified inspectors, it was suggested that WHO should investigate the possibility of organizing training courses for specialists to serve as inspectors of pharmaceutical manufacturing establishments in different countries of Europe, where legislation and manufacturing conditions are fairly similar.

## 9. ORGANIZATION OF SERVICES FOR OFFICIAL PHARMACEUTICAL QUALITY CONTROL

Reference was made to the section of the report of the WHO Study Group on the Use of Specifications for Pharmaceutical Preparations dealing with the organization of a national control authority.<sup>1</sup>

It was suggested that such an agency for quality control could be part of a ministry or department of health, organized as a separate division and headed by an officer directly responsible to the minister or chief of the department. The drugs control division should be divided into three branches :

- (1) administrative and executive branch ;
- (2) inspection services ;
- (3) laboratory services.

### 9.1 Administrative and executive branch

The administrative and executive branch would draft projected legislation or regulations, draw up control procedures, keep records of manufacturers and of analysis and inspection work, and issue licences to manufacturers for the marketing of preparations. It would also be responsible for maintaining statistics on this work, and would provide office management services, keep financial records, and assist in budget work. The administrative branch must be able to obtain legal advice or have people with legal training on the staff.

### 9.2 Inspection services

The inspectors employed by the authority working in this field should be professionally qualified and well trained. They should have a considerable knowledge of manufacturing procedures, record controls, and laboratory examination of raw materials and finished products. It is impossible to exercise control of factories only by analysing samples taken from the market. In addition to the work in the laboratories it is important to ascertain whether each pharmaceutical manufacturer is in a position to exercise adequate control over every batch of all preparations he offers for sale and to make sure that he actually does so. It is therefore one of the most important functions of the authorities to arrange for the inspection of pharmaceutical factories.

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<sup>1</sup> *Wld Hlth Org. techn. Rep. Ser.*, 1957, 138, 21-27.

### 9.3 Laboratory services

The laboratory services branch would be responsible for supplying the technical and scientific services and advice necessary for carrying out the duties of the control division. This would include analysis or examination of samples, the development or adoption of methods of analysis or examination, the preparation or adoption of standards, the scientific investigation of unusual or new pharmaceutical preparations, the critical examination of technical information submitted by manufacturers on their products, and advice to the chief of the control division on all scientific and technical matters.

The laboratory services branch must have specialists who are well qualified and capable, and if they are to maintain their interest in their particular field they must be encouraged to do original work. That research work might be limited to the solution of problems pertaining directly or indirectly to the quality control of pharmaceutical preparations. There was wide scope in such work for people with many different kinds of training. The great importance of such research work being carried out in the laboratories of a control division must be emphasized.

Three types of laboratory are usually needed :

- (a) one for chemical and physical analysis,
- (b) one for assays using physiological and pharmacological techniques, and
- (c) one employing bacteriological and immunological techniques.

The best scientific equipment must be available if the work of the laboratory is to be efficient. A good library of scientific and trade journals and textbooks is a necessity.

### 9.4 Delegation of work for quality control

It was suggested that it might be advisable, or even necessary in some countries, to ask laboratories other than those under the direct authority of the chief of the control division to carry out certain aspects of the laboratory work. In such a case the chief of the control division must have a clearly stated authority over the work done for him in the outside laboratory.

### 9.5 Use of branch laboratories and offices

In some large countries, geographical conditions require branch laboratories for the speedy analysis of samples. Certain samples that cannot be tested in a regional laboratory must be transported to a central labor-

atory. A regional laboratory must have an inspection service and a small administrative staff.

In a country with a federal system of government it may be necessary to use state or provincial laboratories to carry out routine work. This arrangement may have the weaknesses inherent in delegated work (difficulty of ensuring supervision) and those due to widely-separated regions. Care must be taken to ensure clear lines of authority from the chief of the central control division and to use all means of obtaining uniformity in all parts of the country in the observance of legislation.

Finally, no law or regulation should be passed that cannot or will not be enforced.

#### **9.6 Inter-country laboratory services**

It was suggested that in certain parts of the world it would be helpful to set up laboratories common to several countries in order to perform the work with a minimum of cost and trained staff.

However, the participants did not believe there was any necessity for this, but suggested that a system of confidential exchange of analytical results and of doctors' evaluations of pharmaceutical specialities could be introduced between some countries as required.

#### **9.7 Industrial advisory services**

Several participants emphasized that advisory committees consisting of experts from industry and the government, physicians and pharmacists, could play a very valuable role in working out specifications, official methods and regulations.

It was also pointed out that the joint meetings arranged by the International Pharmaceutical Federation between industrial pharmacists and laboratory directors could, to a certain extent, provide advisory services to governmental control bodies. In the United States of America there is a Pharmaceutical Contact Committee which maintains liaison between the industrial pharmacists, the Food and Drugs Administration, the United States Pharmacopeia and the National Formulary. In the United Kingdom the public analysts and the analysts from industry form an expert committee on analytical matters which also makes recommendations on analytical procedures in relation to pharmaceutical preparations.

It was mentioned that in Italy, where the administration and enforcement of pharmaceutical quality control are the responsibility of the Ministry of Health, laboratory work is done by the Istituto Superiore di Sanità. As an experiment, part of the routine control is at present being performed by the regional laboratories.

### 9.8 Experience in countries with a federal organization

In the USSR, drug regulations and standards are the same in all the republics and there is little risk of lack of uniformity in exercising control over drugs in the regional laboratories. Where any problem proves too difficult to solve on the spot, it can always be referred to the Central Institute in Moscow.

In Switzerland, there are various laws on pharmaceutical preparations in the twenty-four cantons, but the cantons combine to give financial support to a Central Institute of Drug Control in Berne, which undertakes chemical analyses. Biological tests are carried out at university institutes. In most cantons, pharmacies are inspected and in some there is factory inspection, too.

In the Federal Republic of Germany, there is no federal control institute nor is one planned under the legislation now being introduced. Control has to be effected by the provincial authorities (Länder). Under the new legislation these bodies must inspect the factories and take samples. They have also to inspect the pharmacies and other places where pharmaceutical preparations are on sale to the public. Analysis of samples is carried out in accordance with systems established by local public analysts.

### 9.9 Research in control laboratories

Finally, emphasis was laid on the need for research in control laboratories with a view to maintaining the interest and qualifications of the staff and also to discover the best methods of analysis. In France, approximately half the work done is devoted to applied research and 5% to pure research. In Canada, some 10% of the control body's budget is used for research. However, it was emphasized that these figures had to be qualified to a large extent by the scope attached to the term "research".

## 10. CLASSIFICATION OF PHARMACEUTICAL PREPARATIONS IN RELATION TO RESTRICTIONS ON SALE

It was pointed out that restrictions on the sale of drugs vary considerably in different countries. There are two extremes:

- (a) the sale of all drugs and pharmaceutical preparations is restricted to pharmacists;
- (b) the sale of drugs and pharmaceutical preparations is unrestricted with the exception of narcotics and some listed "poisons".

It is at present impossible to obtain universal acceptance of the principle that all sales should be restricted to pharmacists as this conflicts with the traditions of some countries.

There is no problem with narcotics, as international agreement on the principle of applying the most stringent conditions of importation, manufacture and sale has already been attained. The number of narcotics is relatively small, however, while the potential number of new drugs is unlimited. Restrictions in the past have depended chiefly on whether a drug was a poison or not. When there were very few synthetic pharmaceutical preparations this rough method of classification sufficed. New pharmaceutical preparations, however, have brought new problems: a substance that could not be classified as a poison in the orthodox sense could nevertheless be a danger to the public when taken without expert advice. Legislation based on a classification of drugs as poisons is too restrictive to be applicable to new drugs, e.g., sulfonamides, sex hormones, amphetamines, corticosteroids, antibiotics, etc. It is possible, however, to suggest a classification on a pharmacological basis as a possible solution to this problem (see Annex 1).

Two main types of restriction on sale may be considered:

- (1) sale on prescription only;
- (2) sale restricted to pharmacists.

#### 10.1 Sale on prescription only—Group R

This is the most stringent type of restriction and is indicated for all pharmaceutical preparations, the consumption of which could be dangerous unless taken on medical advice. Drugs in this category can be divided into three sub-groups:

- (a) to be dispensed once only;
- (b) to be dispensed more than once, but only at times and in amounts stated by the doctor on the prescription;
- (c) to be dispensed more than once in the absence of specific instructions by the prescriber.

In the United Kingdom, under the National Health Service, prescriptions may be dispensed once only, but this is a requirement of the National Health Service Regulations and not of the poisons legislation. In the case of prescriptions for private patients, those for narcotics can be dispensed three times, but only on the prescriber's specific instructions to do so. With other scheduled drugs, the number of repetitions is not restricted provided that the prescriber indicates the number and intervals of time for the repeats. In other cases, there are no restrictions on repeated dispensing. The group might therefore be divided into two classes:  $R_1$ —to be dispensed once only unless repeats were specifically stated;  $R$ —to be repeated without specific instructions from the prescriber. The question

as to whether repeated dispensing from a single prescription should ever be done in the absence of specific instructions by the prescriber is open to question and the opinion of the meeting was divided.

### **10.2 Sale restricted to pharmacists—Group P**

In some countries the sale of all pharmaceutical preparations, including household remedies, is restricted to pharmacists. When there is no such monopoly many drugs unsuitable for general sale are offered to the public through various retail channels. It was suggested that all drugs, excluding only those that by long usage and experience had proved to be safe when widely sold to the public, should be included in this group. All new drugs would automatically be included, but many participants thought it would be more appropriate to place them in Group R.

Conditions of sale by pharmacists also vary with the degree of danger associated with the drug. Toxic and dangerous substances capable of criminal abuse should not be sold without records, since their origin should be readily traceable if required. For such drugs, pharmacists should maintain a register in which the details of the purchase are recorded. Other drugs do not require such records, but the public would be protected if all pharmaceutical preparations were only available from the pharmacist, whose professional duty it would be to protect the public from possible dangers of abuse.

### **10.3 Need for further investigation of restriction problems**

It was agreed that although some countries restrict the sale of all pharmaceutical preparations to pharmacists, universal acceptance of this principle is probably unattainable.

The question of placing new drugs in the "prescription only" group was discussed. It was generally agreed that new potent drugs should be subjected to this restriction, but opinion was divided on the need to include all new drugs, as some might not warrant such a restriction. On the other hand, it was pointed out that it was easier to relax a restriction on the basis of more complete information following extended clinical use than to be forced to apply additional restrictions.

International trade makes uniformity of national restrictions desirable. The World Health Organization could help in that respect and it was agreed that the problem warranted urgent investigation.

## 11. TRAINING OF PERSONNEL

Aspects of the training of personnel suitable for work in control laboratories and as inspectors were reviewed. It was pointed out that after the fundamentals of pharmacy have been learned, further, more advanced education should be provided, because assay techniques tend more and more to require highly specialized apparatus. It was seldom that the necessary training could be given in all countries. To assist in overcoming this problem, WHO could award fellowships for study in suitable laboratories. It was pointed out that such fellowships would provide means not only to start a long-term country project, but also studies of specific subjects.

It was suggested that WHO compile a list of suitable laboratories and organizations in Europe willing to receive and train pharmaceutical control personnel. In this connexion, the possibility of sending fellows to study in industry was discussed. This question could be considered from many angles, but it seemed that the pharmaceutical industry already takes its share of students.

The international aspect of finding laboratories where people from the less developed countries of other regions could study was also discussed. It was proposed that a list should be made of laboratories where such students could be placed. Language is often a matter of importance in this connexion.

It was pointed out that WHO would have to be sure that the fellows had the proper educational background before they were sent to busy laboratories. It is costly to teach students lacking basic theoretical and practical knowledge.

Fellowships for inspectors present a different problem as they are more interested in pharmaceutical legislation and its implementation. It was suggested that WHO should draw up a scheme for such studies. Reference was made to the possibility of organizing seminars for such groups, which might prove to be a way of meeting some of the needs of fellows and students in this category.

### ACKNOWLEDGEMENT

The Meeting records with profound regret the death shortly before the Meeting of Mr J. Mattelaer who had been appointed Regional Office Consultant. He played a very active part in the preparatory work for the Meeting and his skilful and comprehensive approach was much appreciated.

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## Annex 1

**SUGGESTED PHARMACOLOGICAL CLASSIFICATION  
OF PHARMACEUTICAL PREPARATIONS AS A BASIS  
FOR RESTRICTION OF SALE \***

*Preparations acting on the alimentary system* : Antacids (P, U); anti-spasmodics (P); gastro-intestinal sedatives (P, U); laxatives and purgatives (P, U).

*Preparations acting on the cardiovascular system* : Preparations acting on the heart (R); vasodilators (R, P); vasoconstrictors (R, P); anti-hypertensives (R); anticoagulants (R).

*Preparations acting on the nervous system* : Addictive analgesics (R<sub>1</sub>, N); antipyretic analgesics (R, P, U); specific analgesics (R, P, U); barbiturates (R<sub>1</sub>); non-barbiturate hypnotics (R, P); tranquillizers (R<sub>1</sub>, R, P); anti-emetic preparations (R<sub>1</sub>, P); anti-convulsants (R<sub>1</sub>); preparations for the treatment of parkinsonism (R); muscle relaxants (R<sub>1</sub>); stimulants (R<sub>1</sub>, P).

*Preparations acting on the genito-urinary system* : Sex hormones (R); diuretics (R, P); preparations acting on the uterus (R<sub>1</sub>).

*Preparations acting systematically on infections* : Antibiotics (R<sub>1</sub>); sulfonamides (R<sub>1</sub>); anti-tuberculosis drugs (R<sub>1</sub>); anthelmintics (R<sub>1</sub>, P); vaccines and sera (R).

*Preparations affecting metabolism and nutrition* : Insulin (R); oral hypoglycaemics (R); erythropoietic preparations (P); vitamins (P, U); corticosteroids (R<sub>1</sub>); anabolic drugs (R); thyroid and antithyroid preparations (R); antimetabolic preparations (R).

*Preparations affecting allergic reactions* : Antihistamines (R, P); preparations for protein desensitization (R).

*Topical preparations* (not previously specified). Acting on the eye (R, P, U); acting on the ear (R, P); acting on the skin (sedatives and antipruritics) (R, U); antiseptics and disinfectants (P, U).

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\* The letters in brackets refer to the following proposed sales restriction groups :

R<sub>1</sub> — available on prescription only, not repeatable unless so specified; R — available on prescription only, repeatable without specific instructions from the prescriber; P — sale restricted to pharmacists; N — narcotics subject to international restrictions; U — sale unrestricted.

## Annex 2

## LIST OF PARTICIPANTS

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