SEMINAR ON

DRUG CONTROL IN THE AMERICAS

PAN AMERICAN HEALTH ORGANIZATION
Pan American Sanitary Bureau, Regional Office of the
WORLD HEALTH ORGANIZATION

1971

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Introduction

Many of the recent advances in medical science have resulted from the availability of new synthetic chemicals and purified principles obtained from natural sources by modern technological processes. These new medicaments have provided great benefits for humanity but at the same time have given rise to a number of complex problems.

The difficulties surrounding the new medicaments have been considered at numerous meetings of the World Health Assembly, which, as is well known, constitutes a global forum for the study of the world's most important health problems. It is a measure of the seriousness of the current drug control problems to note that during the last 10 years the Assembly has passed not less than 27 resolutions dealing with various aspects of drug control.

The problems that are treated in the World Health Assembly resolutions can be summarized in the following questions:

1. What proof of efficacy and safety must be required from the sponsor of a new drug before the article is allowed to enter the market?
2. How can a drug be monitored after it has entered the market and is being used on a large scale, in order to determine whether it is really effective and whether it causes adverse effects that were not observed or adequately evaluated at the time the drug was permitted to enter the market?
3. What assurances should be required that each lot of medication on the market complies with applicable standards of quality?
4. What requirements should be established to ensure that the claims made for a drug in its advertising are accurate and expressed with scientific objectivity?
5. What measures should be taken to minimize the abuse of drugs that cause dependence and other social injury when employed for nonmedical purposes?

These problems have been a source of great concern to the Ministers of Health of the countries of the Americas, as reflected by their active discussion of the subject at the World Health Assembly and in regional meetings of the Health Ministers such as the Pan American Sanitary Conference.

With the objective of obtaining expert advice regarding solutions to the existing drug control problems of the Region, the Pan American Health Organization, acting in collaboration with the Government of Venezuela, convened the first Seminar on Drug Control in the Americas, at Maracay, Venezuela, from 15 to 20 November 1970. The Seminar was attended by 29 senior drug control officials chosen by the Ministers of Health of 24 countries.

After considering the pertinent documents of the World Health Organization and the Pan American Health Organization, and having heard speakers deliver the papers that are reproduced in this volume, the Seminar participants formed

three working groups to consider selected topics and prepare recommendations thereon. Subsequently, the participants met in plenary session to discuss, modify, and adopt the recommendations emanating from the working groups. The recommendations contained in the Seminar Report constitute the fruit of their labors at this important meeting.

OPENING STATEMENTS

STATEMENT BY DR. J. J. MAYZ LYON MINISTER OF HEALTH AND SOCIAL WELFARE OF VENEZUELA

It is a source of just satisfaction and encouragement to the Ministry of Health and Social Welfare that our country is the host for this Seminar, sponsored by the Pan American Sanitary Bureau.

The holding of this meeting is, for us, the culmination of an idea. Since 1946 a gradual and persistent effort has been under way here to review drugs and pharmaceutical products, with a view to better control of those substances. At the same time, improvement has been sought in all aspects of their processing, packaging, distribution, and sale. In that earlier year there was a multitude of medications, some of them enjoying great popular acclaim, but without any real therapeutic value. Many of them were nothing more than the products of their manufacturers' imagination, while others were based on ancient ideas—obviously incorrect—of the properties of certain substances.

The Pharmaceutical Specialties Review Board, established at that time, undertook, in collaboration with the Ministry's Pharmacy Division, a rigorous program to suppress those substances and combinations that were not backed by well-founded scientific criteria. This work was most arduous at the outset, for it meant direct conflict with diverse interests that were difficult to overcome. Nevertheless, the objective was realized in progressive fashion, and after a certain time the results of what I may call this purification of our therapeutic arsenal became apparent. Concurrently, foundations were laid for standards to provide the most effective possible regulation of the processing and registration of new drugs manufactured in the country.

In those days most therapeutic substances were imported, and an intensive effort was required to make foreign companies aware of the goals sought by the Ministry. This was not always easy, but slowly an attitude of cooperation developed as these firms acquired an understanding of the reasons for this important campaign. Today most of these products are manufactured within the country. Their processing is the work of a dynamic industry, which should examine itself closely and subject itself to appropriate and continuing controls, so that its development will proceed on sound bases ensuring that the industry's scientific and social objectives will be fulfilled.

The fundamental and sole purpose of drug processing is to see that drugs fully perform the action expected of them by the physician. Put another way, that they genuinely and adequately possess the active pharmacological properties attributed to them, without harmful collateral effects or in any case with the minimum of these, so as not to interfere with or nullify the therapeutic action. Further, that they be prepared under rigorous technical conditions that prevent the addition of harmful substances to the product. This is a serious responsibility in view of the difficulty of identifying such substances in time to counter their effects.

In addition, the amount of active ingredients should be as stated on the label, within acceptable variation limits. Otherwise the physician cannot be certain of the effective dosage of the drug; moreover, this situation would represent a fraud on the patient, its gravity measured by the extent to which his health or life is endangered; and it would mean deception of the medical profession and absolute denial of the lofty purposes underlying the manufacture of pharmaceuticals.

Special attention also must be given to packaging, so that preservation of the product will be ensured and contamination avoided; and to labeling, so that damaging confusion will be prevented. All of these considerations take on particular importance in the preparation of injectable substances, and must be of special concern when biological products are involved. Ever since the celebrated—though almost forgotten—tragedy of Lübeck, which resulted in the death of many children through the confusion of an active strain with BCG, and other less notorious but equally appalling cases that occurred at different times, the need has been recognized for national health organizations to exert strict control and vigilance over these processes.

The ministries of health have ultimate responsibility for all activities in this field, and they unquestionably must perform this important function whether stipulated or not in legal provisions. Indeed, the development of this industry would make little sense should its products fail to meet the scientific criteria essential to assure the physician of their curative or preventive effects. This means that the products must be of maximum reliability.

I am certain that our experience will be analyzed thoroughly in this Seminar, so as to contribute in some way to a better understanding of the question through comparison with what has been and is being done in other countries. Undoubtedly, this exchange of information will be very fruitful for our purposes. One of the most significant aspects of this meeting is the study of bases for the organization of an international laboratory for drug control, to advise and assist all countries of the Region in this field.

It is a source of special satisfaction to have with us Dr. Abraham Horwitz, the distinguished Director of the Pan American Sanitary Bureau. He is a man of many capabilities and accomplishments in the field of international public health. His presence here affords an opportunity to underscore the highly beneficial relations, based on a strong spirit of cooperation, between the Venezuelan health organization and the agency that he so wisely and brilliantly heads; and to extend our most sincere wishes that this fruitful association will continue and be strengthened even further in the years ahead.

On behalf of the Ministry of Health and Social Welfare, and in my own name as well, I am pleased to extend to the officials of the Bureau our thanks for their effective work in preparing for this Seminar. To them, and to the distinguished representatives of the countries, I offer a most cordial welcome and a heartfelt wish that their stay among us will be productive in the scientific and technical sphere. I hope that the personal relationships which are always gratifying to establish or renew on occasions such as this will cause them to carry away—along with the satisfaction of a mission accomplished—a favorable image of Venezuela and its people, who stand ready to support enthusiastically any effort for the common good. Finally, I wish all of you great success.

STATEMENT BY DR. DANIEL ORELLANA CHIEF OF THE OFFICE OF INTERNATIONAL PUBLIC HEALTH MINISTRY OF HEALTH AND SOCIAL WELFARE OF VENEZUELA

On behalf of the Organizing Committee of this meeting, I wish to extend a most cordial welcome to the participants and to offer my hope that their coming together here will be a source of abundant professional accomplishment and a rewarding experience.

The Committee has made every effort to prepare a pleasant and efficient setting for your work. The officials of the Pan American Sanitary Bureau and of the Ministry of Health and Social Welfare who have been entrusted with this task have been guided at all times by a desire to fulfill their mission as regards physical arrangements and required facilities.

It has been said—and with reason—that today's world is the world of communications. Indeed, man has never before had access to so many means to meet with his fellows in any remote part of the globe. And as these facilities have expanded, so also has man's obligation to make the best possible use of them for the highest purposes. We believe that meetings such as this one are instruments by which these facilities can be used in greatest benefit to the most productive ends.

We also are aware of the intensity and frequency with which international discussions have been held in recent decades, through meetings of this kind. Sometimes we feel that the possible overuse of such meetings could result in a loss of their utility and of their good standing. Nevertheless, everything hinges upon the importance of the subject matter, the orientation followed, the objectives sought, and the results finally achieved.

In any event, there always will be one intangible and unspecified—but no less important—result: the development of a spirit of friendship and rapport among men of different lands. The bonds forged here between peoples and nations will help to perpetuate a sense of international solidarity. Thus, we believe that as communications facilities become increasingly accessible, people will continue to make use of these instruments, and mankind can only benefit from this activity.

Many of you, of course, have attended meetings like this one in other places. I hope that you will refrain from making comparisons; each event in itself is distinct from any other, and what matters in these meetings is not the pomp that surrounds them, but the spirit in which each of us takes part. The Committee is certain that the proper spirit is now alive in this hall, and that it is the most important element of this meeting. We call upon you, then, to ignore the details of physical arrangements and rather to turn your attention to the common task we are now beginning.

The Committee wishes to thank the institutions and persons who have rendered their assistance, in a spirit of generosity and cooperation. All of them —personnel of the Pan American Sanitary Bureau, the Ministry of Health and Social Welfare (central office and regional offices in Aragua State), and the private sector—were quick to share the Committee's responsibilities. The time is at hand to give due recognition to their interest and readiness to serve.

Tomorrow we shall begin the work of this Seminar. All of us are aware of the importance of the topic to be discussed here. Many countries are awaiting our recommendations on the development of services related to this field, which has so critical an impact on human health and on the effectiveness of medical care. I wish, then, that your only guide during the work ahead may be the full realization of these aspirations.

STATEMENT BY DR. ABRAHAM HORWITZ DIRECTOR OF THE PAN AMERICAN SANITARY BUREAU

This Seminar could not have been held 20 years ago. Not because the human values that inspire it did not exist, but rather because the circumstances precluded those values from overcoming other interests, in order to create a public awareness of the problem. Today, every undertaking is appraised in terms both of its contribution to development and the economy, and of its adverse effects on man and his environment. As with all movements inspired by the common good, the initial phases have seen exaggeration, excessive caution, precipitous action, and in general, the predominance of emotion over reason. Although the pendulum is now swinging the other way, the motivating force has not lost its meaning. And what motivates it is a convergence of diverse currents of opinion that have appeared spontaneously to reaffirm the inalienable rights of man in society. Men must not be the victims of technology, but its beneficiaries; not slaves of machines, but their masters; not at the mercy of material objects, but in command of them for man's welfare. And profit cannot be sought at the price of others' health.

A new image of the consumer—as one who demands to know what he is buying, to take part in development planning, to contribute to that eternal process of learning known as progress—is now taking shape. Already we have examples of this new attitude. It is no longer acceptable for industry to neglect the safety of workers and to contribute to pollution of the air, water, and soil. Nor can additives be used in food to make it more attractive or palatable, when their effects on health are unknown. Nor can crops be sprayed at random with insecticides in disregard of their possible long-range consequences. Nor can automobiles and other passenger carriers be built with defects that may cause accidents later. And now society expects each medication to have the declared composition and to exert the therapeutic activity claimed for it.

In summary, what is sought is the humanization of development—or, in Fromm's poetic words, "the revolution of hope." What seizes our attention is that there are some who are surprised by, and even react violently to these demands of consumers who will not remain impassive when their natural rights are threatened. Such demands signal an attempt to create a more just and healthier society, ruled by values that should ever be our guide, whatever may be the level and nature of our progress.

We are being asked to practice what we preach; to let our actions prove our words; to make our convictions prevail over our interests and the common good over individual enrichment.

Within this conceptual framework, the purposes of your Seminar come into sharper focus, for they concern one of the most sensitive areas of social life and one of the most essential instruments for the prevention and cure of illness, the lengthening of life, and the pursuit of happiness. If we note further that in

Latin America the industry produces over $1.2 billion of drugs at manufacturer's prices each year, we can understand even better the ethical, biological, and ecological importance of your task.

The surveys taken by our Organization show that in general the systems used to evaluate the quality of medicines in the majority of the countries are below the level of technical development required to test the volume of drugs resulting from domestic production and importation. There is a shortage of personnel—whose training must be improved continuously because of the intensive research conducted by the industry itself—of equipment, materials, and even of physical facilities. Legislation is not always up to date, nor does it provide educational standards that will make the consumer a responsible and active participant. Let us keep in mind that a large proportion of accidents involving children are due to the ingestion of excessive quantities of drugs or toxic substances at home, left within their reach by parents.

It should be added that control is terminal, i.e., when the preparation is either on the market or about to be placed there. In other words, only in a few cases are the intermediate stages analyzed to guarantee the final result. What is more, industry does not always have testing laboratories, nor do government services examine their records to assure accuracy.

Funding of the government drug control services is as inadequate as it is essential. We should make special note here of the steps taken by the Government of Argentina to earmark 0.75 per cent of the proceeds of sales of all pharmaceutical substances for the Governmental Department of Quality Control. The Governing Bodies of our Organization have recommended that similar procedures be adopted in accordance with each country's circumstances.

In the search for a drug there is a series of stages, the mere enumeration of which reveals the complexity of the production process. It begins with chemical investigation designed to extract the substances from nature, analyze them, and —if appropriate—synthesize them. This is followed by biological research, which involves tests, either in the laboratory or on experimental animals, of the action of the substance, that is, its pharmacology; of its harmful effects, or toxicology; and its effects on offspring, i.e., genetic studies. If no adverse effects are observed, the substance must be provided with the best possible medium to transform it into an effective, stable, and well-tolerated medication; this stage is known as galenical research. Then comes the final or clinical stage, the purpose of which is to test the drug's therapeutic action on ill persons who are willing to take part. After this comes mass production, or—as it has been well put—"the jump from milligrams to tons." Above all we wish to stress once again the preventive or curative action that prolongs life and fosters well-being and happiness. Whether the preparation of medicinal substances is a state or a private activity, control aimed at guaranteeing the safety, purity, and efficacy of those substances must be exercised with all scientific, technical, and moral rigor.

The tremendous progress of the last 30 years in the identification and preparation of drugs and pharmaceuticals is due in large measure to the efforts of industry. While the universities of the technologically advanced countries, as well as their Governments, have concentrated on the study of basic functions in normal and pathological states (the most conspicuous example of which is

molecular biology), private enterprise has devoted its greatest attention to therapeutic effects and to production. We are convinced that a sound industry, genuinely interested in social well-being as a prelude to and an ultimate consequence of development, prefers that the Governments have efficient and well-equipped institutions to control the quality of drugs, as regards both their composition and their pharmacological effects. When it has its own laboratories, industry cooperates in the implementation of the laws in force.

It is this spirit that led the World Health Assembly and the Governing Bodies of the Pan American Health Organization to include in their policies the provision of advisory services to the Governments in this sensitive field which affects many of their activities. The standards recommended for manufacture and quality inspection of drugs,[1] the system proposed for certification of the quality of pharmaceutical products destined for international trade,[2] the encouragement of the organization of quality control laboratories to serve one or more countries, and the center for international surveillance of adverse reactions to drugs, are manifestations of the universal interest of Governments in this problem. In my judgment, they all reflect the movement now taking shape to motivate the consumer to lay aside his passive role and claim his right to get exactly the article he pays for.

Your Seminar is a first step down a long road. As you proceed you will be subject to misunderstandings, to misinterpretations, to unspoken attitudes, to pressures of every sort. May you constantly find your inspiration in the image of that society we all seek, and in the comforting vision of children you will have helped to save and adults whose happiness you will have fostered.

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[1] Resolution WHA22.50. *Off. Rec. Wld Hlth Org. 176* (1969), 24–25.
[2] *Ibid.*, pp. 104–105.

SEMINAR REPORT

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Under the sponsorship of the Pan American Health Organization and with the collaboration of the Government of the Republic of Venezuela, the first Seminar on Drug Control in the Americas was held in Maracay, Venezuela, from 15 to 20 November 1970. Twenty-nine drug control officials from 24 countries of the Region attended.

After considering the pertinent documents of the World Health Organization and of the Pan American Health Organization, including a report concerning the present drug control situation in the countries of the Americas, and having obtained advice and suggestions from the attending group of consultants, the Seminar participants approved the following recommendations for improving the drug control systems of the various countries:

RECOMMENDATIONS

1. That the Governments of the Region give the highest priority, within the planning of public health services, to the solution of the problem of drug quality control, including adequate financing to obtain the necessary physical resources and the employment of qualified technical personnel.

That the financing be obtained by each Government in accordance with such system as it deems appropriate.

2. That the health authorities of each Member Country formulate a judicious program for controlling the quality of drugs. This program should include pertinent indices of evaluation, with the object of providing at appropriate intervals sufficient information to permit an estimate of the effectiveness of such control.

3. That each Member Country should have its own drug control agency organized as a single entity under a single director within the health ministry, or participate in a regional drug control system. The national drug control agency should have the following functions:

a) Expeditious drug evaluation and registration, and control of labeling and advertising.
b) Collection of drug samples from all stages of manufacture and distribution, and analysis of such samples.
c) Inspection of the production and distribution of drugs.
d) Enforcement of the legal requirements pertaining to drug control.
e) Encouragement of investigations related to its functions, and publication of the results.

4. That the national drug control agency should be staffed with experts—such as physicians, pharmacologists, pharmacists, chemists, and microbiologists—specially qualified in the health sciences, drug manufacturing procedures, and pharmaceutical quality control.

That the scientific personnel and the senior administrative personnel should have highly qualifying university education plus specialized training in drug control procedures obtained in appropriate institutions. To attract and retain qualified personnel, it is desirable that they have job security and adequate remuneration, equal to or greater than that established by private industry for positions having the same responsibilities.

That provision be made for advanced training of technical personnel by means of national or international courses given in the Region, and also by means of fellowships offered by the Pan American Health Organization for training in any country.

That special consideration be given at this time to the education, in increased numbers, of clinical pharmacologists.

That the national control agency experts in drug therapy should cooperate closely with clinical departments of hospitals.

That, if necessary, the national control agency utilize the services of advisory committees.

5. That for effective execution of its work, the national control agency should have adequate laboratory facilities, particularly for quality control of pharmaceuticals and biologicals, and also for pharmacological and toxicological studies.

6. That the independent status of the national control agency and its personnel be ensured with respect to drug producers, whether in the public or the private sector.

7. That special legal requirements apply to the licensing, certification, and control of biological products, and that the unit responsible for the control of biological products form part of the national drug control agency. In the organization of this unit and for adequate training of specialists in this field, account should be taken of the recommendations of the World Health Organization Expert Committee on Biological Standardization (22nd Report).[1]

8. That registration of all drug products should be required and the basic provisions for registration be made uniform for all the Member Countries and follow the details set forth in Annex 1, below. An exemption from registration may be granted for importation of a life-saving drug required for emergency use.

That uniform standards applicable to pharmaceutical preparations be adopted, such as the *Specifications for the Quality Control of Pharmaceutical Preparations (International Pharmacopoeia)* published by the World Health Organization.

9. That in accordance with Resolutions WHA16.36[2] and WHA23.48[3] of the World Health Assembly, the national control agencies should inform the World Health Organization of any action that limits or prohibits the use of a drug or of the refusal to register a drug on account of ineffectiveness or serious adverse effects.

10. That the Pan American Health Organization continue and increase its cooperation with the Member Countries in the achievement of the following goals:

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[1] *Wld Hlth Org. tech. Rep. Series 444* (1970).
[2] *Off. Rec. Wld Hlth Org. 127* (1963), 18.
[3] *Off. Rec. Wld Hlth Org. 184* (1970), 25.

a) The preparation of model legislation and regulations and other legal requirements to help achieve uniform methods of drug control.
b) The expeditious dissemination of pertinent information to all levels of official drug control organizations, as designated by the health authorities.
c) Conducting studies when requested by the Member Countries concerning the financing of their drug control programs and the organization of the official control agencies.
d) The training of the personnel of the drug control agencies.
e) Periodical sponsorship of seminars such as the present one.

11. That the Pan American Health Organization expedite plans for the establishment of the proposed regional drug institute, in view of the urgent need of the countries for such an institute with functions as specified in Recommendation 5 (Chapter XIV) of the Final Report of the Special Meeting of Ministers of Health of the Americas, held in Buenos Aires in 1968 (quoted in Annex 2).

ACKNOWLEDGMENT

The participants wish to express their recognition of the beneficial impact of the activities of the Pan American Health Organization in advising the various countries concerning the solution of their drug control problems, the organization of specific services, the training of personnel, and the distribution of information and technical assistance.

VOTE OF THANKS

The participants wish to express their thanks to:

Dr. J. J. Mayz Lyon, Minister of Health and Social Welfare of the Republic of Venezuela, for the cordial reception accorded to all of the participants;

Dr. Abraham Horwitz, Director of the Pan American Sanitary Bureau, for sponsoring and supporting the Seminar;

The Organizing Committee and the officers of the Seminar for their excellent work, which facilitated the success of the meeting;

The consultants for their valuable and effective collaboration; and

The Secretariat and administrative personnel who provided the many forms of assistance that made the Seminar tasks easier.

Annex 1

BASIC REQUIREMENTS FOR THE REGISTRATION APPLICATION FOR A DRUG

1. Name and address of the applicant, and of the pharmacist who endorses the application with his signature.

2. If the applicant is located in a foreign country, the name and address of the local person legally authorized to represent the applicant, with an authenticated copy of the legal document authorizing the representation.

3. The name under which the product will be sold.

4. The purpose for which the product is intended.

5. A description of the pharmaceutical form and the composition of the product, including the name and quantity of each ingredient, active or not, in each unit dose. The international non-proprietary names recommended by the World Health Organization for drug substances will be used whenever possible.

6. A batch formula representative of that which will be used by the firm, including the name and quantity of every substance used in manufacturing the batch, whether or not the substance is present in the finished product.

7. A complete description of the method to be used in manufacturing and packaging the batch.

8. A complete description, with bibliographic references, of the methods used in the control of the raw materials, regarding the identity, purity, and potency, with a statement of the limits of acceptability.

9. A complete description, with bibliographic references, of the control procedures used during manufacturing and packaging, and the method of control used for the finished product, with a statement of the limits of acceptability.

10. Experimental data regarding the stability of the product in the container in which it is to be marketed. If the data do not demonstrate prolonged stability, the application must propose an expiry period for determining the expiration date of each lot which shall appear on the label, together with a statement of the necessary storage conditions.

11. A declaration that the product will be manufactured and packaged in accordance with the standards of good practices in the manufacture and quality control of drugs recommended by World Health Assembly Resolution WHA22.50.[4]

12. Adequate information to demonstrate that the product is effective and safe when used for the purpose and in the manner recommended. The documentation must include a complete description and evaluation of the preclinical and clinical investigations of the product.

13. If the finished drug product is to be imported, the application must contain a properly authenticated certificate from the health authorities of the country of origin stating that the product is authorized for sale in the country of origin. The application must include the labels, cartons, package inserts, and so on, accompanying the distribution of the product in the country of origin.

If the product is not authorized for sale in the country of origin, the application must state the reason.

14. Specimens of the labels, circulars, and cartons, and of the pamphlets and other literature that accompany the product. The package insert should provide complete and

[4] *Off. Rec. Wld Hlth Org. 176* (1969), 24.

informative data regarding use of the product, including indications for use, dosage information, and necessary precautions, warnings, side-effects, contraindications, and so on.

15. Specimens of the proposed advertising.

16. A sufficient amount of samples of the product and, if the health authorities consider it necessary, samples of the raw materials and of the reference substances necessary for conducting the proposed control testing procedures.

Annex 2

RECOMMENDATION 5 (CHAPTER XIV) OF THE FINAL REPORT OF THE SPECIAL MEETING OF MINISTERS OF HEALTH OF THE AMERICAS [5]

(Buenos Aires, Argentina, October 1968)

5. That the Director of the Pan American Sanitary Bureau continue the actions to improve drug quality control in the Americas, in particular the plans to create a regional drug institute in Uruguay which will assist all of the countries by:

a) Providing advanced training for drug analysts.
b) Providing technical training for inspectors and drug law administrators.
c) Supplying the government agencies with drug control information, including speedy notices concerning drugs that are found to be harmful.
d) Conducting research to improve drug testing procedures.
e) Helping the countries select the best kinds of drug testing equipment.
f) Serving as a reference laboratory with regard to the production and approval of standard materials and the carrying out of special analyses.

[5] *Official Document PAHO 89* (1969), 53.

WORKING DOCUMENTS

THE PRESENT DRUG CONTROL SITUATION IN THE COUNTRIES OF THE REGION

MORRIS L. YAKOWITZ *

In July 1970 the Pan American Health Organization sent to all the countries of the Region a questionnaire requesting information in regard to the drug control situation in each of them. On the basis of the replies, together with the information already available, PAHO prepared and issued a compilation which provides a brief description of the drug control procedures in use and includes a table presenting in summary form data on the magnitude of the control problem and governmental expenditure for drug control in each country. The compilation was distributed to the participants in advance of this Seminar.[1]

I should like to make only a few comments on the data contained in that compilation.

There are approximately 2,000 drug manufacturing establishments of significant size in the 22 Latin American and Caribbean countries included in the survey. Their annual production is valued at US$1,234,000,000 at the manufacturer's price level.

The volume of drugs imported into the Latin American and Caribbean countries exceeds the amount exported by $116,000,000 per year, thus raising the volume of drugs consumed in those countries to $1,350,000,000 annually at the manufacturer's or importer's price level. The cost at the retail price level is higher by a factor which is sometimes called the "mark-up."

Based on estimates of the mark-up factors in the different countries, we calculate that the final retail cost to consumers of the drugs used in those countries is approximately $1,950,000,000 per year.

From these figures, it is obvious that the drug manufacturing industry in Latin America and the Caribbean area has considerable economic importance in addition to its tremendous health importance as the purveyor of articles used for preventing and treating disease.

When we total the government expenditures for drug control in the 22 Latin American and Caribbean countries, we obtain the figure of $3,371,500, which represents an average of $1.7 per $1,000 of drugs consumed.

The 22 countries employ a total of 1,192 persons in drug control activities, including 250 inspectors and 314 scientists performing drug analysis. However, a large number of those workers spend only a fraction of their time in drug control activities and many of the analysts devote their time to testing registration samples submitted by the drug firms rather than testing market samples selected by government inspectors from drug stocks in distribution channels.

Twenty of the countries require registration of drugs but in only 12 of them are the registration applications reviewed by a medical evaluation board.

* Regional Adviser on Drug Control, Pan American Health Organization, Washington, D.C.

[1] See Appendix 1 to this volume, pp. 139–146.

The period of validity of an approved drug registration varies greatly among the 20 countries requiring drug registration: the period is one year for three of the countries, three years for two of them, five years for four of them, seven years for one country, and 10 years for three countries. In one country, the period of validity of a drug registration for a pharmaceutical specialty is 15 years and for a "generic drug," five years. In another, the period of validity for a drug manufactured within the country is 10 years and for an imported product, five years. In five of the countries, an approved registration is valid indefinitely.

Utilization of the available drug testing facilities varies considerably from country to country. More than half the countries devote the major effort to testing registration samples submitted by the companies. Only eight analyze a significant number of samples taken from stocks in distribution channels.

One country utilizes a large proportion of its drug testing capacity for analyzing samples taken from each batch of those products designated as "biologicals" or "biochemicals."

In three of the Latin American countries, drug control activities are conducted by the country's professional societies of pharmacists and physicians, and not by units forming part of a governmental department such as the ministry of health.

In almost all the Latin American and Caribbean countries the unit reponsible for inspecting drug manufacturers and collecting samples is separate from the laboratory testing unit.

In June 1968, PAHO made a similar survey of the drug control situation in the countries and reported the results to the Special Meeting of Ministers of Health of the Americas, held in Buenos Aires in October of that year. In the 1968 report, we made the following comments under the heading of "Problem Areas":

1. The countries of Latin America are expending only $3,221,000 per year for inspecting their 2,200 drug firms and testing the $1,492,000,000 of drugs consumed per year by their citizens. This is an inadequate expenditure for drug control and results in such undesirable conditions as:

a) Lack of modern drug testing equipment.
b) Lack of specialists for each kind of drug testing.
c) Part-time employment which greatly limits the effectiveness of the personnel.
d) Curtailment of the laboratory's capacity for testing samples.
e) Low salaries which result in dissatisfaction among the personnel, particularly if their counterparts in private drug industry are much better paid.

2. In various countries, despite the efforts made by the authorities, there are weaknesses in the internal organization and the performance of the laboratories. A deep analysis of the situation should be made in each case, including a study of such factors as the level of training of the technical staff and the nature of the available testing equipment.

Although the basic training of the analysts is satisfactory, many of them have not had the specialized postgraduate analytical training that is needed for coping with the complex new drugs of today.

3. In all but two of the Latin American countries, the unit responsible for inspecting drug manufacturers and collecting samples is separated from the laboratory testing unit. This often results in an unregulated flow of samples to the laboratory, so that at times few samples arrive while at other times the laboratory has a great backlog of samples awaiting analysis.

The testing unit frequently does not receive adequate information from the inspection unit concerning the drug manufacturer and the reason for collecting the particular sample; consequently the testing unit is handicapped in deciding on the scope of analysis appropriate for the sample.

4. The government drug testing facilities are now devoted largely to analyzing samples submitted by drug firms for registration purposes. There should be increased testing of stocks in

distribution channels, such as samples taken from wholesalers, hospitals, pharmacies, and other distribution levels close to the point of use. This would provide more meaningful information about the quality of the drugs administered to patients.

5. There is a diversity of drug laws and regulations among the countries. This may impede adoption of the common market principle and hinder the area's international commerce in drugs.

When we compare the results of the 1970 survey with the situation as it existed in 1968, we are forced to conclude that the only significant change in those two years is an increase in the magnitude of the drug control problem as measured by the volume of drugs consumed in the Region.

CURRENT PROBLEMS IN DRUG CONTROL

DR. MARCELO J. VERNENGO *

General Considerations

The large-scale use of pharmaceutical preparations in drug therapy, which is a characteristic of the modern age, is the result of the ceaseless thrust of research for new or improved drugs. Since this is a matter of great social significance, pharmaceutical preparations have been a major concern of the public health authorities, and most countries have accordingly begun to organize a system of control, based on the new properties of modern drugs. New drugs which are the end product of large-scale industrial production have complicated and special characteristics and must satisfy new requirements as to their specific efficacy, proven safety, and pharmaceutical quality.

The Final Report of the Special Meeting of Ministers of Health of the Americas (Buenos Aires, October 1968) states that "effective control of the quality of drugs requires that each country have a modern drug law, a well-coordinated government agency staffed with highly trained inspectors, analysts, and administrative officials, plus adequate funds for the agency to carry out a high level of drug control activity." [1]

At this Seminar, these subjects will be dealt with by various speakers. My presentation will deal briefly with a few technical problems involved in drug quality control.

In recent years there has been a marked trend in the control of pharmaceutical products toward greater accuracy in determinations for verifying the performance of a drug for the purposes for which it was designed. The evolution of the science that has come to be called biopharmacy has revived the discussions on the meaning of quality control. In this paper I shall adopt the broadest possible approach to the requirements for drugs to be placed on the market.

The modern drug, which is biologically active and pharmaceutically effective, has paradoxically increased the problems involved in its use, and the study and evaluation of its efficacy and safety must thus go hand-in-hand. Consequently, modern concepts of potency, dose uniformity, specificity and efficacy, safety, stability, identity, and purity must be taken into account in modern quality control. All this has greatly increased the responsibility of the producer, who is legally required to satisfy certain drug licensing and registration conditions; it has also greatly increased the obligations of the health authority and of the agencies responsible for drug control.

"Modern drugs have become cosmopolitan articles to such a point that little room is left in drug legislation for typical variants with national overtones." (*1*) Among new trends, therefore, mention must be made of a gradual move toward the internationalization of concepts and standards such as those contained in the many recommendations and technical reports of the World Health

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[1] *Official Document PAHO 89* (1969), 52.

Organization. It is interesting to note, at the present time, how the same general technical problems inevitably arise in all parts of the world as soon as control activities are begun or intensified.

In most countries a drug cannot be registered and licensed until it has been properly evaluated. Its value and specific efficacy for a given purpose must be verified and demonstrated in terms of its toxic characteristics. In addition, the producer must satisfy certain requirements as to the suitability of the manufacturing establishment, i.e., that proper manufacturing and control procedures can be used.

The health agency must therefore deal with the evaluation of a drug dosage form, whose design must be in accordance with knowledge of the physical and chemical properties of the active ingredient and of the other components of the formulation. The biological and therapeutic performance of the pharmaceutical preparation is closely connected with the development of its formulation, which in turn determines methods for controlling it. It must be borne in mind that the design of a new drug must take on the collaborative character of a high-level scientific task. The specifications of the components must be available to the control agency, which must also know the complete control and assay method proposed and possibly used by the producer to make sure that his product is in accordance with the declared specifications and standards.

The various types of tests of starting materials for the production of drugs and of the finished product do not provide a complete knowledge of their quality. It has frequently been said that quality must be built into the production process. Consequently, the official control agency must carry out inspections and technical checks in order to satisfy itself that the manufacturing procedures being used meet the legal requirements and the appropriate technical standards, for example, those recommended by the World Health Organization.[2]

Special Technical Problems

Mention should be made of the method of *determining the amount or titer of the active ingredient* which can be directly or indirectly controlled by the health authority. Official pharmacopoeias include limits for such content which are the basis for the control agency's decisions in verifying the quality of marketed products.

In the first place, with respect to the evaluation of the method presented for the registration of the drug, it must be borne in mind that the amount or titer of the active principle forms the basis for studies of the efficacy and safety of a pharmaceutical preparation and therefore of its usefulness in therapy, and that its use by physicians is based thereon. Consequently, the acceptance or rejection of certain limits or the establishment of standards for minimal or maximum amounts must be based not only on analytical and technological grounds, but also on the relationship between an ineffective dose and that which is therapeutically useful, and between the latter and a manifestly toxic dose. For that reason, assay limits for a relatively safe drug such as ascorbic acid or aspirin cannot be the same as those for such recently introduced drugs as L-DOPA or ketamine hydrochloride, for which the margins between the useful and the toxic dose are narrower, so that their therapeutic action may be defeated by the appearance of adverse, toxic, and even fatal phenomena.

In these cases, the pharmacological and toxicological properties of the drugs neces-

[2] *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Wld Hlth Org. tech. Rep. Ser. 418* (1969).

sitate accuracy in the assay and in the dose and consequently in the acceptable limits of the active ingredient. Often, a compromise must be reached between the posological requirements and those of the method of assay, as in the case of biological tests. In view of these considerations, the control authority must study a variety of problems, including the revision of the standards still included in pharmacopoeias.

In the second place, for the purpose of reaching a decision about the validity or utility of control and assay methods, it is necessary to know the type and probable level of *impurities arising from the method of obtaining and synthesizing the various components in the formulation* and of the substances which are used or may be formed in the process of pharmaceutical manufacture. This is the case of the presence of the more toxic chloroacetanilide in formulations of phenacetin. Another recent example illustrates this point. The unexpected discovery of ephedrine as an adulteration of ipecacuanha syrups led, on the one hand, to the development of a new method of analyzing active alkaloids and, on the other, raised the question of the need to review compendial standards and specifications by challenging their validity and specificity because they do not always take the most recent scientific advances into account (2). However, it must also be recognized that it is not always possible to previously develop tests for detecting all impurities which may be accidentally or intentionally incorporated as adulterants. Nevertheless, the information concerning probable impurities, supplied by the producer when requesting the registration of a new drug, may be important in solving many analytical problems. Cases such as that described should encourage the laboratories of control agencies to develop techniques and methods that take into account the existence of highly sophisticated new analytical instruments making it possible to considerably improve the official compendial methods or those used in the routine control activities of industry and official laboratories.

A proper system of financing will enable the control agency to obtain efficient equipment so as to keep up with advances in pharmaceutical analysis techniques. Improved drug synthesis, analytical detection, and assay methods justify ignoring the cost of instruments, but if possible a simple methodology should, of course, be developed to ensure constant improvement of specifications, purity criteria, and assay methods.

A drug quality control problem which has arisen in recent years is that of *uniformity in the dosage per pharmaceutical unit*. The variability of the titer is of particular importance, since a physician's prescription assumes that each pharmaceutical unit (tablet, capsule, suppository, ampoule, etc.) contains a specified and fixed amount of the active ingredient. It should be recalled that modern drugs are effective, sometimes too effective, in the doses frequently prescribed.

It has been possible to study the variability or the uniformity of content only relatively recently. The steadily increasing accuracy of modern analytical methods makes it possible, in principle, to determine the content of each of the units of the pharmaceutical product. The literature on this aspect deals almost exclusively with solid oral forms. The problem continues to grow. It is therefore not at present possible to draw definitive general conclusions, if we bear in mind that control of uniformity involves technological problems of a certain scale. It is not solely a matter of the uniformity of content in a given batch, but also of the uniformity of content of the active

principle for the same drug in different manufacturing batches. This is not only a technological problem and, for the control agency, a regulatory problem; it also has therapeutic implications, since it introduces one more variable that must be taken into account, especially in the continuing treatment of chronic diseases such as diabetes.

However, in the opinion of some specialists in quality control, this matter is of purely speculative interest insofar as there is greater variability in the therapeutic performance of the pharmaceutical product for a series of given patients, since it depends on a number of uncontrollable factors, such as purely genetic patterns. Hence, we are faced here with a new aspect of drug control which necessitates a closer relationship between the expert in the pharmaceutical control laboratory, the pharmacologist, and the clinical investigator.

One of the points to which special emphasis should be given is that of *verifying that the pharmaceutical product possesses and keeps its pharmaceutical quality, therapeutic efficacy, and safety* for a reasonable time which is reliably determined or established by experimental methods.

Such a well-known and thoroughly studied drug as aspirin decomposes very easily as a result of hydrolysis, thereby raising serious formulation problems. It frequently happens that formulations are proposed which, owing to the chemical and physical properties of their components, cannot guarantee their stability because of pharmaceutical or chemical incompatabilities. Although it has long been known that ascorbic acid, vitamin B_{12} and ferrous ion products are mutually incompatible, it is still possible to find drugs containing this combination on the market.

A drug's stability should be such that, at the time it is dispensed and used, it possesses all the characteristics and qualities that were established and verified at the time it was produced and manufactured. Stability must be demonstrated experimentally either by accelerated methods or by tests undertaken under experimental conditions similar to those of the marketing and distribution of the drugs. Stability data must also refer to all the quality characteristics and specifications of the product. For example, a tablet which has a greater disintegration time after a life of a few months cannot be considered acceptable although it behaves adequately in physical tests and in determinations of the content of the active principle. It is also advisable for probable degradation products to be examined and investigated, as in the case of amitriptyline, an antidepressant with certain side-effects which decomposes on oxidation by air to produce ketone, which may interfere with the analytical method (*3*). In the case of routine assays of nicotinamide, nicotinic acid behaves in a very similar way to its amide, and consequently they are incapable of detecting a probable hydrolysis (*4*).

Cases arise in which there are probably two modes of decomposition; this occurs in the case of ascorbic acid and certain corticosteroids (*5*). Under certain conditions, solutions of isoproterenol undergo a degradation process resulting in a loss of therapeutic efficacy (*6*).

In the same way, kidney disorders have been attributed to the products of the degradation and transformation of tetracycline, which are formed especially under unsatisfactory storage conditions but also under certain formulation conditions (*7*). Such a well-known drug as PAS (para-aminosalicylic acid) produces, on decomposition in solution, m-aminophenol which is more toxic (*5*).

The evaluation of the *therapeutic efficacy* of a new pharmaceutical formulation submitted for study and for licensing and registration by the competent health agency poses difficult problems. This subject has been widely discussed in many different meetings, in various reports of the World Health Organization, at meetings of international societies such as that held by the Council for International Organizations of Medical Sciences (Geneva, 1968), where the responsibilities of clinical investigators, manufacturing laboratories, and health authorities were discussed.

The shortage of clinical pharmacologists makes it advisable, *inter alia*, for control agencies to use the services of outstanding investigators who are not members of their technical staff to obtain advice on the evaluation of the efficacy and safety of drugs.

Meanwhile, and perhaps as a result of the discussions on the therapeutic equivalence of analogous or similar drugs, it has become necessary to establish experimental criteria for the *biological or physiological availability* of a pharmaceutical product—that is, the analytical determination of the amount of free active principle which is found in circulation, and which has the potential to act therapeutically. This depends on a number of factors such as the presence of certain excipients, the degree of acidity or the basicity of the formulation, the type or form of the granulation, etc., while the therapeutic efficacy depends on other factors which normally produce very varying results. For example, the speed at which nortriptyline is metabolized is genetically determined, differences having been found in the rate of acetylation of drugs such as isoniazid, sulfadimidine, and hydralazine (*8*). There are also environmental factors which obscure comparisons and hamper assays. Genetic variations of this kind can clearly be explained by differences in the behavior of the metabolizing enzymes of drugs, but there is no doubt that they give rise to a major problem in the evaluation of therapeutic efficacy.

As for bioavailability, experimental criteria are more likely to be found, although there is not necessarily any direct correlation between the values which can be obtained, for example, for concentration in plasma, and their biological activity. However, their evaluation is complicated by the fact that most of the drugs have multiple actions. Obviously, objective methods are needed to measure the effect of drugs, because, in addition, the placebo responses in man make evaluations still more difficult.

Physical factors very probably determine the different properties of phenylbutazone preparations and the different blood levels for oxytetracycline and tolbutamide (*9*). Possibly in these and other cases, physicochemical laboratory procedures will have to be found for detecting the most inactive forms and, consequently, for finding control methods relevant to the problems of the therapeutic equivalence of preparations which meet the pharmaceutical standards at present accepted and included in pharmacopoeias.

For example, by infrared spectroscopy it is possible to determine the proportion in drugs of the two polymorphic forms in which the esters of chloramphenicol can be prepared, which give different blood levels in rats and in men (*10*). Recently, differential thermal analysis has been used for the same purpose (*11*). It appears that in this case as in that of griseofulvin, prednisolone, novobiocin, and other drugs, the crystalline condition plays an important role but the official compendia still do not include standards and specifications (*12*). In the same way, there are various methods of

determining the biologically inactive products formed by the degradation of tetracycline, in which sterochemical differences occur (*7*).

There is considerable reserve about the utility of present assays *in vitro,* such as that of disintegration, which incidentally was introduced some 20 years ago into pharmacopoeias, to predict results *in vivo.* These trials are useful indicators to be used in quality control but nothing more. In recent years considerable effort has been devoted to developing dissolution *in vitro* trials as a method of predicting the speed of absorption in man, considering that the process of dissolution appears to be one of the most important stages limiting the availability of the active ingredient.

But should we not perhaps challenge the capacity of studies in animals to predict results in man, or even that of volunteers for determining the performance of a drug in patients? There is no doubt that we are at the stage of increasing development and progress.

The pharmacological activity of a substance is strongly conditioned by the *procedure by which it is given a pharmaceutical form.* The presentation of an active principle in the form of a drug facilitates its administration, but at the same time may interfere with its activity. For example, calcium diphosphate, which is used as an excipient in pharmaceutical preparations, reduces the absorption of tetracycline whereas citric acid and glucosamine increase it.

In the same way, the chemical form in which an active drug is presented is a major factor in its therapeutic performance since it can substantially modify its solubility, absorption, efficacy, or toxicity. There are many cases in which the formulations or even investigational data refer to a drug as a base or as an acid when in actual fact a salt or an ester is being used.

For this reason, even in the clinical investigation of a pharmaceutical product, we need to know the procedure used for presenting the active principle as a drug, thereby conferring on it satisfactory and continuing activity and safety in use.

Therefore, the determination of physiological availability must be faced as a problem to be solved jointly by industry and official control agencies. It is an important factor to be determined in the over-all quality control. Recently the U.S. Food and Drug Administration published some basic guidelines which must be followed by its personnel in dealing with this problem (*13*).

In that communication, the Bureau of Drugs of the FDA recognized that it is not at present possible to determine the biological availability of all the therapeutic arsenal because of the complexity of the problem. The demonstration of biological availability has become in the last three or four years an essential element in the official licensing and registration of a drug. It is one more element in the control of pharmaceutical products which was not included in the traditional approach to quality control aimed basically at determining manufacturing conditions, detection of production defects, and analysis and dosage of starting materials and finished products.

The guidelines of the Bureau of Drugs establish a clear dividing line between experimental data on bioavailability and the results produced in controlled clinical trials. In the former, it is a matter of obtaining blood or urine levels or other physiological indicators which give an indication of the possibility that the active principle is available to be used therapeutically. But it is stated later that, if there is no proper method of determining appropriate physio-

logical indicators, the control authority will accept the best data that can be produced in experiments *in vitro,* that is to say, assays of dissolution, or to a lesser degree of degradation. Clearly, this raises a critical problem for the official control of medicaments in all pharmaceutical forms, but the more so when it is a matter of making comparisons not only of similar or identical preparations, but of new formulations of known active principles, or of new pharmaceutical forms thereof.

A similar position to that indicated by these guidelines has been adopted by our Institute with respect to *preparations based on prolonged action microgranules* which have recently proliferated and for which there is a certain amount of contradictory literature about therapeutic effects. The formulation of a prolonged action drug is particularly important because its administration may result in the liberation of a greater or lesser amount of that which is therapeutically necessary, especially if the active principle metabolizes slowly and accumulates, reaching a blood level which is unacceptable from the toxicological standpoint. We are now studying together with the pharmaceutical industry the comparative performance of other pharmaceutical forms used with the same active principles. We will also have to try to find a relationship with physical and chemical assays. Obviously, it would be very useful, because they are much more simple, if assays *in vitro* were found which could demonstrate the physiological availability of a pharmaceutical preparation. Recently, a modified disintegration assay has been proposed aimed at demonstrating the capacity of tablets and capsules to break up and disintegrate in such a way that the original particles of the drug are formed (*14*). Although it cannot be considered a substitute for more certain methods such as that of dissolution, it may serve as a guide in developing formulations or even be used as a pharmacopoeia method. Of course, it is not necessary to demonstrate the physiological availability of certain pharmaceutical forms, such as solutions used in intravenous preparations, topical preparations, and in general, topical drugs because of the very nature of the drug and its purpose.

Since we have already spoken of biological indicators of drugs, we should mention another which is of special importance from the standpoint of the hygiene of production and pharmaceutical quality. I refer to the establishment of satisfactory *standards for establishing the usefulness of a sterilization process* and of the number of microorganisms for determining the acceptability of non-sterile products, especially where excipients such as starch or talcum are used.

These matters have recently been dealt with in the general chapters of the 1970 United States compendia, U.S. Pharmacopeia (XVIII) and National Formulary (XIII). The present status of the development of therapy justifies an in-depth study to ascertain from the official standpoint whether or not they should be established as legal requirements.

With respect to *experimental toxicity data,* care must be taken not to make the mistake of approving exaggerated or unnecessary standards. However, the control authorities are faced with the problem of evaluating toxicity data of a variety of products whose formulations represent modifications in content, dose, or pharmaceutical form of already approved drugs. These modifications can considerably change the safety of the medicament.

In view of the most recent methodological advances in the use of tagged drugs in electronic microscopy, in the identification of metabolites by chemical means, and in very

sensitive biochemical determinations, official drug control organizations are likely in the not-too-distant future to regard such studies as essential in toxicological evaluations. There is no doubt that we are on the threshold of molecular toxicology. Studies on complete animals will be complemented by histochemical, histoimmunological, electromicroscopic, and tissue culture studies as well as enzyme induction and activation, and in the last instance, by studies on the mechanism of interaction of a pharmaceutical product with protein biosynthesis.

Frequently, in evaluating these data it is necessary to examine applications relating to formulations in which there are *potential therapeutic incompatibilities*, as a result of interactions between active principles or with drugs used for the same treatment. It is recognized that each day it is more probable, in view of the increase in the therapeutic arsenal and of self-medication, that the patient himself may cause dangerous or even fatal interactions. Therefore, special precautions must be taken in the evaluation of new drugs.

Finally, the collection of data on adverse effects, once drugs are placed on the market, and their evaluation to decide the appropriate health measures must be considered a drug control problem.

It is essential to establish or improve national and international systems for collecting and supplying data on the efficacy and toxicity of drugs. In all scientific fields *good information and documentation* is necessary, and even more so in the field of studies on drugs with a view to preventing delays in the introduction of promising pharmaceutical products or for facilitating the withdrawal of dangerous products.

The World Health Organization has been concerned with this problem and a report on its activities will be given at this Seminar.

Final Comments

I have not attempted to deal in detail with all the problems currently confronting drug control, but only with some of the most recent problems which have just begun to be studied. Accepting the broader concept of integral quality of a medicament, official control agencies must take into account and evaluate all aspects bearing on the efficacy, safety, and quality of pharmaceutical preparations intended to be used in human medicine.

"The future of drug control appears destined to provide one of the most interesting areas for studying the impact of technological knowledge on the total social picture of medical care." (*12*)

Obviously, in recent years a new dimension has been added to the complex problem of the design, production, and control of drugs. It is the responsibility of all those involved in official drug control to redouble their efforts to make pharmaceutical products effective, safe, and stable. We trust that these efforts can be undertaken in collaboration and cooperation with a prosperous pharmaceutical industry interested in the well-being of mankind.

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ESSENTIAL ELEMENTS OF A NATIONAL DRUG CONTROL AGENCY

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The broad objective of the Food and Drugs Act in Canada, as far as drugs are concerned, is to protect the Canadian consumer from health hazards and fraud in the manufacture, importation, advertising, and sale of drugs.

The Act is supported by a series of Regulations issued by the Department of National Health and Welfare, but proclaimed by Order-in-Council; that is to say, each new or revised regulation does not have to go back to Parliament for approval. It will be obvious of course that each proposed new or altered regulation is examined by the Department of Justice since the Food and Drugs Act is a part of the Canadian Criminal Code, which is federal, and not provincial, legislation. These examinations by the Department of Justice are based on the Act, its interpretation, and the degree to which proposed regulations meet these criteria. In the case of regulations approved and promulgated by Order-in-Council that come into disputation, the Courts of Law must be approached for final comment on their validity and legality.

In Schedule B to the Act, various pharmacopoeias are accepted whose standards serve as the basis for definition of drug quality. These are:

Pharmacopoea Internationalis
The British Pharmacopoeia
The Pharmacopeia of the United States of America
Codex Français
The Canadian Formulary
The British Pharmaceutical Codex
The National Formulary

In various other places within the Regulations additional standards are defined for those drugs not included in the official compendia, or not considered sufficiently stringent.

In addition there are Official Methods designated for particular circumstances, which are not listed in the Food and Drugs Act and Regulations, but contained in a separate document.

The standards of acceptability of new drugs coming into commercial sale for the first time must also be specified as far as possible. It will be difficult to specify some of the requirements too precisely since they will vary widely depending on the type of drug. However, broad guidelines can be established which will form a frame of reference for subsequent dialogue between manufacturer and authorizing body.

Many standards of manufacturing facilities and controls can be specified, whatever type of drug is involved. In Canada this is done partly by regulations which are part of the Food and Drugs Act and Regulations, and by guides such as the one for drug manufacturers and the guide for imported drugs, manufacturing facilities, and controls.

The above definitions of standards of drug action and quality serve as the blue-

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print for all policies and actions of a drug control agency. Only when these conditions have been determined can one specify what courses of action are necessary for the surveillance and enforcement of these conditions.

The treatment of an application for a new drug will be considered next. A new drug is defined (*1*) as:

a) A drug that contains or consists of a substance, whether as an active or inactive ingredient, carrier, coating, excipient, menstruum or other component, that has not been sold as a drug in Canada for sufficient time and in sufficient quantity to establish in Canada the safety and effectiveness of that substance for use as a drug;

b) A drug that is a combination of two or more drugs, with or without other ingredients, and that has not been sold in that combination or in the proportion in which those drugs are combined in that drug, for sufficient time and in sufficient quantity to establish in Canada the safety and effectiveness of that combination and proportion for use as a drug; or

c) A drug, with respect to which the manufacturer prescribes, recommends, proposes or claims a use as a drug, or a condition of use as a drug, including dosage, route of administration, or duration of action and that has not been sold for that use or condition of use in Canada, for sufficient time and in sufficient quantity to establish in Canada the safety and effectiveness of that use or condition of use of that drug.

In Sections C.08.002 and following sections of Division 8 of the Food and Drugs Act and Regulations, the requirements and obligations are set forth on what is required in a New Drug Submission. This submission is reviewed in minute detail by multidisciplinary teams of physicians, pharmacologists, pharmacists, chemists, etc., in well-defined sequences and orders, before a Notice of Compliance of a satisfactory submission is made. This notice constitutes the authority to sell the product.

I shall not dwell on these requirements at the present time since a revision of this provision is currently in progress. A draft of the proposed regulations was circulated to interested parties recently. Comments and feedback are considered before final decisions are made.

A permanent committee called the Canadian Drug Advisory Committee, with membership from industry, university, medical, pharmacological, and pharmaceutical associations, meets twice a year and provides invaluable comment and advice.

Provision has been made in the proposed regulations for the distribution of new drugs to qualified investigators. The conditions under which a manufacturer may sell a drug to a qualified investigator for the purpose of clinical trials are laid down. The question of time limits for issuing a Notice of Compliance (indicating a satisfactory submission) is one of lively interest to manufacturing organizations.

Consideration is being given to a Guide to Manufacturers concerning the preparation of submissions on new drugs. The information to be incorporated in the Guide should make for a much more rapid treatment of submissions, which are often slowed considerably for lack of particular important items of information.

A number of remedies are offered for sale and are administered under the Proprietary or Patent Medicine Act. The terms of this act require application, prior to sale, for a certificate of registration for every product offered for sale in Canada.

At the time of application for registration the manufacturer must disclose the quantity of drugs contained in the product, which information is regarded as confidential. An annual registration, with accompanying fee, is required.

Excluded from the Proprietary and Patent Medicine products are all pharmacopoeial drugs listed in any document in

Schedule B, all drugs listed in the Narcotic Control Act, preparations exposing the true formula or a list of medicinal ingredients, and prescription drugs in Schedule F of the Food and Drugs Act. There are also provisions for limiting the amount, and requiring the disclosure of the name of, certain more potent drugs, such as analgesics, for example.

Good manufacturing practices based on well-founded principles of pharmaceutical quality control are one of the most desirable features of any pharmaceutical industry. Such principles have been laid down (*2*) and the practices to be encouraged also documented (*3*).

It is obvious that a system of periodic inspections is necessary to ensure that such good manufacturing practices are being observed. In Canada these are performed in a routine manner and form the basis for a rating assigned each manufacturer. This rating is also used as an indicator of further investigations (Regulatory Plant Inspections) for the companies with a low rating. Repeated inspections every six or 12 months are then instituted. It also serves as a guide for other government departments for drug purchases, under an Interdepartmental Drug Standard (74–GP–1b).

Frank discussion of the inspection results with industry personnel is encouraged both at the time of the inspection and in subsequent formal reports. The value of this feedback mechanism cannot be overemphasized. This is a reason why inspection staffs should have as wide a training as possible. Frequent orientation and training courses are a part of inspectors' duties in the Canadian Food and Drug Directorate, involving contacts with research and development in pharmaceutical chemistry, pharmacology, microbiology, and other related fields.

The rigorous inspection just described must be complemented by a continuous checking of manufactured products, on a sampling basis. Priorities are assigned taking into account criticality of the drug, volume of use, knowledge of manufacturer, together with adequate analytical methodology. The priorities in such a system are changeable depending on drug usage and on feedback from the monitoring system.

It is important that the best use possible be made of facilities which will multiply the through-put of drug samples even if this means some slight loss in accuracy. In Canada, a Drug Quality Monitoring Laboratory was put in operation in the Central Regional Laboratory after feasibility studies were completed in the Pharmaceutical Chemistry Division at headquarters. This laboratory acts as a screen to separate those drug specimens needing further investigation from those considered satisfactory. Further investigation is then done by official methods on official samples which are the basis for enforcement.

In the context of automated analytical facilities, one must keep in mind expenditures on personnel and equipment in relation to the total number of specimens of a drug product. In some cases the number of brands or strengths of a particular drug product is insufficient to justify the development of methods suitable for automated techniques, or the actual automated determination.

In such circumstances the possibility of grouping several regional area needs in one central location may make an automated facility feasible.

Not only must the normal physicochemical parameters of drug quality be known, but the absence of other factors must be assured, such as bacterial or microbiological contamination and cross-contamination from other drugs of potential hazard, e.g., penicillins.

Notwithstanding the necessity of determining the normal physicochemical parameters just mentioned, it is prudent to consider in addition the question of bioavailability of solid oral dosage forms. Simply expressed, this is the fraction of a drug from a dosage form that is absorbed or excreted (via the urine) compared to the pure drug substance administered in solution.

In all new drug submissions (*4*) this information will probably normally be included since it should be developed, methodology permitting, in the course of preclinical and clinical examinations, sometimes to the point where clinical results can be correlated with bioavailability data.

For drugs not in "new drug" status, it is necessary to establish in some way that the drug is available to the body. Many examples have been described (*5, 6*) of drug products satisfying pharmacopoeial requirements yet releasing very little of the medication to the body. It goes without saying that the principle of adherence to pharmacopoeial standards is academic if the drug is only 50 per cent available, that is, corresponding to only one-half of a tablet.

Much research has been done in the pharmaceutical chemistry and pharmacology divisions of research laboratories of the Food and Drug Directorate to determine the factors affecting bioavailability and the extent of the problem. Over the past years many drugs have been studied, with as many commercial brands as available being investigated. Some of the drugs are tolbutamide, phenylbutazone, PAS, sulfadiazine, sulfisoxazole, triple sulfas, aspirin, amphetamines, ferrous ion products, nitrofurantoin, acetaminophen, tetracycline, hydrochlorothiazide, chlorthiazide, and sulfamethizole.

Measurement of blood level and urinary excretion of unchanged drug and metabolites in human volunteers, mostly within our organization, has been the approach to comparison of marketed drugs with some standard. The standard is usually a solution of the pure drug substance in water, or an emulsion in some fluid. Comparisons are more useful if the data from the innovator's product (the product with the longest history of use) is also determined.

Our policy in this critical area has been one of research and education. It is not proposed that we can experimentally determine the bioavailability of all brands of all drugs on the Canadian market. This is a manifest impossibility though there have been voices that would propose this approach.

Our research has gone into the principles whereby bioavailability might be adversely affected; and since slow dissolution of an active ingredient from a solid oral dosage form may be a rate determining step, we have concentrated on drugs of low solubility and have emphasized correlations of human bioavailability with *in vitro* dissolution measurements.

In these efforts we have collaborated closely with the United States Pharmacopeia and the U.S. National Formulary through a USP/NF Joint Panel on Physiological Availability, in which the U.S. Food and Drug Administration was also very active. As a result of these and other activities, a dissolution test has now become a pharmacopoeial requirement for some 14 drug substances, but the correlation of bioavailability with dissolution testing needs to be investigated in much greater detail.

The definition of standards for bioavailability is no easy matter, particularly for products that are not subject to the "new drug" requirements. Until these standards become available, we must use arbitrary ones, and utilize broad regulatory action that would permit us to request bioavail-

ability data from the manufacturer of a particular brand that gave cause for concern. There are a number of markers, or screens, that could be used to pinpoint such a concern. These could be:

a) Disintegration time compliance.

b) Dissolution time compliance.

c) Pharmacy or hospital complaints of ineffectiveness (via drug adverse reaction monitoring).

d) Comparison of blood levels or urinary excretion of the brand in question with a reference standard or the innovator's product in animals.

e) Same comparison in a small human study.

The penalties to be meted out when there are violations of the conditions described at the beginning of this paper should form a documented portion of the legislation. Far more difficult is the determination of the level at which a violation occurs. For example, a percentage point outside drug content requirements for an otherwise incompliance manufacturer may be far less serious than an antibiotic capsule that far exceeds the disintegration time requirements.

Severity of the offense, repetition of the same offense, complicating circumstances (e.g., joint responsibility), and many other factors may have an influence on the type of action necessary in the event of violations. An internal set of guidelines for administrative use could be useful in this context. Minor potency or weight variation errors in solid dosage forms are less serious than errors in identity or labeling.

At the manufacturing and primary distribution level, the federal agency has control. At peripheral levels of distribution, and those where there is direct contact with the public, essential liaison with local or municipal medical and pharmaceutical authorities and associations is a valuable mode of exercise of authority.

A recent development in making the information available to practitioners is the publication within my own Department of a monthly bulletin on drugs. Although the first few issues generally contained Product Monographs (a description of a product agreed to by the manufacturer and the Food and Drug Directorate), plans are well in hand to report the results of analytical and other tests.

The impetus for this informational service came from a Special Committee of the House of Commons under the chairmanship of Dr. H. C. Harley. One of the conclusions of that Committee was that participants in the health team had too little information in their daily practice on which to base the sound choice of drugs. The Harley Committee's recommendation that gave rise to the monthly bulletin is as follows: "That the Food and Drug Directorate publish not less than once a month an informative bulletin to the medical profession giving complete details on drugs and their actions and reviewing major drug uses in Canada."

It is the intention of the Directorate to implement these proposals by the action just outlined. Response to the early issues has been very favorable.

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SUPPORT OF DRUG CONTROL BY THE PAN AMERICAN HEALTH ORGANIZATION

DR. ALEJANDRO SOTELO *

Because of the harm that badly prepared food and drugs can cause, it has been recommended for some time that the Governments maintain supervision of production in order to guarantee that the public receives safe foods as well as safe and effective drugs and therapeutic substances. It has also been recognized, in recent years, that the Governments should prevent the distribution of harmful cosmetics and protect the public from dangerous items such as insecticides, caustic agents, solvents, etc., which may be found in the home or contaminate foods.

The volume of products governed by consumer protection laws is enormous. For example, the present retail value of pharmaceutical products consumed annually by the Latin American people has been estimated at $1.9 billion. The annual value of food consumed is naturally much greater.

Numerous problems arise in connection with food and drugs. The most important are related to the following aspects:

Drugs

a) Efficacy and safety.

b) Adulterated drugs and drugs that are defective due to failure to follow proper procedures during manufacture.

c) Unstable drugs and the loss of potency by drugs while still in distribution channels.

d) False claims for the curative powers and safety of drugs.

e) Restriction of the sale of habit-forming drugs such as narcotics and psychotropic drugs.

Food

a) Contamination from harmful bacteria, such as *Salmonella*.

b) Residues of pesticides and chemical substances used on vegetables and fruits.

c) Safety of chemical substances (food additives) used by food processors.

d) Antibiotic residues in food (for example, penicillin in milk from cows treated for mastitis with this drug).

e) Safety of new foods and new forms of food preparations such as frozen foods, precooked foods, and other "convenience foods."

f) Safety of coloring agents added to foods.

g) Lack of food hygiene.

h) Standards for the composition of essential foods such as bread, cheese, jelly, etc.

i) Methods for deceiving the public, such as inexact weights and deceptively large packages.

To the extent that available resources have permitted, the Pan American Health Organization has assisted countries in formulating adequate consumer protection laws and in establishing effective government agencies to implement these laws. In the important area of drug control, PAHO lends

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support as follows:

1. General advisory services have been furnished to the Governments, and adoption of the following principles has been recommended:

a) Each country should enact a comprehensive drug law. We have suggested that the laws of the various countries should be uniform to facilitate international commerce in drugs manufactured in the Americas, and to guarantee the preparation of drugs of uniformly high quality.

b) Each country should have a well-coordinated agency to administer its drug laws. The drug control agency should form part of the national health services and should be directed, preferably, by a person with well-defined authority so far as compliance with the appropriate legislation is concerned.

c) The agency's inspectors, analysts, and administrators should have the specialized training which will enable them to cope with the complex problems currently facing drug control agencies.

d) The Governments should support the drug control agencies with sufficient funds to enable them to carry out high-level control activities.

e) Countries which are unable, because of their limited technical resources, to establish national drug analysis laboratories, should send drug samples to centers of recognized competence, such as the Specialized Analysis Laboratories of the University of Panama. An alternative course of action might be to join with other countries to establish a group laboratory.

2. In addition to providing general advisory services, PAHO has answered requests for technical advice on special aspects of drug control. In the past 10 years, it has sent technical advisers for this purpose to Argentina, Brazil, Chile, Costa Rica, Mexico, Panama, Peru, Uruguay, and Venezuela, and to the English-speaking countries of the Caribbean. The experts have remained in these countries from one week to three months. In each case, PAHO has provided the Government with a report of the experts' findings.

It is interesting to note that although different advisers have participated in these studies, their opinions and recommendations have been uniform and consistent. In general, the reports have pointed out the need to improve the organization of national drug control agencies, supplement the training of personnel, and increase the funds available for control activities.

3. On numerous occasions, PAHO has provided government agencies with reagents, laboratory texts, and other items. To the extent that resources permit, the Organization fulfills the technical assistance requests presented by the countries.

4. Since personnel is the most important element in any organization, PAHO has devoted a large part of its activities and available funds to training government health officials. This same course of action has been followed in connection with drug control, and over the years PAHO has sponsored the award of fellowships for the training of numerous analysts and other drug control officials in the countries of the Region. These fellowships have made possible the training of personnel in scientific institutions throughout the world. Activities have been concentrated, however, in the U.S. Food and Drug Administration and the Food and Drug Directorate of Canada.

Recently an intensive five-week training course was offered in Washington, D.C., for drug analysts from nine Latin American countries and the Caribbean area, the U.S. Food and Drug Administration being responsible for the training. This was PAHO's

first attempt at sponsoring a group training program for drug analysts.

PAHO's concern with the need for high-level training of analysts and other drug control officials has led it to sponsor the establishment of a regional institute for drug quality. The proposal to create this institute was first formulated in a report prepared in 1965 by Dr. C. A. Morrell, former director of Canada's Food and Drug Control Laboratory. This proposal was supported on various occasions by the Ministers of Health, most recently at the Special Meeting of Ministers of Health of the Americas (Buenos Aires, October 1968).

The creation of this institute is still in the planning stage for lack of the necessary funds. Nevertheless, it is expected that the realization of this project will have an important and lasting effect upon the drug control situation in the Americas. The institute will provide the following benefits:

a) It will facilitate high-level training for drug analysts in Latin America and thereby increase the effectiveness of this personnel.

b) It will serve both as a training center for senior drug control administrators and inspectors and as a forum for the exchange of ideas and experiences among officials charged with applying the drug laws. This training will enable administrators and inspectors to better orient the personnel under their supervision.

c) It will improve the professional prestige of drug analysts, drug control administrators, and inspectors in the Member Countries and thereby increase the scope of their activities and their effectiveness in verifying the quality of drugs in each country.

d) It will prompt each Latin American drug manufacturer to make sure its analysts are as well trained as the Government's, thus improving drug quality at the production site.

e) It will act as an information center, providing national laboratories with reliable analytical procedures obtained from a worldwide array of scientific publications.

f) It will aid countries in solving unusual analytical problems.

g) It will carry out research to establish examination procedures uniformly applicable to new drugs introduced in Latin America.

h) By fostering uniformity of analytical procedures and standards, the institute will have a beneficial effect in facilitating uninterrupted trade of drugs between countries, thus giving support to Latin American common market principles.

i) It will improve Member Governments' capacity to examine drugs and guarantee their quality. This in turn will increase the confidence of government administrators of treatment centers, social security systems, and other services which make large-scale drug purchases based on relative prices offered by competing suppliers.

j) It will benefit the Latin American scientific community, particularly in the country where the institute is established. This beneficial effect will be felt in diverse branches of biomedical research.

It should be pointed out that the proposed institute will not act as a control laboratory for any country, nor will it have juridical powers of any kind. Its purpose will be simply to facilitate the task of national drug control agencies; all its activities will therefore be aimed at supporting and strengthening the work of national authorities.

5. Since 1965, PAHO has sponsored annual meetings of officials responsible for control of food and drugs in Costa Rica, El Salvador, Guatemala, Honduras, Nicaragua, and Panama. The meetings have promoted these neighboring countries' traditional cooperation in resolving their common health

problems, and have caused attending officials to form a better idea of the area's food and drug quality problems. These officials have submitted proposals to their Governments for application of uniform procedures dealing with these problems. PAHO believes that its support of these regional meetings has proved very worth while.

In connection with its advisory activities in Central America and Panama, PAHO sponsored the establishment of the University of Panama's Specialized Analysis Laboratories. This facility performs an important role in food and drug analysis within the area, and the Central American countries accept its analyses as official for purposes of meeting their legal food and drug registration requirements.

Another regional drug control project being studied would affect the Caribbean area. The Ministers of Health of Barbados, Guyana, Jamaica, Trinidad and Tobago, and the other English-speaking countries of the Caribbean met in 1969, and again in April 1970, to examine health matters of regional interest. At the second meeting they approved a resolution requesting that PAHO carry out a study to determine the feasibility of establishing a drug analysis laboratory in the Caribbean to serve the interested countries of that area. The necessary data on this matter have been collected; conclusions based on the data will be presented at the third conference of Ministers of the Caribbean area, which is scheduled for early 1971.

MODERN DRUG CONTROL LEGISLATION

ROBERT S. ROE *

Food and drug regulation in some form has been practiced by most societies since ancient times. In earlier centuries, and even until recently in some countries, such regulation was minimal and was directed mainly against crude frauds such as short weight or worthless substitutions or against products that were seriously harmful or poisonous.

As trade and commerce developed and as manufactured products replaced home-grown and locally prepared products, more sophisticated substitutions and adulterations occurred. In modern industrial societies, it has become recognized that action by the government is essential to assure wholesome foods and safe drugs and to protect the public against fraud and deception in the sale of these products.

Scientific and technological advances in recent decades have enormously increased the necessity and importance of adequate and well-conceived laws and regulatory enforcement programs to ensure the proper potency, the purity, and the safety and effectiveness of modern drugs. The scientific advances and technical capabilities that have produced the spectacular events of orbiting satellites and men walking on the moon have also produced perhaps less spectacular, but possibly even more important and significant, developments in chemistry. These developments have resulted in thousands of new chemical compounds—never before in existence—that have provided new building and packaging materials, new agricultural chemicals, and new potent drugs.

It has been estimated that more than 80 per cent of the drugs now in active use by physicians were not available 20 or 25 years ago. A comparison of the listings in pharmacopoeias of the 1940's and those current today readily demonstrates that change.

Crude vegetable drugs have largely been replaced by purified extracted active ingredients or by new synthetic compounds. Many products of microbiological processes and many synthetic chemicals having rather specific physiological activities are now available for treatment of serious diseases. Some of these new drugs, such as the antibiotics and steroids, are very potent. Often the difference between therapeutic and toxic doses is small. While these new drugs make possible the successful treatment of serious diseases that previously could not be managed, they also pose the possibilities of harmful side-effects if misused or if not of the intended purity and potency.

It is important that physicians and hospitals have assurance as to the safety and effectiveness—the purity and potency—of the drugs they prescribe and administer. It is important that patients be provided with drugs that are of represented identity, composition, strength, and quality and that the drugs be adequately and informatively labeled to ensure safe and effective use.

It is the aim of drug control laws to protect the public health with respect to the use

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of drugs; and through adequate and competent enforcement facilities to prevent distribution of dangerous, unfit, worthless, or misrepresented drugs. Many countries have found it necessary to amend or completely revise their drug control laws and regulations in order to cope with problems arising from our present era of new drugs.

In the United States, the first federal law dealing with regulation of drugs generally was the Food and Drugs Act of 1906. That law was in effect until 1938, when it was replaced by the Food, Drug, and Cosmetic Act. The act of 1938 contained the very important requirement that new drugs be shown to be safe under the conditions of intended use before they legally could be marketed. But this law soon became outdated because of the rapid advances in science and industrial technology. A number of important and profoundly significant amendments reflecting the problems of this scientific age were enacted in the 1950's and 1960's—the pesticide chemicals amendment, the food additive and color additives amendments, and the drug amendments of 1962. The 1962 law requires that drug manufacturers must prove that their products are effective as well as safe, and establishes other important requirements.

Considerable revisions in the Canadian law were made in 1953–1954 to update the requirements and enforcement authority of that statute, whose stated purpose is ". . . to protect the public against health hazards and fraud in the sale and use of foods, drugs, cosmetics, and medical devices. . . ." And subsequently, additional amendments to the Canadian Act and Regulations have been adopted.

There is worldwide recognition of the need for governmental regulation of drugs to ensure quality control and safety, and to prevent misrepresentation and fraud, and there is also recognition of the desirability of some uniformity of requirements and enforcement procedures among the various countries.

This is reflected in a report of a conference of European countries held in Helsinki in November 1968 under World Health Organization sponsorship on "The Quality Control of Pharmaceutical Preparations." The report contains this statement of the purpose of the conference:

> The main objects of the Conference were: (1) To study present arrangements for quality control of pharmaceutical preparations in the respective countries of the participants; (2) To examine the work of WHO in this field; and (3) To review the work now being done by different groups of countries, including a number of European countries which under multilateral agreements are endeavoring to achieve a certain unity of views and to coordinate their action.
>
> This is in keeping with efforts throughout the world to ensure the adequate quality of medicinal products moving in national and international commerce and in order to facilitate their registration. The Conference was also intended to further the application of existing knowledge to the quality control of medicinal products at laboratory level, as well as through the inspection of manufacturing establishments. . . .[1]

The Special Meeting of Ministers of Health of the Americas (Buenos Aires, 1968) reflected the interest and concern of the Latin American countries in regard to drug control. The Health Ministers urged that increased attention be given to drug control and that the countries should have adequate laboratory facilities for analysis of samples.

The V Seminar on Food and Drug Control for Central America and Panama, held in 1969, requested the Pan American Health Organization to prepare a draft of basic law

[1] "The Quality Control of Pharmaceutical Preparations." Report on a Conference, Helsinki 25–29 November 1968, Regional Office for Europe, WHO, Copenhagen, Document EURO–2032, p. 3.

for modern drug control for presentation at the 1970 seminar. In response to this request, a suggested form of a "National Drug Control Law" [2] was prepared and presented at the seminar held in Panama in May 1970. It is believed that this suggested "model law" might be of interest to all the Latin American countries, since it offers practical guidance for regulating drug manufacture and distribution within a country and its form and content can easily be adapted to accord with the prevailing customs of the individual countries.

For the preparation of the draft law, a review was made of the existing laws and regulations of the Central American countries and Panama. It was found that, while all of these countries require drug registration, there are significant differences regarding (1) the categories of drugs that are required to be registered; (2) the information that a company must present in an application for registration; (3) the qualifications of the persons responsible for deciding whether or not an application should be approved; and (4) the length of time for which an approved application is valid.

We think that registration of drugs is a sound requirement, and this is retained as an important item in the suggested law. The proposed law states (Article 3): "A drug may not be imported, manufactured, repacked, relabeled, stored, distributed, or sold unless there has been filed with the Minister (the Minister of Health) an application for registration of the drug and such application has been approved by the Minister."

The proposed law authorizes the Minister to issue regulations specifying the information that should be included in applications for registration; it provides for a scientific advisory committee to judge the registration applications; and it provides that an approved registration shall be valid for five years, after which renewal of registration must be obtained. However, any significant change in composition, labeling, or advertising within the five-year period would invalidate the registration unless such change is approved by the Government.

It is believed that a well-selected and qualified scientific advisory committee can serve a very important and essential function in assisting the Minister in reaching sound decisions in respect to registration of drugs by providing a reasoned opinion based on the available scientific data. The activities of such a committee may also incidentally serve to acquaint the medical community of the country with the significance and importance of the law to public health and gain the understanding support of the country's physicians.

The proposed statute states: "The scientific advisory committee shall have such composition as the Minister shall determine but in no event shall it consist of less than three members, including a physician, a pharmacologist, and a pharmacist."

The proposed law also provides that if new information not previously available should indicate that a registered drug may not be effective or safe for use in the manner and for the purposes approved in the registration, the Minister may require such revisions in the composition of the drug, its packaging, labeling, or advertising as may be necessary to ensure safety and effectiveness—or if such revision is not feasible or practicable, he may simply revoke the registration.

A drug already legally in commerce within the country at the time of enactment of this proposed law would be given an ex-

[2] The model law appears in Appendix 2 to this volume, pp. 147–154.

emption from the new registration requirements under stated conditions to permit orderly change; such a drug would have a temporary exemption provided the sponsor submits an application for registration within six months after enactment of the law. Such temporary exemption would expire when the Minister rendered a decision on the application, or two years after enactment, whichever came first.

Other important provisions of the suggested law are discussed under the following headings:

Licensing of Manufacturers (Article 4)

The proposed law states: "No drug shall be manufactured, repacked, or relabeled in a domestic establishment that is not licensed by the Minister for such purpose."

It authorizes the Minister to issue regulations specifying the requirements for a license.

It provides that a license is valid for a year and must be renewed annually; it authorizes the Minister to revoke a license if:

a) The establishment fails to maintain current good practices in the manufacture and quality control of drugs;

b) Authorized agents of the Minister are refused permission to inspect the establishment at a reasonable time;

c) The operator of the establishment refuses to provide information requested by the Minister's agents concerning any aspects of the manufacture, repacking, or relabeling of drugs at the establishment.

Prescription Drugs (Article 5)

The suggested law contains the provision: "The Minister shall publish a list of drugs which must be restricted to dispensing on prescription because they are habit-forming or are otherwise unsafe for use by the public except under the supervision of a licensed physician. . . ." It also specifies the information that must appear in labeling and advertising. It authorizes the Minister to issue such regulations as may be necessary to carry out these provisions.

Non-Prescription Drugs (Article 6)

The suggested law requires that the package of a drug that is safe for direct sale to the public must supply the following information: name and quantity of each active ingredient; the recommended dose; such warnings as may be necessary to ensure safety; the quantity of contents in the package; the name and place of business of the manufacturer, packer, or distributor; the lot number; and the conditions for which the product is to be used.

List of Diseases (Article 8)

The proposed law authorizes the Minister to ". . . publish a list of diseases, disorders, abnormal physical states, or symptoms thereof, which cannot be treated successfully without the supervision of a physician and for which drugs may not be promoted in labeling or advertising directed to the public."

Names of Drugs (Article 9)

If a drug product is commonly referred to by a non-proprietary name, the proposed law would require that the label, labeling, and advertising bear such name as the identifying name for the product; also it would require that the name used in labeling or advertising to designate an ingredient be the non-proprietary name commonly or usually employed for designating the substance.

The proposed statute authorizes the Min-

ister to determine the non-proprietary name that must be used for a particular drug or ingredient if confusion has arisen because two or more names have been used.

Proprietary names may also be used in addition to the required non-proprietary names provided such use does not create a misleading impression as to the identity or composition of the drug.

Adulterated Drug (Article 10); Misbranded Drug (Article 11)

The proposed law defines a number of conditions which would cause a drug to be classed as adulterated or misbranded.

A drug would be deemed *adulterated*:

a) If it is represented as an article listed in a recognized pharmacopoeia or formulary and its identity or strength differs from, or its quality or purity falls below, the standards set forth in the pharmacopoeia or formulary.

b) If it is not represented as an article listed in a recognized pharmacopoeia or formulary and its identity or strength differs from, or its quality or purity falls below, that which it purports to possess.

c) If it consists in whole or in part of any filthy, putrid, or decomposed substance.

d) If it has been prepared, packed, or held under insanitary conditions.

e) If it has been manufactured, processed, packed, or held in premises or equipment, or under conditions that are not in conformity with current good manufacturing practices.

f) If it contains for purposes of coloring a substance which is not generally recognized as safe for coloring that particular type of drug.

g) If it is packed in a container which introduces harmful substances into the drug or otherwise reacts with the drug in a manner which significantly alters the properties of the drug.

A drug would be deemed to be *misbranded*:

a) If its labeling or advertising is false, misleading, or deceptive in any particular or is likely to create an erroneous impression regarding its identity, composition, quantity, usefulness, or safety.

b) If its labeling or advertising fails to conform with the requirements imposed by the various sections of the law.

c) If it is represented as an article listed in a recognized pharmacopoeia or formulary which specifies a particular form of packaging for the article and it is not packaged in the specified form.

Prohibited Acts (Article 13)

The proposed law specifically prohibits:

a) The importation, manufacture, storage, transportation, distribution, or sale of any drug that is (i) in violation of registration requirements, (ii) adulterated, or (iii) misbranded.

b) The manufacture, repacking, or relabeling of any drug in a domestic establishment not licensed as required.

c) The use of any representation in labeling or advertising of any drug which is inconsistent with labeling accepted for registration.

d) The refusal to permit the Minister's agents to inspect drug establishments, facilities, records, equipment, or raw materials, etc.

e) The refusal to provide the Minister's agents with pertinent information.

f) The improper disclosure of information obtained in the course of administering or enforcing the law which is entitled to confidentiality.

Penalties (Sanctions) (Article 14)

The penalties provided by the proposed law include:

a) Seizure or embargo of violative stocks or shipments.

b) Fines or imprisonment of persons convicted by appropriate courts of violating any provisions of the law.

The proposed law also includes authorization for the Minister to: (a) provide quarters, facilities, equipment, and staff to carry out the provisions of the law (Article 15); (b) establish and collect reasonable fees for registration and for licensing (Article 16); and (c) promulgate regulations giving effect to or interpreting the purposes and provisions of the law (Article 17).

It is believed that a statute with these provisions would be a satisfactory legislative tool for achieving modern regulatory drug control. Through active enforcement based on adequate financing, such a law would provide reasonably dependable assurance of public health protection with respect to the safety and usefulness of the country's drug supply.

HEALTH REGISTRATION PROCEDURES FOR NEW-DRUG PHARMACEUTICALS

DR. SIEGBERT HOLZ *

Introduction

This report on the registration of new drugs, requested by the Pan American Health Organization, is presented by me in my capacity of temporary adviser to that Organization. I am pleased, however, to have been asked to speak principally about the conditions prevailing in this particular field in Venezuela, since those are the ones I am most familiar with and which I wish to submit to the consideration of this Seminar.

The essential goal of any governmental control of pharmaceuticals is a permanent health surveillance which fosters the development and maintenance of a modern, high-quality, effective, and safe pharmaceutical arsenal (*1*).

Such control constitutes a health activity of great importance, for almost all therapy and prophylaxis of disease, as well as part of its diagnosis, are based on industrial pharmaceuticals. Moreover, the extensive use of these products could lead to serious and widespread harmful effects. The prevention of such occurrences also requires a strict control on the part of health authorities.

Approval or Rejection of New Drugs Submitted for Public Health Registration

The principles governing the requirements for effective governmental control of such products can be summarized as follows:

1. There should be obligatory health registration of all manufactured pharmaceutical products. Each of these represents, to a certain extent, a new product owing to possible variations which can exist between different products, even those having the same composition, with respect to purity of the raw material, compatibility, quality of machinery and other factory installations, skill of the professional and other workers, etc.

2. New drugs and drug combinations, as well as new effects ascribed to them, require serious, objective, well-controlled scientific studies. These should be supported by sufficient numbers of experiments and clinical trials to conclusively prove the therapeutic value and relative harmlessness of the product.

3. A pre-registration pharmacological study and report should be submitted on each product to be considered by the health authorities (reports on sera, toxoids, vaccines, and similar products should be prepared by microbiologists). This pharmacological (or microbiological) report should provide a rigorous and objective evaluation of the product under study.

4. All products should undergo laboratory analysis (chemical, pharmacological, microbiological) prior to registration.

5. Health registrations should be valid

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for no more than five years. In the course of time, therapeutic concepts and pharmaceutical technology can change, sometimes drastically; a product may be outlawed in its country of origin; and new drugs may appear which are more powerful, more specific, and/or less toxic than the present ones. Therefore, a periodic review is necessary every five years to confirm or annul a registration's validity (*2*).

Registration of Pharmaceuticals in Various Countries

Registration practices vary considerably; requirements are strict in some countries, more relaxed in others. We shall not go into detail on this point since it is beyond the scope of this study. More detailed information on the subject can be found in specialized publications of the WHO (*3–8*).

We do, however, wish to insist on the need, at the conclusion of this Seminar, to continue conversations at the international level with a view to conducting a comparative study of the various national registration and control systems and preparing a set of international guidelines which countries could, if they wished, incorporate into their respective legislations. Such guidelines would reduce the great differences now existing among national registration and control systems. This would increase both their efficiency and the quality of the pharmaceuticals registered; it would also protect importing nations from invasion by inferior products manufactured in other countries.

It should be mentioned that WHO recently submitted a set of international guidelines on drug quality control to Member Governments for their consideration. These guidelines, which have evoked favorable response, could be adopted and used productively by many countries (*9*).

Pharmaceutical Registration Procedures in Venezuela—Registration of New Drugs

Venezuela's pharmaceutical registration program, especially as regards new drugs, meets many of the requirements mentioned above, though improvements are needed in some areas. The program's principal features are as follows:

History

Venezuela was one of the first countries to establish governmental control and systematic registration of pharmaceuticals. Control began in 1883 with adoption of the Code of the Physicians' Council of Venezuela (*10*), which expressly forbade "the sale of secret or patented medicines which are not authorized by the Physician's Council" (Article 44). From 1905 on, a systematic record of all pharmaceutical registrations has been maintained (*10, 11*). In 1937 the Pharmaceutical Specialties Review Board was created (*12*), and in 1944 presentation of a preregistration pharmacological report was made obligatory.

Registration Procedure

The registration process involves administrative, evaluative, analytical, and decision-making activities coordinated by the Pharmaceutical Specialties Review Board. The Board decides on the approval or rejection of each product submitted for consideration to the health authority.

a) *Administrative activities.* Administrative tasks related to preparation of product files, study of legal safeguards, and processing and issuance of registrations are the responsibility of the Pharmacy Division. This agency also makes certain that required samples and documents are submitted along with each registration application. The necessary documents include a

certificate of origin; powers of attorney; tax certificates; the prospectus; samples of labeling and packaging; and papers giving the product's complete formula, describing its therapeutic capabilities, and discussing methods used in its analysis. The Division reviews all the legal documents presented by the interested parties.

b) *Evaluative activities.* Scientific study of products undergoing registration (both those based on new drugs and those based on known drugs) is carried out by the Pharmacology Section of the National Institute of Hygiene (Ministry of Health and Social Welfare). This section prepares a technical report critically evaluating the scientific literature published on the product in question. The evaluation covers the product's formula, pharmacological and clinical properties, its therapeutic, prophylactic, or diagnostic usefulness, and possible toxic or teratological side-effects. The report also covers the manner in which the drug is presented for sale and the claims included on its labeling. Once prepared, the report is used as a basis for discussion by the Pharmaceutical Specialties Review Board before it arrives at a decision on the product being considered.

In the preparation of a pharmacological report, very strict criteria are applied to scientific works supporting the product, particularly in the case of new drugs or new associations of drugs. These works must be of an objective, well-controlled experimental and clinical character. They must also have been exposed to criticism by other researchers through publication in scientific journals.

With respect to importation of new drugs for use in clinical pharmacology studies, the Ministry of Health and Social Welfare has established a series of requirements. These are contained in the "Standards of the Pharmaceutical Specialties Review Board" and are aimed at guaranteeing the quality and objectivity of research as well as the safety of the patients (*13*).

Technical reports on sera, antitoxins, toxoids, vaccines, and similar products are prepared by the Microbiology Section of the National Institute of Hygiene. Veterinary products are considered by the Ministry of Agriculture and Livestock.

For better documentation of a case, the Pharmacology Section can recommend that the Review Board request additional reports from distinguished specialists and national and international scientific and health organizations (*14*).

c) *First decision of the Pharmaceutical Specialties Review Board.* The Board is responsible for considering all matters relating to the processing of a registration application, for discussing each product's characteristics on the basis of the reports received, and for issuing a statement of approval or rejection. If the product is basically unacceptable the Board rejects it outright. If it is acceptable, the Board forwards it via the Pharmacy Division to the National Institute of Hygiene laboratories for further analysis. Defects in form are communicated to interested parties so that the faults may be corrected, additional literature sent, etc.

d) *Analytical activities.* There are three analytical laboratories: the chemical laboratory, the pharmacological laboratory, and the microbiological laboratory. All three are administered by the National Institute of Hygiene. Each pharmaceutical product being registered undergoes chemical, physiochemical, pharmacodynamic, biochemical, and microbiological analyses in these laboratories.

e) *Second decision of the Pharmaceutical Specialties Review Board.* After the product has been analyzed, it is again submitted to

the Review Board. The Board studies the results of the analyses, the responses of interested parties to observations formulated, and any additional reports from the Pharmacology Section or from specialists and specialized organizations. When the data have been evaluated, the Board announces its approval or rejection of the product; the Pharmacy Division is then responsible for implementing this decision. If sufficient data are still not available, the product may come before the Review Board and the Pharmacology Section one or several times more.

Comments on Venezuela's Pharmaceutical Registration System

Professional Responsibility

It should be emphasized that the presence and managerial guidance of a professional pharmacist is required all during registration processing, as well as during preparation and control of the pharmaceutical product. This pharmacist assumes all responsibility for these activities and cooperates directly with the Ministry of Health and Social Welfare. It might be said that he represents a health watchman in the heart of the pharmaceutical laboratory, who makes sure of a product's correct preparation, high quality, activity, and safety. These requirements are derived from the Law on Pharmaceutical Practice currently in force (*15*). Article 7 of this law established the principle of pharmaceutical product sponsorship by a professional pharmacist. Also, Article 29 of the Regulations of the above-mentioned law (*16*) requires that pharmaceutical laboratories be directed by pharmacists, who therefore have total responsibility for the products prepared by these establishments.

The above-mentioned regulatory decree also promotes professional responsibility by stating that the composition of the Pharmaceutical Specialties Review Board must provide for cooperation between pharmacists and physicians. This mutual cooperation has proved indispensable and has produced good results in the control of drugs in Venezuela. Such cooperation exists not only on the Board of Review but also in the Pharmacological Section; without it, it would be impossible to consider the quality, pharmacological properties, and therapeutic value of drugs from all angles.

Other important points stipulated in the decree which have led to strict processing of drug registrations are as follows:

Quality Requirements

The stipulation that every pharmaceutical specialty must have "true pharmacological merit" (*17*) imposes the need for a preregistration pharmacological (or microbiological) report; presentation of objective, well-controlled scientific literature; and inquiries that the Ministry of Health makes to specialists and specialized national, international, and foreign organizations. While the demonstration of "true pharmacological merit" is necessary for all pharmaceutical products proposed for public health registration, it is especially important in the case of new drugs. Neglect of this requirement could lead to flooding of the pharmaceutical market with poorly studied, doubtful, or useless products, some of which may be clearly dangerous to individual and collective health.

In this connection it is worth noting that registration of thalidomide was delayed two and a half years in Venezuela (1959–1961) because a scientific study reaching the Pharmacological Section and the Pharmaceutical Specialties Review Board raised doubts about the drug's harmlessness. (The

study indicated thalidomide might cause metabolic disorders through possible antithyroid activity). This was prior to discovery of the teratological havoc wreaked by this drug (*18*).

Subsequently, the Review Board adopted a set of standards for experimental study of teratogenic activity. New drug registration procedures now require that manufacturers carry out teratological trials on at least three species of animals in accordance with specifications listed in the book of "Standards" (*19*).

Prior Analysis

Besides preventing registration of defective products, the pre-registration analysis required by Articles 52 and 53 of the Regulations tends to make manufacturers more aware of corrections which may be needed in their production processes.

"Certificate of Origin"

Article 51, paragraph 5, of the Regulations requires that a "certificate of approval and sale in country of origin" must accompany foreign products being registered in Venezuela. This requirement is important because it protects against importation of low-quality pharmaceuticals not acceptable in their country of origin and manufactured "purely for export."

Standards of the Pharmaceutical Specialties Review Board

This is a manual which governs Review Board actions in a more detailed manner than the Law and Regulations on Pharmaceutical Practice. It contains pharmacological, therapeutic, galenic, and legal standards and summarizes most conditions required for approval of pharmaceutical products in Venezuela. The manual thus helps the pharmaceutical industry to carefully study the acceptability of its products before submitting them to the registration process, to take all the necessary legal and scientific precautions, or to abandon their efforts to register certain drugs.

Despite the rigid quality and therapeutic utility requirements that must be met, we believe the entire registration and control process should take place in an atmosphere of scientific discussion between the agencies of the Ministry of Health and Social Welfare and professionals representing the industry. No rejection or official criticism of a product is made without informing the professional presenting the application of the scientific or legal reasons underlying such measures. Moreover, no rejection or objection is final, and the interested parties are given ample opportunity to demonstrate the validity of their claims through presentation of scientific studies.

Control of Publicity during the Registration Process

Publicity prepared by pharmaceutical laboratories for their products is generally released after these products have been approved. The control of such publicity is beyond the scope of this study. However, it is possible to view the texts of prospectuses, labels, and labeling as publicity. These are corrected during the registration process in strict accordance with the guidelines in Article 53 of the Regulations of the Law on Pharmacological Practice, which provides that claims for the product should maintain "appropriate reserve in such a way as to avoid deceptive implications or exaggerations compromising professional ethics." Consequently, the health authority deletes any mention of pharmacological, toxicological, and clinical properties, therapeutic advantages, or other data not duly proven by authorized scientific studies. (For some

drugs, the "Standards" require deletion of indications and dosage as well) (*20*).

Furthermore, during the registration process the interested parties may be obliged to agree to include warnings, precautions, contraindications, and information on side-effects when advertising their product, in accordance with requirements established by the respective standard (*21*).

Summary

The report points out the public health importance of governmental registration and control of industrial pharmaceutical products, and discusses the principles governing the requirements for an efficient control system. It then describes Venezuela's present system, concentrating on registration procedures for new drugs; advantages and defects of this system are pointed out, and present and possible future improvements are mentioned.

Recommendations

In the form of a proposal, it is suggested that the following recommendations be brought to the attention of the Pan American Health Organization and the Governments of the Hemisphere.

1. That the collaboration of the Governments be obtained in order to continue at the international level conversations on the registration and control of pharmaceutical products, with a view to establishing international guidelines which, once incorporated into the control system of the countries that wish to adopt them, would help to improve the efficiency of these systems and, ultimately, the quality of the pharmaceutical products registered.

2. That the Governments be urged to place industrial pharmaceutical products under strict control prior to registration; this applies especially to products using new drugs, new drug combinations, or ascribing new properties to previously known drugs.

3. That pre-registration control be informative and analytical in character, encompassing chemical, pharmacological, and microbiological analyses, and critical study of scientific literature and pharmacological and/or microbiological reports.

4. That the Governments be urged to create joint agencies (boards) to evaluate the reports and analyses of each product submitted for registration, and to decide on the approval or rejection of the application.

5. That the Governments be urged to provide agencies dedicated to registration and control of pharmaceutical products with sufficient well-trained professional and auxiliary personnel, particularly analytical chemists, pharmacologists, microbiologists, and pharmaceutical inspectors; likewise, laboratories should be provided with the equipment, instruments, reagents, and space necessary to effectively carry out their functions.

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(*19*) *Normas de la Junta Revisora de Especialidades Farmacéuticas.* See ref. (*13*), p. 30, Standards 8 & 9.

(*20*) *Ibid.,* p. 25, Standard 30–j.

(*21*) *Ibid.,* p. 37, Standard 21.

EFFICACY AND SAFETY: ELEMENTS OF DRUG REGISTRATION

DR. H. H. FRIEBEL *

General Considerations

Areas of Drug Control

During the last decades the production and use of drugs have been increasing in all parts of the world. Each country, in its own context, is seeking to take advantage of that progress. There has also been a greater awareness by physicians, the public, and Governments that the specificity, potency, and growing variety of drugs have been increasing the difficulties of ensuring optimum therapy without undue risk. Though efficacy as well as safety of pharmaceutical products must be the preponderant concern of the manufacturer, and safe use the preponderant concern of physicians and consumers, Governments feel an obligation to exercise an efficient level of control over the efficacy, safety, and pharmaceutical quality of available drugs, as well as over the appropriate information on indications and use.

Health authorities, as a rule, consider problems of efficacy and safety of a certain drug when the manufacturer requests permission for clinical investigation or marketing of a drug. The staff of the drug control agency studies and evaluates the submitted documentation with the intent of safeguarding the health of man. The investigation should ensure that the drug possesses three basic qualifications: it must be therapeutically efficacious for the specified use; it should not expose the patient to undue risks from side-effects; and the pharmaceutical quality of the drug must meet established standards.

Significance of Drug Efficacy

Three areas of control deserve special consideration: efficacy, safety, and pharmaceutical quality. Their sequence is logical from the point of view of the consumer, whose primary concern is to be treated effectively. Many countries have already taken steps to establish an organization able to perform all these services, but in others it has to be developed.

Governmental drug control activities often lead off with the development of machinery for pharmaceutical quality control, extending later to problems of drug safety (monitoring of adverse reactions to drugs). The control of therapeutic efficacy has, in some countries, been introduced at a relatively late stage. This approach may be pragmatic, and the consequence of certain spectacular drug disasters caused by misbranding of drugs or insufficient awareness of their adverse effects. But, however dramatic and grave the consequences of spectacular drug disasters (stalinon, thalidomide) were, it should be recognized that the silent harm to human health produced by treatment with inefficient drugs is estimated to be even more disastrous, and that "ineffective drugs are wasteful of individual and

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public economic resources." (*1*)

New drug legislation of some countries mirrors the growing realization of this logic. In the United States of America, for example, the requirement "substantial evidence of efficacy" has been added to the existing drug control legislation by the Drug Amendments of 1962. The amendment requires that in a New Drug Application evidence should be presented for the cited indications of use. If, however, drug legislation of some countries does not yet reflect explicitly all three areas of drug control, the control organizations should nevertheless be aware of the need for a comprehensive approach.

Definition of Efficacy and Safety

Drug control organizations considering and deciding whether claims for the registration of drugs are sufficiently backed by documentation of "substantial evidence of efficacy" need an appropriate interpretation of the terms "efficacy" and "safety."

"Substantial evidence" as used in the U.S. Food and Drug Legislation indicates "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended or suggested in the labeling or proposed labeling thereof."

A comparable legal definition of the criterion "safety" has not been found in the literature though that term is used throughout in the medical, pharmaceutical, and juridical literature on drugs—which does not necessarily indicate unanimous interpretation. The reasons for the lack of legal definitions may be explained by a statement in the 1964 report of the U.S. Commission on Drug Safety: "In making its judgment as to the drug's safety, the Food and Drug Administration did consider effectiveness. It regarded effectiveness and safety as being completely intertwined. It concluded that maximum safety is attained when a drug's value for therapy is weighed against the possible toxic effects of this same drug as well as against the risk and effectiveness of other agents which might be available."(2) This understanding of "safety," being an inseparable part of the complex "efficacy and safety," is likewise to be found in the resolution on drug efficacy adopted by the Twenty-Third World Health Assembly (*1*). The resolution invites the Member States to communicate to WHO decisions regarding the availability of a drug "if the decision is taken because of lack of substantial evidence of effectiveness in relation to its toxicity and the purpose for which it is used."

The quotient benefit/risk contains therefore three elements: effectiveness, toxicity, and conditions of use. The importance of the latter is easily understood; the permissible risks in the administration of a drug to a patient with, for example, cancer or a massive systemic infection are very different from those in the use of a mild analgesic or a drug to relieve the symptoms of coryza. The relations of benefit/risk must be evaluated separately for each recommended indication.

This implies that regulatory agencies in pursuance of their investigations may need the assistance of specialists in the various fields of drug treatment though they should themselves be widely experienced in drug evaluation. But practical experience in this type of evaluation gained in certain coun-

tries has shown that even availability of such expertise does not exclude all difficulties which may arise in applying the criteria "effective" and "safe," and this is especially true if the therapeutic value of older drugs is to be reviewed.

Difficulties which can arise in this connection are vividly described in the report on the Drug Efficacy Study of the Division of Medical Sciences, National Academy of Sciences, in Washington (*3*). The Food and Drug Administration requested the expert panels of the National Academy to review a large number of older drugs. The FDA asked the panels to give a drug, individually evaluated by them for efficacy, one of four categorical ratings. These were:

Effective
Probably effective
Possibly effective, or
Ineffective

for the cited indication. The report states: "It is not surprising that the 30 panels for drug evaluation participating in the Study have not always been consistent with each other in their use of these ratings. These panels were faced with the difficulty that, in many cases of drugs which have been in the market for five to 30 years, no reports on well-controlled studies of their efficacy could be found. How much weight should they give to the opinion of the market place?"

Documentation of Efficacy and Safety of Drugs

Documents submitted to authorities in order to receive permission for marketing of a drug should refer to the whole picture of biological responses provoked by experimental and therapeutic administration of drugs. The completeness, reliability, and thoroughness of the studies so documented should be examined first. The next step might be the control of the soundness of interpretation and evaluation of recorded biological potentialities. Both these processes of investigation may be facilitated by making use of the expertise compiled in WHO reports on principles for testing and evaluation of drugs (*4*).

These reports advise on the basic principles governing the testing of drugs for therapeutic safety, i.e., safety under the circumstances of therapeutic practice. This form of guidance would appear to be all that is possible and desirable at this juncture. Detailed technical and administrative requirements, with their inherent tendency to be specific, and conducive to rigid application, would be difficult to establish on a truly scientific basis in view of the great variety of drugs, indications, and therapeutic practices. Besides, they would have little chance of being generally accepted.

It should be the principal aim of the preclinical testing of drugs to explore the pharmacological actions of drugs in animals, to assess the potential therapeutic properties, and to explore their adverse potential. The toxicological studies fall into two types: first, acute or subacute studies of less than three months' duration; and second, long-term or chronic studies of three to six months' duration; and finally, life-span toxicity studies. The probable teratogenic, carcinogenic, dependence-producing effects, and the whole question of sensitization to drugs require special studies on laboratory animals.

Biochemical studies, including studies of absorption, distribution, excretion, and metabolism of a drug are of fundamental importance for the proper evaluation of the results of pharmacological as well as toxicological studies. Experiments of this type

(which might be called standard procedures) involve the administration of single or repeated doses by various routes to animals and measurement of drug concentrations in their body fluids and tissues. The purpose of these studies is to estimate the rate and degree of absorption and accumulation as well as the rate of disappearance from the body, with or without metabolic breakdown, by renal and other pathways of excretion. Quantitative studies of this type facilitate the extrapolation of animal data to man, disclose metabolic products with therapeutic or toxic effects, and provide the rationale for development of suitable human dosage regimes by animal experimentation.

These studies, though essential for the initiation of drug studies in man ("human pharmacology"), have inherent limitations. In the main they arise from species-dependent differences in response to drugs rendering the extrapolation of results from one species to the other, and particularly to man, difficult. There are many factors concerned with species-dependent differences, of which the most influential is the species-specific metabolism of drugs. The ways in which the drugs are absorbed, distributed, and excreted also differ widely between species and even strains of a certain species. However, progress in research methodology is developing fast, e.g., the development of techniques sufficiently sensitive for the detection and analysis of small concentrations of drugs and their metabolites in body fluids and tissues. It may be reasonably expected that the interpretation of species-specific differences in drug response will thus be facilitated, and that existing difficulties in the transferability of results of drug testing from one species to another or to man will decrease in the future. Simultaneously will the risk at present associated with the first and subsequent administrations of a new product to man be diminished, though not totally excluded, by the progress in pharmacological and toxicological methodology.

The guiding principles for the clinical evaluation of new drugs are the following:

In initial trials of any new agents, the investigator must be genuinely open-minded concerning the possibility that the drug is worth a trial and that it may be as good as, or perhaps better than, one or more of those already available. The clinical investigation of drugs, whether new or old, and whether used for a new action or in a new physical form or combination, has to include planned scientific studies in man of pharmacological actions, occurrence of adverse reactions, absorption, distribution, metabolism, and excretion.

The study of efficacy and toxicity of the new substance in comparison with a well-known standard drug is essential. Any hazards which may arise from interaction with other drugs, domestic remedies, alcohol, or food should be considered and investigated where indicated. It is unethical to introduce into general use a drug that has been inadequately tested along these guidelines.

The evaluation of documents submitted for drug registration should result in a recommendation for the appropriate action, i.e., refusal or registration, or the need for more or complementary studies. In approving a drug, authorities will also decide whether it should be freely available to the public or subject to different degrees of limitation. The regulations on distribution, which would be attached as a condition of the individual approval, may vary from country to country depending on the properties of the drugs as well as on environmental factors.

Special Aspects of Efficacy and Safety

Environmental Factors

A group of experts recently advising the WHO Drug Safety unit on principles of the organization of governmental drug control pointed out that drug control authorities of drug importing countries may bear in mind the fact that differences in average body weight, nutritional state, climatic and other environmental conditions, and genetic factors can influence the efficacy and safety of drugs. This consideration relates to requirements that may be imposed on producers of drugs when approval of new drugs for sale is requested (*5*). Drug houses have the responsibility to anticipate those factors if conditions in the consuming population differ from those in the geographic region where the drug has been investigated clinically in the first instance. They should encourage competent institutions to study the consequences of such differences for the efficacy and safety of drugs whenever necessary and possible.

Traditional Medicines

Traditional medicines are to be found everywhere in the world, especially in areas where modern medicine is not available. Traditional medicines may continue to play some role in the treatment of the diseased, but as the general educational level, especially that of medical education, rises and as the per-capita income increases and therefore allows for larger contributions to health care, the role of those medicines is likely to decrease and to be replaced by modern means of treatment.

The Drug Safety unit has recently been advised by a group of experts that efficacy and safety of traditional medicines are, as a rule, not evaluated in accordance with the principles established by national or international groups of experts or authorities. This situation does not allow an acceptable comparison to be made between the therapeutic value of traditional medicines and that of drugs which fulfill these requirements. Traditional medicines therefore cannot be regarded as a desirable and valuable contribution to public health and the national economy. Drug registration agencies may wish to consider this in pursuance of their duties. The only form of integration of traditional medicines into modern drug treatment which seems possible is their scientific investigation and the incorporation of products so obtained into the arsenal of modern medicine.

Therapeutic Equivalence

Newly established pharmaceutical industries and authorities controlling their products may be especially interested in the problems of therapeutic equivalence of pharmaceutical preparations.

Dale C. Friend (*6*) stated recently: "Unless a preparation has been proven to be as effective as the standard preparation, it should be considered as a possible source of therapeutic non-equivalence."

The topic is not a new one, but has gained in importance by recent findings that some brands of well-known drugs, although fulfilling official requirements for chemical purity, were found to be less active or more active than the original brand. Differences in absorption rate can be the cause of such deviations, but there are others like micronization of drugs, etc. Examples of non-equivalence have been found among brands of chloramphenicol, oxytetracycline, diphenhydramine, sulfafurazole, erythromycin, and tolbutamide. Some experts believe that this may be true of many more generic drugs.

Certain drug control authorities, confronted with such findings, have set out specific requirements that must be fulfilled

by the manufacturers of generic preparations. Others maintain a flexible position. During a recent symposium on the subject, held in Ottawa, speakers recommended avoidance of too hasty codification in an area that is governed by natural laws which we only very incompletely understand (*7*).

The White Paper on the Therapeutic Equivalence of Chemically Equivalent Drugs prepared by a subcommittee of the American Drug Efficacy Study (*8*) contains the following statement: "With some drugs, there are reasonably good analytical methods for biological assays, whereas for others a meaningful test is virtually impossible at this time. Consequently, the problem of the biological equivalence of drugs should be approached expectantly and progressively. Critical evidence of chemical and physical equivalence is the first order of business. Obviously, new drugs and accepted drugs of greatest pharmacodynamic action or therapeutic importance may additionally require careful biological scrutiny.

"It would seem reasonable for the FDA to require that the generic manufacturer submit, in addition to evidence of chemical equivalence and purity, data on dissolution rate and data from other *in vitro* tests demonstrating equivalency. However, if there is evidence that *in vitro* evaluation of animal tests does not correlate well with pharmacodynamic effects in man, there may be need to resort to clinical tests. In this way, the principle of generic prescribing based on therapeutic equivalence may become acceptable to the medical profession and be supported by the pharmaceutical industry."

Intergovernmental Information on Efficacy and Safety of Drugs

The responsibilities of governmental drug control organizations with respect to a particular drug, whether new or old, are not completed when it has been accepted for registration. After introduction of a drug into general medical practice, new information will accumulate on its efficacy and safety. This information may lead to regulating authority to modify the terms of the original approval.

In Resolution WHA16.36 (*9*) the World Health Assembly requested Member States "to communicate immediately to WHO any decision to prohibit or limit the availability of a drug already in use . . . if these decisions are taken as a result of serious adverse reactions." The resolution also requested the Director-General of WHO to transmit immediately to Member States the information thus received.

In May 1970 the Twenty-Third World Health Assembly, in Resolution WHA23.48 (*1*) broadened the scope of the service thus provided, inviting the Member States "to communicate to WHO any final decision made by health authorities to withdraw or restrict the availability of a drug already in use if the decision is taken because of lack of substantial evidence of effectiveness in relation to its toxicity and the purpose for which it is used."

The value of the drug information circulars for services concerned with drug registration can be considered from two viewpoints. First, governmental authorities have their attention drawn promptly to a specific drug or group of drugs which has given rise to concern and subsequent action at government levels in another country. After evaluation of the data relevant to their own territory they may decide whether any action is needed. Second, Governments with limited facilities for drug control, when made aware of the action taken by other Governments, can request more information from or through WHO, and thus add to the scientific and adminis-

trative background of a decision to be taken by them. However, there is at present no means of knowing whether the present rate of reporting to WHO corresponds to the actual number of decisions worth reporting and whether the content of the reports fulfills the needs of the recipient authorities.

The Director-General of WHO therefore transmitted a statement on the experiences gained during operation of that service to the health authorities of the Member States in August 1970 (*10*). The statement contains a number of suggestions for improvement of this international reporting system, and invites the authorities to comment on them.

In concluding this exposé on efficacy and safety as the basic elements for consideration by governmental control authorities, I would like to say that the value of such an approach is dependent on the professional competence of the regulatory agency for the evaluation of drugs. Such an agency should be adequately staffed with experts in clinical pharmacology, experimental pharmacology, and pharmaceutical quality control. Since it is impossible to have expert advice in all disciplines concerned within the governmental structures, it will be necessary to utilize the services of competent and independent professional advisory bodies.

WHO will continue to advise on the principles governing the technical requirements for drug evaluation, to promote international agreement on procedures, standards and regulations, to facilitate intergovernmental exchange of information, and to support relevant professional education and training.

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THE EXPIRY DATE OF MEDICINES

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The Instability of Drugs and Medicines

Drugs and pharmaceutical preparations[1] conform to a general law of nature which states that all material things are subject to aging. Drugs, even when correctly packaged, can undergo physical and chemical alterations such as changes of crystalline form, racemization, hydrolysis, decarboxylation, oxidation, reduction, etc., as a consequence of exposure to moisture, heat, oxygen in the air, light or other radiation, microorganisms, and other factors.

Pharmaceutical preparations, even when they have been properly formulated, prepared, packaged, and stored, are generally less stable than drug components, in the case of more complex systems, because in addition to the aforementioned causes of deterioration there are interactions between the different components of the preparation and the packaging. Furthermore, the list of physical changes becomes longer and takes on special importance: increase in the time needed for tablets to dissolve, separation of emulsions in phases, variation in the fusion point of suppositories, changes of particle size in suspensions, etc.

In addition to these intrinsic aging factors there are also extrinsic factors that are attributable to the producer, the wholesaler, the pharmacist, or the consumer. These extrinsic factors include formulation, preparation and packaging methods that do not provide adequate stability, and storage and transport environments that depart markedly from ideal or recommended conditions.

The problem of drug instability has always been of concern to pharmacists, but views on the subject have changed considerably during the latter half of this century (*1*). Given the diversity of factors affecting drug deterioration and the wide variety of substances used in drug preparation, it is understandable that the useful life of different present-day drugs should vary greatly. A small number of products will only keep a few months even when stored under optimum conditions, while another small number of extremely stable preparations will maintain their properties for many years without any special storage requirements.

This being the case, a pharmaceuticals manufacturer has to answer the following questions:

a) What is the useful life of the preparation he produces or intends to produce?

b) Within that period, how should he define his moral and legal responsibility concerning the quality of the product?

c) How will his business be affected by the measures that he takes as a consequence of the answers to these questions?

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[1] "Pharmaceutical preparation" and "medicine" are used here as synonyms, referring mainly to pharmaceutical specialties, i.e., industrial pharmaceutical preparations characterized by trade names and produced and packaged prior to being prescribed.

These points reflect, in brief, the technical, legal, and economic aspects of the problem of instability of pharmaceutical preparations.

Technical Considerations

Since the term "useful life" is a little vague, we shall endeavor to define it, bearing in mind that the closer we come to a definition the clearer the problem will become. To arrive at a precise definition it is first necessary to consider some characteristics of the preparations whose maintenance requirements during their period of useful life are of interest to us.

Physical and chemical properties. During the period of useful life, certain physical and chemical properties of the preparation should not vary by more than certain predetermined values. For example, the pH must not be greater than A or lower than B, the dissolving time must not exceed C minutes, the specific area of the particles must not be less than D cm^2 per gram, the fusion point must not be higher than E°C, and the concentration of the active drugs must not be lower than F% of the value declared on the label, the actual numbers depending in each case on the pharmaceutical product involved.

Practically all the stability studies being carried out at present are concerned with solving such problems, especially where variations in concentration are involved. However, other drug stability features of equal importance must also be considered.

Toxicity. The possibility that degradation products will be toxic adds to general problems involved in ensuring the safety of pharmaceuticals. If according to an initial approximation the drug concentration is to be maintained at 90 per cent, it is necessary to consider 10 per cent as degradation products, the toxicity of which must be known. The LD_{50} values of these products may be such that the preparation must be considered toxic once the drug's concentration has fallen to 90 per cent of declared value. In this case, 10 per cent degradation would be excessive from the toxicological point of view, even if it were considered acceptable in terms of therapeutic value.

Despite abundant literature on toxic effects of drug decomposition products, there have been few systematic studies of toxicity versus stability. In fact Dearborn, referring to the subject at the Wisconsin Conference in 1969 (*2*), stated that numerous authors have concerned themselves with the problem of the loss of activity and have developed elaborate mathematical methods for predicting expiry dates from accelerated stability trials. On the other hand, and although he did not claim to have covered the literature exhaustively, he could not quote a single article which reports on toxicity trials carried out with samples which had been the subject of accelerated stability studies.

Therapeutic effectiveness. Experience has shown that a medicine's therapeutic effectiveness may change with time. In some cases the variation can be correlated with obvious factors, such as the reduction in drug concentration; but in others the correlation with physical and chemical properties observed during stability trials is not so apparent. In principle it should be possible to correlate any variation in the effectiveness of a medicine during aging with one or more of its physical or chemical properties. However, this would require much more detailed knowledge about both the drug and the recipient than we have at present. When the correlation is not obvious, the best apparent solution from the scientific point of view is to carry out

trials *in vivo*.

Nevertheless, technical and economic difficulties involved in such trials may necessitate other approaches, such as study of causes which most frequently play a part in diminution of curative properties. According to Tingstad (*3*), apart from reduction in drug concentration, these are: (a) polymorphic changes in the crystalline structure of active ingredients; (b) an increase in particle size, especially in the case of suspensions; and (c) physical and chemical interactions between the preparation's components, leading to significant reduction of over-all solubility and/or the speed with which the active drug dissolves.

It should not be forgotten, however, that studies of these variations are only approximations and that, to quote the same author, ". . . in the last analysis, only trials *in vivo* can tell us what we want to know." (*3*)

In short, the technical problem presented by pharmaceuticals' instability lies in ascertaining how long a product will retain its purity, potency, safety, and efficacy, within certain limits; i.e., how long it will maintain its quality.

Attempts at definitions. This view of the technical problem helps us arrive at the definition of "period of useful life of a medicine" as the length of time the preparation will maintain its quality when stored under conditions prescribed on the label.

Obviously, the expiry date of a given batch indicates termination of its useful life, counting from the date of manufacture. Taking into account the concept of useful life, the expiry date of a medicine can be defined as the time up to which it remains safe and therapeutically effective, within certain specified limits, provided it has been stored under the conditions specified on the label. We consider this definition to be more general than those, such as Bhate's (*4*) or the definitions suggested by the U.S. Pharmacopeia (*5*) and the U.S. National Formulary (*6*), which only take into account a diminution of the concentration or potency indicated on the label.

Methodology. The methods used to study stability of pharmaceuticals are really beyond the scope of this discussion, so we shall restrict ourselves to some general comments.

It should be noted that experiments conducted without considering the toxicity of degradation products and making only very approximate correlation between physical/chemical properties and therapeutic effectiveness will not yield precise results.

Furthermore, published data about the stability of each component of the formulation, and possible interactions between components, just constitute starting points of the investigative process. By themselves they give sufficient grounds for a final decision only when they provide reasons for abandoning the project or taking the product off the market. This would be the case, for example, with a product containing dissolved ascorbic acid and ferrous sulfate. On the other hand, if published data indicate the substances concerned are reasonably stable, it would still be risky to make such indications the sole basis for conclusions about the preparation's stability. Even published data confirming the stability of formulations identical to the one proposed may not be used as final arguments for setting expiry dates, when it is not certain that the proposed starting materials, manufacturing processes, etc., will reproduce precisely the same conditions, or that markets with different climates or different drug distribution and sales arrangements will affect the product the same way.

The experimental phase of stability trials takes up considerable time and effort, so that it should be carefully planned before

work is started. No great problems are involved in making the basic choice between the accelerated or the natural aging method, when the drawbacks and limitations of each are known. Generally speaking, the natural aging method is more commonly employed because it makes possible the study of both straightforward chemical reactions and those changes whose kinetics are not well understood. An example from outside the pharmaceutical field will help to clarify this point. As Carbon 14 breaks down it emits beta particles and gives off nitrogen. The kinetics of this process are well known, but no accelerated method could have helped to study the "stability" of Carbon 14, since until now nobody has found any agent or factor (temperature, pressure, radiation, etc.) capable of modifying its speed of change. On the other hand, the natural aging method is not affected by certain factors which occasion a degree of uncertainty, such as possible initiation under stress conditions of reactions which do not take place under normal circumstances; such reactions in turn can create degradation products that act as catalysts for other changes.

Against the limitations of the accelerated aging method Garrett (*7*) sets the following advantages: (a) a shorter time is required; (b) it permits rapid determination of how variations in particular batches or components affect stability; (c) several different formulations can be compared quickly to determine which is best; (d) statistical methods can be applied easily; and (e) the analytical results show fewer variations of the type that tends to arise when there are long time intervals between determinations. Yet despite these advantages, stability data obtained by the accelerated aging method always require corroboration from the irrefutable results provided by long-term natural aging trials.

Whichever method is chosen, special attention should be given to the specificity of the evaluation methods used. If knowledge of the concentration of some non-degraded substance at a given moment is desired, it will be necessary to use a method that correlates the parameter observed as closely as possible with the number of intact molecules present. For example, if we determine the strength of an amino-alcohol ester with an acid, the observed parameter (the volume of acid consumed) relates exclusively to the presence of amino groups; therefore, the method cannot inform us about the extent of any hydrolysis which the ester component has undergone. In many other cases, of course, the nonspecific nature of the results will not be so obvious, especially when the degradation mechanism or mechanisms are unknown. Whenever there are doubts about the specificity of the method employed, it is essential to analyze the degradation products. This point was stressed by Casola (*8*) recently, in presenting the position of the U.S. Food and Drug Administration on this matter.

Storage conditions. Another technical consideration is the relation between expiry date and the environmental conditions under which drugs are stored.

Stability data obtained from proper trials will make it possible to establish realistic expiry dates when recommended storage conditions are stated on the product's label. This practice is especially necessary for medicines with short useful lives that have to be kept at low temperature. When storage conditions are not specified on the label the producer is unable to control these conditions from the time the product is delivered until it is used. Disregarding the possibility that the distributor or pharmacist may keep it under less than

optimum conditions, it becomes vitally important to know the climatic conditions of the place where the product is ultimately sent.

This, in essence, is the problem which Levi and Benney (*9*) discussed in detail at the Wisconsin Conference in 1969.

Legal Considerations

According to Dolique (*10*), contemporary legislators admit that there are no absolutely stable pharmaceutical preparations. This view is reflected by Argentine legislation regarding registration of new medicines, which requires a declaration stating how long a preparation submitted for registration will remain therapeutically effective (*11*).

However, legislation on expiry dates varies considerably from country to country. Some nations, such as France (since the reform of 1960), require expiry dates to be stated in all cases, except when the health authorities grant special permission to omit it (*12*). Some other countries leave all decisions to the health authorities, who must make a ruling on each case.

According to one widely accepted criterion, expiry dates are unnecessary when the preparation's period of useful life exceeds five years. The criterion is justified in terms of stock turnover rates indicating that the normal storage time for medicines is from one to three years. This period is cited by Pradham (*13*), and we feel that it conforms to the actual situation in our market. However, thorough analysis of this criterion would undoubtedly provide a basis for major objections, a fact which has led certain producers to indicate expiry dates on all their products even though the law does not require it.

An intermediate situation prevails in other nations where general legislation has been introduced regarding certain groups of products. In Canada, for instance, expiry dates have been required on the labels of all vitamin preparations since 1964 (*14*).

With respect to over-all moral and legal responsibility, we concur with Viratelle (*15*) and Dolique (*10*) that when a medical product's label gives no expiry date the producer is responsible for its quality throughout the time it is kept in the pharmacy. When a date is indicated, the producer is only responsible up to that date; if the product is sold afterwards, responsibility shifts to the pharmacist.

Since the expiry date constitutes a guarantee to the purchaser of the product's quality, the producer should be held legally responsible for fraudulent practice if a later date than the correct one is cited. On the other hand, the seller is guilty of fraud if he supplies the product after the date indicated, particularly if he has attempted to hide this fact.

Economic Considerations

A direct consequence of dating a product is that it loses its commercial value after the date shown. In the case of medicines the producer generally absorbs this loss, accepting the outdated products and crediting the buyer with the amount of purchase or supplying him with products of recent manufacture in exchange.

Other important economic problems involve such things as the producer's decision to include or omit the expiry date when its inclusion is optional. Such matters are not dealt with here, since they depend partly on each producer's policies with respect to profits, prestige, and quality.

Conclusions

1. Studies of pharmaceutical preparations' stability will devote increasing future

attention to problems occasioned by variations in their safety and therapeutic effectiveness.

2. Legislation on medicines will tend to require expiry dates on all products.

3. Certain economic problems that face competing producers will disappear when all pharmaceuticals have to show expiry dates.

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CONTROL OF BIOLOGICAL PRODUCTS

DR. L. GREENBERG *

In order to deal adequately with this topic, it is essential to have an understanding of what a "biological product (drug)" is. Not all countries use the same definition. In Canada, for example, biological drugs are defined by law as: (a) drugs, other than antibiotics, prepared from micro-organisms, (b) sera and drugs analogous thereto, and (c) antibiotics for parenteral use. In the United States of America, arsenicals are included but antibiotics are not. Regardless of the definition used, however, biological drugs are usually products that present difficulties and some potential hazard in their manufacture, control, and use. They therefore require special consideration and for this reason are generally controlled separately and very much more stringently than "pharmaceutical" drugs.

The first requirement for the control of any drug, biological or pharmaceutical, is that a country have laws which will enable those responsible for control to carry out their functions properly. I will not go into this aspect here since that is not the purpose of this presentation, except to state that the laws should be such that they can be effective in protecting the public against health hazards and fraud, and that there are facilities to make changes in and additions to the laws quickly, when required. It is preferable, of course, that the release of a biological drug be on the basis of scientific (laboratory) evidence, and be not subject to economic or political pressure. These drugs are simply too dangerous.

A skeletal schema for a government biologics control laboratory is shown in Figure 1. This outline is basically that in use in Canada today. It will be noted that the schema shows a research section in addition to one for control. Such a section is highly essential for any control laboratory, for unless the laboratory is continually striving to develop new and improved methods of testing, its procedures will gradually become out of date and inadequate to meet the challenges offered by constantly developing new technologies.

The type of person required for performing control tests of biological drugs will depend on the volume, variety, and complexity of testing that can be undertaken. The World Health Organization has recently produced a brochure (*1*) outlining in some detail the general requirements for a national control laboratory. This brochure deals with situations where control is carried out by "protocols" alone, and then progresses to the carrying out of simple tests, i.e., sterility and acute toxicity, and finally to the more sophisticated safety and potency testing of bacterial and viral preparations. The schema shown in Figure 1 is a basic one and, depending on space, equipment, and available staff, could carry out a range of tests from the most simple to the most difficult.

Technicians, when properly trained, can

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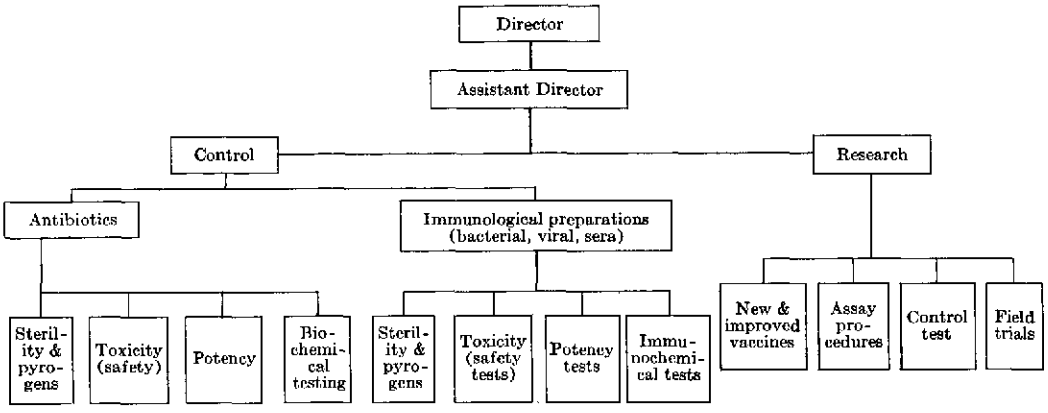
FIGURE 1. Skeletal Schema for a Biologics Control Laboratory.



and often do perform the actual testing, but the responsibility for the results and their interpretation must be assumed by an individual who has a suitable university background, that is, a degree in the appropriate scientific discipline, and who has had adequate training and experience in the tests involved. For practical application of this principle, let us look again at Figure 1. All of the control tests involved—namely, sterility, pyrogens, acute toxicity, potency, and biochemical testing—can be performed in an acceptable manner by a well-trained, alert technician, but the procedures adopted, the control of the testing, and the interpretation of results should be carried out by a university graduate, or graduates, with training in microbiology and biochemistry. The biochemist would be particularly useful for chemical assays and for tests on degradation products, for example, the development of epi-anhydrotetracyclines in tetracycline products.

Similarly in the control of vaccines and antisera, scientists with appropriate background and university training should be used. The control of bacterial vaccines should be performed by, or under the supervision of, a microbiologist, the viral vaccines by a person trained in virology, and the serum products by a bacteriologist-immunologist capable of performing the more sophisticated type of tests, such as immunoelectrophoresis, gradient analyses, etc.

The research laboratory should complement the control section in its program of work and may in some instances be required to perform control tests which present special difficulties or which require special skills, for example, infrared or X-ray photometric analysis. Research staff should have considerable formal training and a special aptitude for investigative work. Studies on assay procedures and control tests should be started as soon as practicable once a control laboratory is functioning. This is essential if the laboratory is to keep up-to-date and operate efficiently. Studies toward the development of new or improved types of vaccines can only be carried out in larger laboratories that are well staffed and well equipped, and should not be undertaken until the control laboratories have become well established and are functioning properly. Field trials would probably be the last function such a research laboratory would undertake. Such trials would have

much value in establishing the merit of the experimental drugs and also the value of the laboratory tests in use. In carrying out these tests, the ultimate use of the drug under test must be kept in mind. If the drugs, for example, are to be used in man, then the value of the laboratory tests is directly related to the accuracy with which the results predict their effect in man.

It is not my intention to discuss in great detail the problems involved in the inspection of biological manufacturing establishments since this by itself could take up the time of an entire seminar. I would like to emphasize, however, a statement that has been made by many experts in the control of biological drugs and which has been included in recommendations in WHO technical reports, namely, that the "inspection" of a manufacturing plant is by far the most effective weapon we have in our armamentarium for controlling drugs—providing it is carried out by a competent official who has a thorough knowledge of drug manufacture. The testing of random samples of the finished drug, no matter how thorough or completely done, is not by itself sufficient for the best control of "drug manufacturing." Such sampling and testing must of course be done, but they are not a substitute for a proper inspection in which every stage of manufacture, from the receipt of raw material through the intermediate and final stages of manufacture, including packaging and labeling, has been examined and approved.

Up to this point I have referred to the control laboratory as a governmental agency. Control laboratories in biological drug manufacturing establishments can be established along similar lines. Care must be taken, however, to ensure that the control laboratories are entirely independent of manufacture. The scientific qualifications of a person required to carry out control functions are the same whether the control laboratory is private or governmental.

I have also been asked to say a few words on WHO's procedures for developing standards for biological drugs and on the availability of such reference materials.

The biological standards program is one of WHO's oldest activities, one it inherited from the League of Nations. A very excellent review outlining the history and progress of this responsibility has been presented by Mathews (2) and will not be dealt with here. Briefly, WHO has, through successive Committees on Biological Standardization, established an impressive number of international standards, international reference preparations, and more recently, international reference reagents for biological substances.

International standards are preparations for which international units have been established through intensive international collaborative studies. Examples of such standards are: diphtheria and tetanus antitoxins and diphtheria and tetanus toxoids. These are used to measure the potency of test samples so that when the final potency is expressed in international units, the result will have the same meaning regardless of what part of the world or in which laboratory the test was carried out.

International reference preparations may be used for a similar purpose, but are preparations for which *full* international collaborative studies have not been completed or are preparations in which such collaborative studies have shown them to be unsuitable. Occasionally, to avoid confusion, international units are assigned to such preparations, for example, diphtheria antitoxin for the flocculation test.

International reference reagents are used

in laboratory tests for the identification of specific microorganisms.

The international standards and reference preparations are intended for the calibration of national or laboratory standards which, in turn, are used for controlling the potency of market preparations. None of the international standards or international reference preparations are available in sufficient quantities for use in routine control testing within laboratories. For this reason, their distribution is generally restricted to national laboratories charged with responsibility for the control of biological standards and to other biological laboratories not national but which serve the purpose of the national laboratory when the latter is nonexistent.

There are at present a large number of international biological standards and international biological reference preparations. In the last report of the WHO Expert Committee on Biological Standardization (*3*), the list of these and reference reagents covered some 40 pages, and this list will undoubtedly be added to during the Expert Committee meeting that is currently being held in Geneva.

In this paper, no attempt will be made to list in detail these various preparations, or where they may be obtained. WHO, however, has three main reference laboratories which maintain and distribute most of these preparations. Antigen (i.e., vaccines) and antibody (antisera) standards are maintained and distributed by the Statens Seruminstitut in Copenhagen, Denmark; antibiotics, hormones, vitamins, and enzymes by the National Institute for Medical Research in London, England; and standards for veterinary preparations are held and distributed by the Central Veterinary Laboratory, Weybridge, Surrey, England. A number of other laboratories also participate and specific details concerning them may be obtained from the aforementioned report (*3*).

In recent years, WHO has, in addition to providing international standards and reference preparations, undertaken the formulation and publication of requirements for biological substances. The first sets of requirements published in 1959 were: (a) General requirements for manufacturing establishments and control laboratories, and (b) Requirements for poliomyelitis vaccine (inactivated). These and other requirements formulated since then by international groups of experts have been published in the Technical Report Series of the World Health Organization.

The requirements are not legally binding unless a country so wishes. A number of countries have adopted them per se, whereas others have based their requirements on them. The requirements may also be used in international exchange of biological drugs and are of particular value in purchases by countries with limited control facilities of their own. WHO makes considerable effort by direct approach and contact with Governments to encourage them to use these requirements and to establish national centers to carry out this work.

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DRUG MANUFACTURING PRACTICES

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My personal experience during 30 years in the pharmaceutical industry, and more recently as a college administrator and consultant, has been divided between supervision of production and quality control functions, and I have found that these two activities have the same basic objectives, namely, to prepare and distribute a safe, effective, and high-quality product.

Production personnel build quality into a product by the procedures and materials they use and the workmanship they employ, while quality control (sometimes referred to as quality assurance) monitors the production and packaging operations, examines and tests the product as an independent auditor, and passes judgment on it.

My assignment was to begin with raw materials and trace the important drug practices which should be employed to ensure that a safe, effective, high-quality product reached the consumer or user. Before going into that subject, I would like to mention that many standards covering good manufacturing practices have been drafted or approved by various countries throughout the world. Most of these are similar in scope and describe personnel requirements and standards for premises and equipment. I will say very little about those standards except to emphasize that a satisfactory product cannot be made under insanitary conditions with untrained personnel who may not have the proper equipment to do the job. Reference to personnel, premises, equipment, and sanitation requirements is made in the WHO Technical Report Series (No. 418, Annex 2) on Good Practices in the Manufacture and Quality Control of Drugs.

There is no need to describe the Good Manufacturing Practices proposed by WHO, with which you are all certainly familiar, but I would like to point out a number of problems that have arisen in the industry and some of the solutions recommended in order to meet requirements of those Practices. It should be kept in mind that the WHO standards state what must be done to prepare a satisfactory product. For very good reasons they do not, in most instances, describe how it is to be done.

Raw Materials

The chain of events leading to the distribution of a satisfactory product begins, from a manufacturing viewpoint, with the ordering of raw materials. In order to place an order for raw materials, whether they be active or inactive ingredients, one must have adequate specifications to relate to the supplier. These specifications are usually the joint responsibility of quality control personnel and of personnel responsible for development of the product. Production can and sometimes does make a contribution to the development of adequate specifications, such as particle size desired and details re-

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garding the size and kind of container in which the raw material is to be received.

There are many satisfactory systems employed for identifying each shipment received and each manufacturer's lot number of raw material. Any system which enables one to trace the history of each manufacturer's lot number of raw material and to account completely for its use is adequate.

The extent of sampling of raw materials has been fairly well standardized by most firms. The most frequently used method requires sampling of the square root of the number of containers within each manufacturer's lot. There are some exceptions to this, such as the sampling of suspensions and samples withdrawn for the purpose of microbial examinations. It is customary to run an appropriate identification test on the individual samples and then prepare a composite sample for further laboratory examination.

One must remember that there is some risk involved in approving unsampled containers when using the square root scheme of sampling. For this reason, there is a growing tendency to perform an appropriate identification test on every container in order to ensure that none are mislabeled. Most firms depend upon trained production operators to note and report to the quality control department the contents of any containers which do not have the usual physical attributes of the material.

Some important considerations in the handling and acceptance of raw materials are as follows:

1. Some materials may be delivered by tank truck or tank car. It is important that consideration be given to the cleanliness of storage tanks, pipes, and pumps used to store and move the material from one location to another. Unclean storage and pumping equipment has often been a source of microbial contamination in the handling of such items as wine and glucose.

2. Certain expensive containers may be required to be returned to the supplier after they have been emptied. All markings except the supplier's name should be removed or obliterated prior to return. In one known instance in which an analytical approval stamp affixed by the purchaser was not removed, the purchaser received the same refilled containers and they had the appearance of having already been sampled, tested, and approved.

3. There is a trend toward the use of numbers to identify raw materials usage in production operations. This is especially true with firms that are computerizing their operations. Although this may be of some benefit to the accountants, it is to be hoped that the dispensing of raw materials will continue to be on the basis of the name on the container.

4. There is a tendency to permit less stringent standards to govern the handling of inactive ingredients. My own experience indicates that poor quality products have often resulted from not knowing enough about the presence of impurities in inactive ingredients at the time of approval.

Processing Operations

With respect to the manufacture of specific dosage forms, it is of course mandatory to establish and maintain a system whereby the correct quantities of the proper ingredients are measured out and added to each batch in accordance with the instructions and precautions for the manufacture of the product. Assuming that a satisfactory system of double checks has been worked out, what are some of the special precautions and controls which one should consider during the processing operation?

Liquids. Liquids (other than suspen-

sions) usually are the least complicated dosage form to prepare. In spite of this, problems do occur. For example, in one case a liquid vitamin preparation was assayed for vitamin content and other required tests were performed. After approval of the batch for filling, and without the knowledge of the quality control department, the batch was given a final filtration to ensure that it was crystal clear. A check of vitamin content in the finished package by an independent laboratory revealed that a significant amount of the vitamin was being routinely retained by the filter. This case points up the need for the quality control department to have an intimate knowledge of the manufacturing directions and ready access to production facilities, and also the importance of testing the product in its finished package form.

Quality problems with liquid products may also arise if these are held for extended periods in bulk and under unfavorable conditions subsequent to quality control approval, or are filled intermittently without proper re-examination just prior to each filling cycle. This may be especially true of suspensions and preparations containing volatile ingredients.

There was an instance some years ago in which a whitish turbidity was noticed in the filled packages of a pediatric product which was normally clear. Just prior to the packaging of this product a batch of a sulfa suspension had been filled through the same pipeline and valve. Investigation revealed that some of the sulfa had become trapped in the valve and was later dislodged by the filling of the next scheduled product on the packaging line. The valve was replaced with another type which corrected the problem and proper washing procedures between products were instituted. Fortunately none of the unsatisfactory batch reached the market place.

The preparation of suspensions requires special care during manufacture and packaging. The quality control department must be sure that samples truly representative of the batch are received and tested and that the batch is uniform throughout. Special precautions must be taken to ensure that the bulk material remains uniform while it is being filled. Special mixers may be required to keep the bulk uniform and at the same time not permit the introduction of excessive amount of air into the batch, as this might result in a short fill or lack of uniform composition.

Tablet manufacture. The prime objective in the manufacture of tablets is to produce individual units of exactly the same composition and weight. (Obviously there are also other important quality attributes.) On the surface this would appear to be not too difficult a task except for the fact that today there are increasing numbers of very potent drugs on the market and the smaller the amount of active ingredient per tablet, the more difficult the problem of achieving uniformity—especially if the mixture is made up of widely varying particle sizes. In one known case a product labeled to contain 1 milligram of active ingredient per tablet was shown on assay to contain 106 per cent of the labeled claim when 20 tablets were ground and a subsample was analyzed. Another group of 20 from the same batch assayed at 104 per cent when similarly treated. Individual tablets from the same batch, when tested singly, yielded results from 70 to 130 per cent of labeled claim. The problem was traced to wide variations in the particle size of the active ingredient. Specifications had to be established for particle size to ensure uniformity in subsequent batches.

Another problem that is receiving increas-

ing attention involves the controls employed to ensure that the proper punches and dies are used in a tablet press. The frequency with which punches of the same diameter but with slightly different concavity or other differences find their way into a set on a tablet press seems to be on the increase. Some of this is probably due to the fact that many firms differentiate physicians' samples from the commercially sold product by using special punches on which the word "Sample" or some equivalent phrase is embossed. This problem could become more acute as the tendency grows to identify tablet products by means of a combination of numbers and letters embossed on the surface. There was an instance of one firm in which an entire batch of tablets was compressed with one wrong punch (out of a set of 37 punches) inadvertently put on the press. In spite of periodic checks by production and quality control personnel, this batch was released and the mistake was found by a consumer. The entire batch had to be recalled. More extensive and independent checks have now been established to prevent a recurrence.

Another important check point in tablet manufacture has to do with controlling the amount of granulation in the tablet machine hopper. As the end of the compression nears, one must be certain that the hopper is not permitted to run all the way out. Should this occur there is a strong likelihood that the last few hundred tablets may be somewhat variable in thickness and weight.

There are a number of important in-process tests routinely employed to ensure uniform quality of tablet production. These are as follows:

Moisture of the tablet granulation prior to compression, average weight per group of 10 tablets at periodic intervals (usually every 20-30 minutes), individual weight variation, thickness, hardness, and disintegration time. The last named test will doubtless be supplemented or replaced by a test for dissolution time, as technology develops. In some firms many of these tests are performed at routine intervals by production personnel, with the quality control department monitoring the recorded data as one of the prerequisites for final release of the batch. Special types of tablets, such as molded hypodermic tablets, require a test for microbial contamination, while effervescent tablets must be tested to ensure absence of moisture and completeness of solution.

Capsule manufacture. Much of what has been said about the manufacture of tablets applies to the filling of hard gelatin capsules. Procedures must be established to control the weight of net contents of the filled capsules. Studies of individual weights obtained across the cross section of the capsule filling ring indicate that considerable variation can occur from the inside to the outside ring if care is not exercised in preparing the capsule mix and operating the filling equipment. Tests for disintegration time or dissolution rate should also be performed. It is quite important to ensure that the gelatin does not form a gummy mass with the capsule contents and thus impede disintegration in the gastrointestinal tract.

Suppository manufacture. Automatic equipment is being used increasingly in the manufacture of suppositories. Although this represents an advance over hand molding, it is not without problems. Air pockets can form in the mold cavities and go undetected unless weight checks on individual suppositories are made at periodic intervals. To ensure uniformity of the suppository mass during molding, the mass must usually be kept molten and well mixed. The introduction of too much heat for too long a period of time may be inadvisable for certain drugs

and may require that periodic samples of the mass be analytically tested for drug content to make sure that chemical breakdown has not occurred.

Sterile products. Of the various types of dosage forms manufactured, sterile products, particularly injectables, require the greatest care and attention. Properly designed areas and equipment, and properly trained and garbed personnel, are of paramount importance.

Since the test for sterility of the final product is somewhat presumptive, in-process controls such as periodic sampling of the air, filling of bacteriological media to demonstrate that conditions are satisfactory, recording devices on autoclaves to ensure that time and temperature requirements have been met, and the use of biological indicators, are all indispensable.

Maintaining product identification of every vial and ampoule is of the utmost importance. It is a cardinal sin to have one unlabeled vial or ampoule on the plant premises. Some firms use preprinted vials in preference to paper labels. Although this would appear to be a step in the right direction, several cases have been observed in which the supplier of the preprinted vials has inadvertently mixed up two or more product names within a shipment. In some instances the several names were for products not even manufactured by the same firm. I personally prefer to see the application of the label made by way of printing on the vial or ampoule immediately after the filling of each vial. This can be done without impairing later inspection of the vial or ampoule for particulate matter. It is important to choose an ink which will withstand the conditions to which the vial or ampoule is exposed between the time of filling and eventual use. In this type of operation the same form of control must be exercised as that used to control paper labels.

A check of finished package yield against bulk solution delivered to the filling operation is an important check to ensure against product mix-up, just as it is with all other dosage forms. A recording of all types of defects found during the inspection operation is also of value in detecting and correcting trouble spots in the operation.

We could spend a great deal more time discussing the quality and treatment of containers and closures, the control of water for absence of pyrogens, etc., but that would not be within the scope of this brief over-all review of manufacturing practices.

Packaging operations. One of the most important responsibilities of every drug manufacturer is to make sure that every finished drug product is properly labeled. This is not to say that proper identification of all containers of the "half-finished product" is less important. Because of the large number of containers handled, the trend toward use of higher speed packaging equipment, and the desire to control costs in the area in which the plant payroll is highest, the incidence of packaging errors has been high in recent years. Many of these errors reflect a need for greater care in the handling of labels.

There are several cardinal rules which should be followed if packaging errors are to be avoided.

1. Before each job is run, a thorough check and double check should be made in order to be sure that the packaging line and all pertinent equipment have been purged of material from the previous job.

2. Not more than one job should be permitted on the packaging line at a time.

3. Packaging lines should be so arranged, in regard to spacing, as to avoid any possibility of product mix-up between lines.

4. Material falling from the line onto the

floor should preferably be destroyed. Well-intentioned personnel may pick up and return material to the wrong job.

5. Only labels which have been thoroughly inspected and counted and issued by authorized personnel should be permitted on the packaging line.

6. Labels should be stored under conditions which prevent any possibility of a mix-up, and access to the label storage area should be limited to authorized personnel.

7. Upon completion of each job, a reconciliation of the labels used against the number issued (including those damaged or destroyed) should be made. Any discrepancy found should be investigated and the results of the investigation entered into the packaging record.

Drug Product Storage

Provision should be made for storage of the drug product under conditions which will maintain its quality characteristics. Some products require refrigeration, while others should not be exposed to excessive temperatures.

In some firms quality control personnel re-examine each batch of finished product just prior to shipment to ensure that no physical change has occurred and that the product is being shipped on a first-in-first-out basis.

Summary

The points discussed above can be summarized briefly as follows.

For a firm to apply good drug manufacturing practices, it must have written procedures which are understood and followed with respect to:

1. Specifications for raw materials, half-finished product, and finished product.
2. All manufacturing operations.
3. All packaging operations.
4. A system of independent checks which ensures that points 1, 2, and 3 are complied with every time. Also personnel must be qualified and trained to do the job required, and premises and equipment must be suitable for the intended purpose.

THE DRUG INSPECTION

DR. JOSEPH J. DI LORENZO *

During the past two decades the pharmaceutical industry has been growing steadily in many countries. In some of them the increase has been tremendous, with the introduction of new drugs and new formulations intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man and animals.

Drug manufacture today is a complex science, involving many intricate details and procedures to arrive at a finished drug form. Most of the drugs of our present-day armamentarium are produced either by biological processes or by chemical synthesis.

No one will take exception to the statement that the drugs made available to the public should, and must, be safe and efficacious, and that the public should be able to use them with full confidence that they will achieve the desired effect for which they were prescribed. In our present age of scientific and technical knowhow, there is certainly no place for second-rate drugs. Today, drugs are not only prescribed for the sick and the ailing, but are also administered to the healthy (i.e., birth control drugs, antianxiety drugs, vitamin drugs).

Responsibility for producing life-saving and life-sustaining drugs rests directly upon the drug manufacturer. He is in the best position to determine that his operations will assure safe and effective drugs.

And yet, the responsibility for high-quality drugs does not end at the manufacturer's level. It becomes the responsibility of the government authorities to see that the manufacturer observes and follows all of the governmental regulations required for assuring the production and distribution of quality drugs. Thus, it becomes necessary that the government authorities exercise the most comprehensive surveillance of each and every drug manufacturer within their jurisdiction. This can be accomplished by: (1) the testing of drug samples in the drug laboratory, and (2) a physical inspection of the drug manufacturing establishment. While it is true that most government controls, in many countries, are exercised by the testing of samples collected from the drug manufacturer, or from the domestic market, unfortunately only limited information on the manufacture of drugs can be obtained by means of an analytical control of the drug samples. However, when the analytical work is supported by an inspection of the drug firm, then a true and more complete picture comes into view. Thus, while the analytical testing of a product, as performed by the government laboratory, is a means of providing a government control over drugs, it is at best only a partial or incomplete control. The inspectional finding, together with the analytical testing, would be more meaningful and would indeed represent a truly comprehensive control.

The main purpose or thrust of the drug inspection is to uncover weaknesses and deficiencies in manufacturing procedures and

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operations. It is also aimed at searching out actual or potential errors in production and quality control procedures. And finally, the drug inspection also serves to assure that the drugs are produced under acceptable and good manufacturing procedures, thereby preventing substandard and ineffective products from being distributed for use by the consumer.

Unfortunately, the complexities and continuing advancements in drug production and quality control techniques, as well as the variety of drug firms to be inspected, preclude a prescribed format to be followed for any given drug inspection. For example, a firm may be inspected for one or more of the following reasons:

- The newness of a plant, one that is about to, or has just started, the manufacture of drugs.
- Followup of a drug product that has been recalled from the market because of loss of potency, injury complaint, change in composition, etc.
- Changes in a firm's manufacturing operations and procedures, whether major or minor, including the manufacture of new or revised formulations, or the manufacture of more potent and intricate drug products.
- Major changes in plant layout, such as the enlargement or alteration of production areas, especially sterile areas.
- Routine, periodic, annual inspection as required by the national drug authorities.
- When followup inspections are desired, or required, to determine whether recommendations or suggestions made on a previous inspection have been put into effect.
- When it is necessary to collect samples of a drug product, for one reason or another.
- When it is necessary to review and obtain scientific information regarding a specific drug product.

These are but a few reasons for a drug inspection, and no doubt one can think of others. But the fundamental reason is that the drug authorities must be kept alert and current as to what goes on within the drug plants under their jurisdiction. This can only be accomplished by the drug inspection.

The drug inspection is a very challenging assignment. It is also a vital and necessary function of the government authority which is responsible for the health and welfare of its people. To make the drug inspection worthwhile and meaningful, the inspector must be fully qualified and have training and practical experience in drug control and drug production. He must have a scientific education that includes a general knowledge of chemistry, bacteriology, and the pharmaceutical sciences. His professional qualifications should preferably be no less than the requirements set by law for the qualifications of experts and key personnel in charge of drug manufacturing and quality control. The drug inspector must be an individual who possesses the ability to win the respect and confidence of all those he comes in contact with. He must have aggressive intelligence. Above all, he must realize fully that he is a representative of government and that the manner in which he conducts himself reflects directly upon the very government he is representing. The well-qualified inspector also keeps abreast of new developments and technical trends in the field of drugs since he often is called upon to assume the role of "consultant and adviser."

It has been said over and over again that the drug inspector serves as the "eyes and ears" of the drug control authorities, and nothing could be truer.

The drug inspection starts at the inspector's desk, where he begins to acquaint himself with the operations of the drug plants he is scheduled to inspect. To determine the amount and degree of coverage that is to be given a drug firm, he must have a general knowledge of the firm and its problems, the previous history of the firm in regard to the

manufacture of drugs, and the conditions as they existed in the plant during the previous inspection. Therefore, the inspector should review very thoroughly such documents as reports of previous inspections, drug applications on file with the national authorities, analysis reports on the firm's products, any past recalls, any complaints received, any regulatory actions taken against the firm by the national control authorities, etc. From previous reports he should note what manufacturing areas or phases of production may require special coverage. From the drug application he should note, for example, what drug items are produced, what quality control specifications have been laid down by the firm, the firm's manufacturing operations, and if possible, the layout of the plant. If the inspector has done this preliminary work well, he will then be in a better position to conduct a more comprehensive and a more meaningful inspection.

Proposed inspections should be planned for weeks and even months in advance. If possible, drug plants should be given coverage twice a year and those firms that have a violative history should be inspected as often as the need arises to bring them (and to keep them) in compliance with the laws set forth by the national drug authority.

Even if the inspector has familiarized himself with the plant and its operations by reviewing reports of previous inspections, he may find it desirable to make a preliminary "walk-through" inspection in order to orient himself with regard to the actual layout of the plant. This is particularly important if the plant is a newly established one that is being inspected for the first time.

During this preliminary inspection, the experienced inspector can single out apparent weak spots or potential hazards that may affect the final quality of the drug, and these are given closer attention later in the inspection.

Although the actual inspection may start at any of several areas, for the sake of continuity and a well-planned inspection it is best to begin in the area where raw materials and components are received, and follow their normal pathway through the production stages, the packaging and labeling stages, etc., to the final laboratory testing of the finished drug product. It is also advisable to select a specific product or products and follow these, by the various production records, to their final destination in a drug plant.

In many cases it is also advisable for the inspector to select, for special inspectional coverage:

- Drug products which are difficult to manufacture and present problems in mixing (minute quantities of active ingredients), granulation (time release drugs), incompatibility of ingredients (amylnitrate in aluminum gel, ascorbic acid with ferrous sulfate).
- Drug items in which the formulations have been revised, or items which are entirely new with the firm and for which the firm has little or no experience as to their manufacture.
- Drug items which contain two or more active ingredients and may present problems in assay controls.
- Drug items for which there are no official or established methods of assay.
- Drug items that are susceptible to light, heat, temperature changes, moisture, etc., and require special handling and precautions during manufacture and packaging (penicillin, epinephrine, aminophylline).
- Drug items which are known to be unstable, such as some antibiotics, or other drugs in solution.
- Drug items which require special methods and techniques for their manufacture because of bioavailability factors (chloramphenicol capsules, oxytetracycline tablets).
- Drug items which have been recalled from the market or those which have been violative in the past.

If, during the actual inspection, objectionable practices and serious deficiencies

are noted, samples of the firm's drug products should be collected and submitted to the government testing laboratory to determine whether or not the objectionable procedure and serious deficiencies noted have had any deleterious effect upon the quality of the final product. Needless to say, samples collected should be sealed by the inspector to preserve their continuity until they reach the hands of the government analyst.

While time does not permit a complete and detailed dissertation as to what specific areas and items should be given intensive coverage by the drug inspector, the set of inspectional guidelines, or inspectional checklist, included in the Annex to this paper will serve to delineate certain basic and minimal procedures pertaining to the inspection of drug firms. It may, of course, be necessary to modify these suggested guidelines for various firms and various operations, in order to achieve the desired coverage of all establishments engaged in the manufacture and handling of drug products. It may also be necessary to alter these basic inspection procedures to meet special or unusual situations or conditions that vary from one drug plant to another. However, I wish to direct interest to certain factors that should receive particular attention because they are critical areas and contribute substantially to the final quality of the drug.

The drug inspector should look into:

- The degree and extent of testing practiced by the firms on raw materials to determine their adherence to prescribed specifications. Actually, the control exercised over raw materials has a special significance since it constitutes the beginning of a long series of rigid controls. One might even say that this stage of production is the first line of defense against the inferior quality of drugs. In reviewing the firm's analytical records of raw materials, the inspector should note instances in which borderline assays of such materials were reported and these materials were eventually used.
- The completeness of manufacturing reports kept by the firms. The over-all operations of any given drug plant are dependent upon the written records maintained for all phases and stages of manufacture, including packaging and labeling operations. These written records, if properly kept, reflect the entire manufacturing history of a batch of drugs. From these batch or manufacturing records, the inspector can trace a particular batch of the drug, from its initial stages to its final release and eventual distribution. Also, from the same records a determination can be made of what factor or factors contributed to the rejection or acceptance of the batch.
- The finishing operations, that is, the packaging and labeling, conducted by the firm. These operations are very frequently the major source of errors and serious mishaps. It has been noted that more costly errors have been made during packaging and labeling than in any other stage of production. Therefore, the drug inspector should give attention to these areas in order to search out actual or potential defects and deficiencies.
- Manufacturing operations are conducted by people, and people are prone to making errors. Consistency in manufacturing operations and quality control can only be achieved by people, and therefore the human factor should be given adequate coverage in drug inspections. Particular attention should be directed to manufacturing and laboratory personnel in order to obtain information on their qualifications and responsibilities.

Upon completion of the inspection, the drug inspector should meet with top management and key officials to discuss the inspectional findings. If objectional practices and deficiencies are found, or any significant deviations noted in manufacturing procedures (as compared to those listed in the drug manufacturing documents on file with the national drug authorities), they should be discussed thoroughly with management. It is advisable to present management with a written copy of the inspectional findings to be discussed. The inspector should ask management to correct or eliminate the deficiencies noted, and to indicate

how soon such changes are to be made. For the official records, the firm should also be advised that it should notify the national drug authorities, in writing, when the changes have been made, since another drug inspection may be necessary to determine if the changes made are in accordance with the inspector's recommendations. The inspector's knowledge in all phases of manufacturing and control procedures qualifies him to assume the role of adviser and consultant; therefore, he can discuss with management the best means to avoid or correct manufacturing deficiencies. He should offer reasonable suggestions and make specific recommendations aimed at bringing the firm's operations into compliance with the country's drug laws and regulations.

The write-up of the drug inspection is vital since the written report serves as a permanent and current record of the firm's operations. The report becomes a permanent record for the national control authorities' files. Needless to say, it must be precise and factual since it often serves as a basis for determining whether or not regulatory action should be initiated. Since the report includes a detailed account of the firm's operations, as well as any objectionable practices and deficiencies noted, any suggestions and recommendations made, etc., it further serves as a valuable informative document that can be used later for briefing other inspectors who will be reinspecting the firm.

With respect to guidelines dealing specifically with good manufacturing practices, as they relate to the production and quality control of drugs, it should be pointed out that all national drug authorities would be well advised to develop such guidelines, or adopt existing ones. If need be, such guidelines could be made part of the drug regulations, and would serve two distinct purposes: (1) the manufacturer would be made aware of what is expected of him, to produce drug products of defined quality; and (2) the national authorities could use the guidelines as the basis for regulatory and compliance activities.

The World Health Organization's report dealing with Principles of Pharmaceutical Quality Control, and Good Practices in the Manufacture and Quality Control of Drugs (WHO Technical Report Series No. 418) is an excellent document. It was formulated by a group of experts for use as a general guide by nations that have need for such guidelines. The document brings together a number of good and acceptable procedures which, if adhered to meticulously, will assure the production of quality drugs. I highly recommend that nations lacking such guidelines make use of this WHO document.

Summary

Drug sampling and analysis, together with drug inspections, are the bulwark of surveillance activity. They must go hand-in-hand; one without the other is meaningless and would not afford the complete coverage of drug establishments, as required by conscientious drug authorities. The drug manufacturer has his responsibility. The national drug authorities have their responsibilities. Neither can permit laxity to creep into their operations and both must be alert to carry out their respective functions. When it comes to the production of life-saving and life-sustaining drugs, there is no margin for error.

Let us again point out the importance of the drug inspector's role in drug quality by placing particular emphasis on the fact that the inspector cannot carry out his duties and responsibilities unless he is thoroughly trained and is a master of his demanding speciality.

Annex

SUGGESTED GUIDELINES FOR THE DRUG INSPECTION

Raw Materials:

- Are raw materials properly identified upon receipt, and recorded by the warehouse in a bound ledger; are they assigned an incoming raw material number? Is this number perpetuated in subsequent operations?
- Are raw materials properly quarantined pending release by the firm's quality control department?
- Has the drug firm established appropriate specifications (e.g., requirements for microbiological and chemical purity, potency, identity, etc.) for those incoming raw materials which are not recognized in some official compendium, such as the U.S. Pharmacopeia, the British Pharmacopoeia, etc.?
- Are the supplier's protocols or records of assay on the raw material checked to determine compliance of the material with the firm's specification or compendium requirements?
- Are those raw materials received without a supplier's protocol of assay tested by the firm for compliance with appropriate specifications?
- Are accepted raw materials clearly identified and properly stored to prevent mix-ups and contamination?
- Are rejected raw materials properly identified, isolated, and disposed of by returning them to the supplier, or are they destroyed? Are the rejected raw materials reconditioned or reprocessed, where possible, and are adequate records kept of the reconditioning or reprocessing procedures?
- Are bulk drugs which are subject to deterioration periodically retested for potency, prior to use?
- Are appropriate written records (e.g., origin or supplier, date and amounts received, examinations and assays performed, etc.) maintained on all raw materials received, including those that are rejected? Are records kept as to the disposition of the approved raw materials, as well as those that have been rejected?
- Are raw materials sampled by a representative from the quality control department, and are they sampled in the warehouse or is the container of raw materials taken to quality control, where the sample is removed?
- Are raw materials undergoing testing by quality control properly identified to show that they are "under test," and are they quarantined to prevent their use before control tests are completed?
- Are the raw materials approved by quality control labeled to show that they have been "approved"?

- How are approved raw materials requisitioned for use by the various production departments?

Manufacturing Operations:

- Has a master formula record (for each drug product manufactured) been prepared, initialed, and dated by a competent responsible individual, and endorsed by a second qualified individual? If certain changes or modifications are required in the original master formula, who has the responsibility and authority to make the necessary changes?
- Does the master formula record include clear and adequate manufacturing and control procedures, and a specimen copy of all labeling which will accompany the finished package of the drug? Does it include adequate instructions for packaging and labeling of the drug?
- Does the batch (production) record include an accurate reproduction of the appropriate master formula, and has it been checked and endorsed (initialed) by a competent, responsible individual?
- Is each critical step in the manufacturing process (e.g., selection, weighing, measuring of components, addition of active ingredients, determination of the theoretical yield, in-process controls to be followed, etc.) performed by a competent, responsible individual, and is it checked by a second qualified individual?
- Are all containers and equipment used in the production of a batch distinctly labeled as to their contents, stage of processing or manufacturing, batch number, etc.?
- Is the equipment used for weighing and measuring periodically checked for accuracy?
- Is the manufacturing equipment, including mixers and blenders, of suitable size and type for processing or manufacturing the batch?
- Between batches, are the utensils, containers, mixers, homogenizers, etc. (all manufacturing equipment), thoroughly cleaned and properly stored? Are all previous batch identifications removed? Is some manufacturing equipment (e.g., tablet presses) disassembled to facilitate thorough cleaning?
- Is there adequate physical separation between the production lines of batches of different drugs to preclude mix-ups or the cross-contamination of one batch with another?
- Are in-process control tests conducted to ensure uniformity in mixing or blending of a batch?
- Are the in-process control tests adequate to ensure the integrity of the batch, and are written records kept of these controls?
- Is the air filtration system supplying all production areas (except the sterile areas) adequate to eliminate or minimize the cross-contamination of drug products?
- Is negative air pressure (e.g., exhaust hoods) provided in areas requiring it (e.g., handling of highly potent drugs, tableting, micronizing, etc.)?
- In the filling operations, are in-process controls followed to ensure proper fill of containers?

Sterile Operations:

- How do operators prepare themselves for sterile operations? Do they take showers, are they completely covered and gowned from head to foot (head caps, masks, gowns, shoe coverings, rubber gloves, etc.)?
- How are the sterile areas (walls, floors, benches, etc.) treated to render them clean and aseptic?
- How is the sterile air supply to the sterile areas treated to ensure that it is sterile? Is the air under positive pressure?
- Is there an air-lock at the entrance of the sterile area? Is the pressure lower in these air-locks, so that the flow of air is from within the sterile areas to the air-locks?
- What controls are made to determine the microbial populations of the entire sterile area? Are culture plates exposed? How often, how many, in what locations, and for what periods of time? Are records of plate counts maintained in a record book and for how long?
- How do materials and equipment, used in the sterile operations, gain access to the sterile areas?
- Are there ultraviolet lights in the areas?
- When, and by whom, are samples taken of the drugs packaged or filled under aseptic methods?
- Are controls made, and of what kind, to ensure that the filling equipment is sterile? That it delivers the correct quantity?
- In the lyophilization procedures, are temperature and vacuum controls made at the freezing stage and at the drying stage? Is filtered inert gas of "sterile" dry air used when releasing the vacuum in the final stage of drying?

As for those drugs that are to be sterilized in their final market container:

- What type of terminal sterilization is used? Does the firm use biological indicators to check their sterilization procedures?
- Are flame-sealed ampoules effectively tested for leakage?
- What procedures are followed to render the drug product pyrogen-free?
- Are the components used tested for their bacteriological content, even though the drug product itself is terminally sterilized?

Labeling (Finishing) Operations:

- Prior to packaging and labeling, is the theoretical yield versus the actual yield of each batch checked and reconciled by a competent, responsible individual?
- Is any discrepancy in batch yield appropriately investigated and recorded?
- Is there adequate physical separation between the various labeling operations of drug batches to prevent mix-ups?
- Are all labels and labeling checked against an approved final copy by a responsible individual prior to release for a labeling operation?
- Is access to the label and labeling storage area restricted to authorized personnel?
- Are the labels for each drug product, for each dosage form, and for each strength stored separately, to prevent mix-ups?
- Are the labeling facilities (machines, tables, etc.) inspected prior to use to ensure

removal of other drugs and previously used labeling from the labeling line?

- Is the labeling checked by a competent, responsible individual for identity and conformity to that specified in the batch control record, immediately prior to the issuance of labeling for use?
- Are all excess labels bearing the lot or batch control numbers destroyed, after the labeling of a batch is completed?
- Are records maintained of the number of labels issued, used, and destroyed?
- Are all discrepancies in the quantity of drugs labeled and the number of labels used thoroughly investigated and recorded?
- Are the control or batch numbers meaningful with respect to the manufacturing history of the batch to which these numbers are assigned?
- Is each batch quarantined immediately after the labeling operation until it is tested and released, as satisfactory, by the quality control department?
- Is a chronological record maintained for each labeling line, which reflects when and what batches were labeled on that line?

Quality Control Laboratory:

- Does the quality control department have the final decision as to whether a batch is to be released or rejected? To whom does quality control report?
- Does the laboratory have the necessary equipment and apparatus to conduct all of the control tests required?
- Does the laboratory periodically check the reliability and accuracy of the laboratory instruments and equipment used?
- Does the laboratory periodically check the reliability and accuracy of the laboratory test procedures and methods used?
- Are the laboratory instruments adequate for the test procedures conducted?
- Are tests also conducted on the effectiveness of preservations, when such agents are incorporated in a drug product?
- Does the control laboratory record and maintain all data of the tests conducted for each batch?
- If the firm performs animal tests, are the test animals healthy and suitably housed?
- Are rejected batches identified, isolated, and promptly disposed of by reworking or destruction, and are records maintained on reworking and the disposition of these batches?
- Is each finished batch checked for compliance with established standards or specifications prior to release of the batch?
- Has the stability of the finished drug product been determined by reliable and specific testing methods?
- Does the quality control laboratory keep reserve samples of all batches tested, to be used for future reference (e.g., for retesting in cases of product complaints, injuries, loss of potency, physical changes in the product, etc.)?
- Is a written record maintained of all verbal and written complaints concerning a drug product?
- Are all complaints evaluated and a written record maintained of the action taken?

Personnel:

- What are the qualifications of the personnel in the production departments; in the laboratory sections; in the packaging and labeling departments, etc.?
- Are the personnel suitably dressed (except for sterile area) for the operations they conduct?
- To whom do the operators and key personnel report?
- What is the attitude of the individual toward his work? Is he happy, content in what he does? Is he aware of the role he plays in contributing to the quality of the product?
- Does the firm provide adequate facilities for recreation, lunch, washrooms, etc.?
- Are the workers' surroundings pleasant and cheerful?
- Are the working areas well lighted and well ventilated?
- Are operators provided with the necessary safety devices (e.g., shatter-proof eyeglasses, immersion showers for fires, etc.)?
- Are the personnel involved in any outside activities that may be considered a "conflict of interest"?

Warehouses, where drugs are stored and held for distribution, must also be given adequate coverage. The inspector should inspect these warehouses, and pay particular attention to the following:

- Are the drugs properly stored (e.g., under proper temperature)?
- Is the warehouse temperature controlled?
- Are records maintained of all drugs received?
- Are records maintained of all drugs distributed?
- Are the records complete enough so that in the event a drug must be recalled and removed from the market, the drug shipments can be readily traced and recovered?
- Are all drugs stored in the drug warehouse within their expiry dates?
- Are there any returned drug stocks?
- Does the warehouse rotate the stocks, so that the older drugs are distributed first?

In the case of retail outlets or pharmacies, similar observations are made as to whether the drugs are properly stored; whether records of distribution are kept; whether drugs which carry a prescription legend are sold only upon the presentation of a written prescription issued by a licensed physician; whether any drugs in stock are outdated (have reached their expiry date); etc.

The inspection report should include the following information under the suggested headings:

- Name and address of the drug establishment.
- Dates of inspections.
- Name of the inspector.
- Reason for the inspection.
- Names of all persons interviewed and their responsibilities.
- List of drug products produced.
- Volume of production (on monthly or yearly basis).
- Raw materials, their storage and controls.
- Manufacturing operations, including master formulas, production records, and all controls followed.

- Sterile operations (if firm produces sterile drugs).
- Nonsterile operations (capsules, tablets, ointments, etc.).
- Packaging and labeling operations and controls, including the coding system used.
- Manufacturing equipment, its condition, and the working capacities of mixing and blending equipment, tablet compressors, coding and polishing drums, filling equipment, etc.
- Laboratory equipment and laboratory controls.
- Record of distribution.
- Complaints received (as well as returned goods).
- Samples (if any) collected and reasons for their collection.
- Deficiencies, objectionable practices, etc., noted and reported to management.
- Recommendations and suggestions made to the firm.
- Corrective action promised by the firm.
- Cooperation or resistance received during the drug inspection.
- Inspector's over-all impression of the firm.

LIMITED REVIEW OF VETERINARY DRUG PROBLEMS

DRS. PEDRO N. ACHA AND HAROLD B. HUBBARD *

Attempts made at analyzing veterinary drug problems quickly lead the analyzer to a state of *diplopia,* commonly called "double vision." Instead of seeing two identical objects, the viewer observes the two heads of veterinary drug problems which are similar in some aspects but different in others. This presentation will attempt to explain this two-headed *Hydra.* You will remember *Hydra* as the nine-headed monster slain by Hercules, who would strike off one head only to have two more grow forth in its place. Drug problems related to veterinary medicine indeed call this monster to mind.

The significance of the use of drugs in veterinary medicine is associated with the fact that a drug must not only be safe for the animal receiving it, but residues remaining in the animal tissue must also be demonstrated to be safe for man. The complexities involved in determining such levels of safety pose growing technical problems.

Why should we be concerned about whether a drug is safe for the animal and the residues remaining in this animal safe for man? What is meant by safe for the animal? What is meant by safe for man? It would be pretentious on our part to try to answer these questions before this distinguished body of scientists. However, we shall attempt to point out some of the problems involved in the use of drugs in veterinary medicine and the consequences that have followed. Is it possible to maintain progress in the field of animal production, with the goal of providing animal protein to the people of the world deficient in this nutrient, without jeopardizing the public health?

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Safety for the Animal

Margins of safety for the use of drugs in veterinary medicine are well spelled out by the manufacturers for products intended for parenteral use and for medicated feeds. Observance of these margins of safety by the user of the drug is frequently neglected. A drug is generally considered safe for the animal when it is used under the supervision of a licensed veterinarian or when "adequate directions for use" can be prepared. Therefore, drugs marketed with "adequate directions for use" can be sold over the counter and are available to the general public. Within this group fall those drugs used in the medication of feed for animals.

It is common knowledge that medicated feeds have contributed significantly to improved feed efficiency, productivity, and weight gain, but the indiscriminate use of drugs has also had many undesirable effects. Many of the detrimental effects experienced by the livestock and poultry industry with the use of medicated feeds have been caused by the unrestricted addition of these drugs. Some examples of the unwanted reactions encountered are the

following:

1. *Digestive problems in adult ruminants.* High levels of antibiotics such as chlortetracycline given as a single dose may cause as much as 75 per cent depression in the flora of the rumen within two hours; this condition may last up to two days (*1*). Fermentation in the rumen is depressed; organic acids are produced at about 30 per cent of the normal rate; the ruminal pH is lowered considerably; and appetite is diminished, with a resultant loss of body weight. It has also been reported that prolonged administration of some antibiotics to feed-lot cattle produces chronic indigestion and atony of the rumen (*2*).

2. *Drug-induced anemic reactions.* Numerous instances have been reported where the use of sulfonamides and certain antibiotics in excessive quantities in the feed has caused a significant increase in hemorrhages and anemia in poultry (*3, 4*).

Clinical and pathological changes characteristic of the hemorrhagic disease syndrome have also been related to liberation of mycotoxins by certain fungi (*5, 6*).

3. *Organic arsenical toxicity in swine.* Arsenicals are available without restrictions to any one who wishes to buy them. As a result of promotion and advertising by commercial houses, the farmer often believes that the drugs are relatively harmless and can be used indiscriminately. Although the margin of safety is rather broad for arsanilic acid, many cases of toxicity in swine are observed each year, involving hundreds of animals throughout the swine-producing areas (*3*). It is not uncommon to find the case of a farmer who has already incorporated arsenicals in the feed for his swine; and who, when evidence of diarrhea appears, and knowing from past experience that arsenicals are used in the treatment of diarrheas, purchases additional supplies and adds them to the feed or water. Obviously this creates an overdose of the product and a toxic reaction in the animal. Signs and symptoms of arsenical toxicity in swine include a gradual weakening of the limbs associated with poor coordination, exaggerated stepping movements, and reluctance to get up. The animals become progressively paralyzed and are unable to walk; blindness is also observed. Clinical signs associated with the toxicity usually indicate peripheral nerve involvement; the animals show normal central nervous functions. A necropsy will reveal some atrophy, but no other gross lesions. Histopathologic examination usually shows demyelination and gliosis of certain nerve plexus.

The toxicity experienced by these animals due to drugs in the feed is associated with the presence of the chemical in the water. Adequate water is essential for normal metabolism and also for excretion of many of these drugs. Interference with the palatability of the water causes the animals to reduce its intake, thereby increasing the hazards involved. Arsenicals and sulfonamides are toxic to swine if adequate water is not ingested simultaneously. The problem is compounded when the water also contains the same medication as found in the feed.

An important problem associated with medicated feeds stems from the practice of administering two or more drugs simultaneously. This is particularly significant when the veterinarian or livestock producer is not aware of other drugs that the animal is receiving. Diagnosis becomes extremely difficult when the investigator is trying to determine if an interaction is occurring between the chemicals known to be administered to the animals or is associated with the other chemicals present in the food or water.

4. *Development of pathogens resistant to drugs.* This topic is so broad and complex that we can only touch briefly on its relationship to veterinary medicine. The crisis of hospital-acquired staphylococcal infections probably brought into focus the serious problems of antibiotic-resistant organisms, which began to develop as a result of overconfidence in the use of those agents and a relaxed attitude toward antisepsis. Although this was a hospital-oriented problem, it did call attention to the fact that antibiotic-resistant organisms probably were developing in animals as a result of preventive levels of the drugs used in their food and water. It is important to point out that the therapeutic concentrations of antibiotics administered to hospital patients were far higher than the concentrations used in animal feeds to promote growth. However, resistant strains of organisms proliferate not only in response to high concentrations of antibiotics used therapeutically, but also to much lower levels used to prevent disease or to promote growth. Therapeutic levels may be as high as 2,000 ppm, as compared to a minimum of 20 ppm needed for growth stimulation (*7*).

The enterobacteria common to man and animals are probably the leading microorganisms to be considered in regard to resistance to antibiotics. Some of these enterobacteria cause diarrhea and urinary tract infections. Antibiotic-resistant organisms seem to possess a survival advantage over antibiotic-sensitive strains in an environment *free* of antibiotics. The reason for this is difficult to determine. Equally perplexing is the evidence that resistant organisms grow more slowly than their sensitive counterparts. The ability to resist antibiotics probably existed in a minimal number of the microbial population before commercial antibiotics were developed, and may have evolved in response to natural substances resembling antibiotics in some particular way. Strains of enterobacteria preserved in the days before antibiotics have shown resistance to streptomycin and tetracycline, antibiotics that were developed many years after the strains were preserved.

Antibiotics can provide a survival advantage to some organisms, give a disadvantage to others, and leave others unaffected. In general, antibiotics seem to bring out differences that already exist, rather than cause an essential genetic change in the individuals of the population. Complicating the total picture is the apparent discovery of some enterobacteria with resistance to experimental antibiotics to which they obviously had never previously been exposed. Such activity suggests the possibility of a basic mechanism in many bacteria for developing some varieties of resistance. Another complicating factor is that a single antibiotic may induce bacterial resistance to other antibiotics. For example, some *Salmonella* organisms exposed to ampicillin can resist sulfonamides and neomycin, although never before exposed to either of these drugs. It is well known that some bacteria have resistance to as many as nine antibiotics at one time.

This multiple resistance can be transmitted not only within strains but also between different strains and species. We shall not go into the details of the R-factor (resistance transfer factor), but merely point out that this factor can be given and received by nonpathogenic as well as disease-producing bacteria (*8*). Obviously, this permits the storage of resistance without the manifestation of disease. A sensitive pathogenic organism can therefore acquire this resistance after it has infected a healthy animal. In this way, treatment of the infec-

tion becomes a much more difficult problem. A few years ago it was shown that pigs receiving tetracycline in feeds developed tetracycline-resistant *E. coli*. Removal of tetracycline from the feed produced a reduction in the proportion of resistant *E. coli* strains. These observations show that manipulation of different types of antibiotics in the feed can produce an alteration of antibiotic-resistant strains. Indiscriminate use of alternating types of antibiotics likely to produce a variety of antibiotic-resistant strains has undoubtedly contributed to many of the problems discussed here. The ways in which antibiotics used to encourage growth and production affect the development of resistant or sensitive bacteria in the digestive tract is obviously an extraordinarily complex area of investigation. The differences between various animal hosts, and the variety of chemical environments found along the intestinal tract, compound the difficulties confronting researchers in this field.

Human Safety Problems

As veterinarians, our concern for safety cannot stop with safety to the animal receiving the drug. We have an even greater concern for the harmlessness and wholesomeness of products derived from treated animals. There is great controversy and disquiet over the impact which drugs given to food animals may have on public health. The possible presence of residues in edible products (meat, milk, eggs, and poultry) derived from treated animals is the primary factor to be considered today in the approval given to market drugs for use in veterinary medicine. Concern has been expressed in many ways, not only by members of the veterinary profession but also by government officials and leading producers of livestock, feeds, and drugs. Through the use of many of these drugs in treating animals, we have found ways to produce healthier, heavier animals, and the increased production of meat and milk has aided the peoples of the world deficient in these foods. But we return to the question posed previously: How can we continue to make progress in animal production without jeopardizing the public health?

In spite of regulation and control of the use of drugs in veterinary medicine, sampling programs of the U.S. Department of Agriculture reveal that antimicrobial drug residues are occurring. Such residues were detected in 1.7 per cent of red-meat animals randomly sampled in 1968. Results so far in 1970 indicate that the incidence of drug residues may show an increase over 1968. The Department of Agriculture's Meat Inspection Division and the Food and Drug Administration are currently trying to arrive at a truly representative random sampling program to produce reliable data about the incidence of these residues in animals. When the residues are detected, it can be concluded they result from the improper use of the drugs. Whether the misuse was deliberate or accidental is extremely difficult to determine. Observation of recent injection sites indicates a possible deliberate misuse. Failure to observe the proper drug withdrawal time is another important factor creating residues in meat and poultry products.

The residue problem has economic as well as public health implications. If animals subjected to inspection are found to contain drug residues, parts or entire carcasses may be condemned. Condemnation results in a sizable loss to the slaughterer, who may attempt to pass on his loss in one way or another to the livestock producer. If a veterinarian has been involved in the treatment of animals and can be alleged to be

responsible for the occurrence of the residues, action can be taken against the veterinarian. It is relatively simple to inform the thousands of veterinarians about the public health hazards associated with the presence of drug residues in treated animals; however, to conduct an educational campaign reaching the millions of livestock producers and others involved is an awesome task. Suggested ways of dealing with this problem are included in the recommendations appearing later in this paper.

Evaluation to determine the safety of additives in foods is based principally on chemical and physical properties, biological considerations (which include toxicological, biochemical, metabolic, and nutritional factors), and anticipated levels and patterns of consumption. One of the most difficult problems is how to interpret the data in terms of human use levels and margins of safety. Each substance or residue presents problems peculiar to itself and requires individual consideration by those competent to exercise objective judgment of all the available evidence.

A study of the use of antibiotics in the livestock industry and veterinary medicine was recently conducted in Great Britain. The results are known as the Swann Committee Report (*9*). The Committee's concern in regard to health hazards was not only the toxicity of the residues that persist in food, but principally the development of resistant organisms as a result of continued long-term exposure to antibiotics. As was previously stated, when antibiotics are used for a continuous period of time in animals, usually at low levels, the bacterial flora of the gut develops a drug resistance. It is also known that bacteria originating from animals can be transmitted to man either directly by contact, or indirectly through food (*8*). Whether or not organisms which are resistant to antibiotics (and can transfer this resistance) can establish themselves in the human intestinal tract and reinstigate the entire cycle in man is subject to much speculation. Confirmation that this has occurred is yet to be established. An editorial in a veterinary medical journal once stated: "The chance of resistance in human bacteria pathogens having an animal origin is quite good because use and distribution of antibiotics in animals is so widespread." However, a review of the situation after 15 years of experience with medicated feeds reveals that the virulence of resistant *Salmonella* appears to be no more than that of the sensitive *Salmonella*. Mortality rates and incidence rates of salmonellosis seem to be stable. Nevertheless, it must be kept in mind that more and more resistant bacteria are being identified.

Besides the hazards to man relating to the use of antibiotic drugs in animals, dangers from other products have to be considered. For example, we can mention the case of organic mercury poisoning that occurred in December 1969 in Alamogordo, New Mexico.[1]

On 4 December 1969 an 8-year-old girl in Alamogordo developed an illness characterized by ataxia, decreased vision, and depression of consciousness which progressed to coma over a period of three weeks. Two weeks after she became ill, her 13-year-old brother developed a similar illness, which also progressed to coma in two to three weeks. At the end of December, their 20-year-old sister became ill with similar symptoms and became semi-comatose. All were hospitalized in El Paso, Texas, and were given supportive therapy.

During the investigation it was learned that in October 1969, 14 of 17 hogs owned by the family became ill with blindness and a gait disturbance; 12 of these 14 died and two became

[1] Adapted from the *Morbidity and Mortality Weekly Report* of the Center for Disease Control, U.S. Public Health Service, Atlanta, Georgia.

blind. In September, one hog had been butchered for family food and the meat eaten by seven of nine family members from September through December. Further investigation revealed that in August 1969 the father had obtained waste seed grain which had been treated with methyl mercury dicyanodiamide (a fungicide) and had included this grain in the food for the hogs.

Because of the possibility of organic mercury poisoning and compatible clinical pictures, mercury determinations were then done on urine specimens from two of the patients and three other family members, the pork, and the seed grain. Abnormally high levels of mercury were found in all of the tested well and ill family members, as well as in the grain and pork, and confirmed the diagnosis of organic mercury poisoning.

Three other Alamogordo hog farmers fed their hogs the treated seed grain and have marketed some of these hogs.

A later report from the same source stated:

The condition of two of the three New Mexico children previously reported as suffering from organic mercury poisoning remains essentially unchanged, with the 8-year-old girl and the 13-year-old boy comatose. Their 20-year-old sister has continued to improve and is now able to walk and speak with difficulty.

The 40-year-old mother of the children, who had had abnormal levels of mercury in both urine and serum, although she had no symptoms of mercury poisoning, was delivered of an apparently normal infant on 9 March 1970.

Of the pork embargoed in Roswell, New Mexico, because of suspicion of mercury contamination, all but one carcass was found free of mercury and released. The contaminated carcass was destroyed.

At the time of the investigation, there were 215 live hogs belonging to the six men who had obtained treated grain. These animals, which had presumably been fed the treated grain, were placed under embargo by the New Mexico Health and Social Services Department and most were subsequently voluntarily sacrificed by their owners.

As a result of this incident, the Pesticide Regulation Division of the U.S. Department of Agriculture suspended the registration of cyano(methylmercury) guanidine (methylmercury dicyanodiamide) for use as a seed treatment on 19 February 1970, and on 9 March extended the suspension to include all alkylmercury compounds used as seed treatments. Suspension of registration means that the product can no longer be shipped or sold. Subsequently, one of the manufacturers successfully sought a preliminary injunction against the suspension, allowing the shipment and sale of fungicide.

This episode occurred as a family tragedy and was brought to the attention of the authorities more quickly than if the meat products from these animals had been distributed throughout the consumer market. If they had been distributed, the attempt to pinpoint the source of a wide variety of illnesses in people in widely scattered regions could have become a sizable epidemiologist's dilemma.

The veterinary medical meat inspector in the slaughterhouses is trained to detect animals showing signs indicative of recent treatment and to examine these for possible residues (*10*). During antemortem inspection he tries to determine if the animal is experiencing any effect of a drug. He looks for the presence of swellings in the gluteal or other heavy muscle regions, discolorations in the regions of the body orifices, and other abnormalities associated with the administration of drugs. On postmortem observation, he looks for lesions in the muscles and subcutaneous tissues, discoloration of tissues, and characteristic odors associated with drug residues. These inspectors must consider not only the presence of drug residue in the tissues, but also any abnormal physiological or pathological effects it may have on the animal or meat derived from such an animal. These abnormal physiological or pathological effects may interfere with the preservation of the meat (shelf-life) or may produce an unwholesome condition which is unacceptable or repugnant to the consumer.

In the 30 October 1970 issue of the *Federal Register* (*11*), the U.S. Department of Agriculture's Consumer and Marketing Service published the revised version of the Meat Inspection Regulations pursuant to the Wholesome Meat Act. The section dealing with biological residues states that "carcasses, organs, or other parts of carcasses of livestock shall be condemned if it is determined that they are adulterated because of the presence of any biological residues."

Besides drugs used in veterinary medicine that produce recognizable signs of the products in the animals, there is great concern about other substances not so easily detected. These include hormone-like, carcinogenic, and mutagenic substances. For example, a number of compounds are now used to control the time of ovulation in each of the major meat-producing species of animals. In addition, it is estimated that about two-thirds of all cattle in feed lots in the United States are being treated with estrogenic compounds. Diethylstilbestrol is being used in cattle feed and also in the form of implanted pellets, which are usually placed subcutaneously at the base of the ear. Another synthetic compound closely related to diethylstilbestrol is available for oral use in poultry. Since these compounds are not destroyed by cooking, it is important to know the amount of these hormones which may be present in the meat at the time of consumption. The two vital factors involved here are the withdrawal time of the drug to assure that no residue remains in the meat, and also the placing of the pellets in the animal in such a way and at such a location that they will be effectively separated from the edible portion of the carcass as the animal is processed for human food.

RECOMMENDATIONS

1. Drugs, including antimicrobials, should not be used for prophylactic or curative purposes in animals from which human food may be derived except on the advice, and preferably under the control, of a veterinarian.

2. Residues of drugs in human food that may result from prophylactic or curative use of these agents should be as low as possible.

3. Adequate information about each drug should be printed on the label of each container and in promotional literature. Since there is a risk that undue reliance on the hope for prophylactic effects of the drugs may lead to faulty practices, all concerned should be fully informed of the dangers of misuse.

4. A satisfactory procedure should be devised to ensure disclosure of the continued presence of drug and biological residues in slaughtered animals, particularly those residues that result from the use of depot preparations. The possible use of markers for antibiotics in particular should be studied further.

5. If antibiotic residues are unavoidable, evidence should be available (including appropriate life-span studies) to permit adequate assessment of the long-term hazards (*12*).

Summary

In summarizing, it is important to point out what we know:

1. The use of certain levels of antibiotics results in resistant strains of bacteria.

2. Long-term therapeutic levels of sulfa drugs cause renal calculi.

3. Some internal parasites have developed a resistance to certain anthelmintics.

4. Some external parasites have developed a resistance to certain pesticides.

5. Some bacteria developed a resistance to certain antibiotics which they can transfer to other bacteria.

6. Some drugs are prone to cause adverse reactions under specific conditions.

7. Certain antibiotics remain in the tissue much longer than previously thought possible.

8. Food animals tend to concentrate drugs in the organs where the drugs are metabolized actively, for example, the liver and kidneys, and in storage sites such as depot fats.

9. Investigators must be alert to the possibility that levels of drugs in the tissues that may not harm the animal in which they are found may be toxic to man who consumes the animal products. Evidence of good health in an animal receiving a drug does not necessarily ensure that its tissues do not contain levels of the drug or its metabolites that are toxic to man.

The use of drugs in animal feeds is accepted as an essential part of modern livestock production. The meaning to man of drug residues in edible animal products must therefore be evaluated for each drug on an individual basis. Investigations must include an evaluation of the safety of the drug residue in the form in which it occurs in the food product under examination. To extrapolate from data obtained in animal species may be slightly presumptuous in making predictions regarding the assessment of safety in man.

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INTERNATIONAL ASPECTS OF DRUG MONITORING ROLE OF THE WORLD HEALTH ORGANIZATION (ABSTRACT) *

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Introduction

The main objective of drug monitoring for adverse reactions is to aid in the assessment of the therapeutic value of a drug from the benefit-risk point of view. In addition, drug monitoring should help in the identification at the earliest possible moment of the liability of a drug to produce undesirable effects which were not detected during its clinical trials. This requires a reporting system covering large populations and a variety of endogenous and exogenous conditions. Hence, there is an obvious need for international cooperation.

This abstract has been prepared to outline briefly systems which are being studied and developed by the World Health Organization in order to provide Member Countries with the most useful assistance possible in dealing with problems caused by adverse reactions to drugs used in medical therapy.

For the purposes of the international program, *drug monitoring* has been defined as: the systematic reporting, recording, and evaluation of adverse reactions to drugs generally available with or without prescription. Information on adverse reactions can be obtained either through voluntary reporting by practicing doctors and hospitals to designated centers (*spontaneous monitoring*), or by epidemiological techniques aimed at systematic coverage of separate hospitals, or representative samples of the population (*intensive monitoring*).

General Considerations

The responsibilities of WHO in this field began in 1962 when the World Health Assembly adopted a resolution requesting the initiation of a program for the promotion of the safety and efficacy of drugs. This was reinforced the following year in Resolution WHA16.36, which requested that Member States communicate immediately decisions to prohibit or limit the availability of any drug as a result of serious harmful effects, and that a systematic collection of information on drug reactions should be undertaken in Member States. Scientific groups were convened in 1964 and 1965 to examine and advise on the ways and means by which the World Health Assembly's resolutions might be implemented. Three related areas were considered to be appropriate for development at the international level:

1. Resolutions WHA16.36 and WHA23.48 call for the communication to WHO, Geneva, of any official action taken by a Member State to restrict or limit the use of a drug for reasons of its adverse effect or insufficient efficacy, together with the reason for such action. This information, when notified, is

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subsequently passed on to all Member States in suitable terms agreed to between the reporting country and WHO. Since 1963, 81 drug information notices have been sent by WHO to Member Countries under these provisions.

2. Member States should be encouraged and assisted to develop drug monitoring programs on a systematic basis in order to record the occurrence of suspected adverse effects, to establish the means by which the recorded data could be studied by expert groups, and where necessary, subjected to appropriately designed followup programs. Attention has been directed to the interchange of personnel between monitoring centers at the national level, provision of fellowships to personnel from countries interested in establishing such programs, and assistance for the development of intensive monitoring systems.

In addition, meetings of groups of experts in the field of drug monitoring were convened to advise on methods of studying the occurrence of adverse reactions during the therapeutic use of drugs. The report, published in 1969 in WHO Technical Report Series No. 425, *International Drug Monitoring—The Role of the Hospital*, is an example of this activity.

3. The World Health Assembly in 1967 requested formally the initiation of a *pilot research project* with the aim of eventually establishing an international system of monitoring adverse reactions to drugs on the basis of information obtained from appropriate national centers.

WHO Drug Monitoring Project

Based on the recommendations of the WHO Scientific Group on International Drug Monitoring in 1965, the aim of the project has been to investigate *inter alia* the feasibility of an international drug monitoring system for "early signalling" of suspected adverse reactions of drugs, according to the following objectives:

a) To assess the feasibility of an international system of drug monitoring;

b) To develop systems for recording case histories of adverse reactions to drugs, searches on the types and patterns of such reactions, and analysis and feed-back of data to national monitoring centers;

c) To undertake, on an experimental basis, analysis of instored data; and,

d) To study the possible contributions of drug monitoring to pharmacology and therapeutics.

National Monitoring Systems

On what foundations should an international system be based? This depends first and foremost, and indeed entirely, on the level of development and quality of reporting programs at the national level, i.e., upon the willingness and ability of individual doctors, in medical practice and in hospitals, to observe and report suspected cases of adverse reactions to drugs to designated centers on a systematic basis. As the existing national monitoring systems utilize various types of *spontaneous reporting programs*, it was realized that data from these sources would need to form the basis of the WHO feasibility study. In addition, data from *intensive monitoring programs*, particularly from hospitals, could be included when national systems are in a position to receive and transmit this information. Provision has been made to incorporate in the WHO recording system data from intensive monitoring systems channelled through national monitoring centers.

Spontaneous monitoring is, of necessity, based on the voluntary submission of individual reports by medical practitioners to

a local or national center. The extensive voluntary reporting systems developed in the United Kingdom, Sweden, Canada, New Zealand, Netherlands, and Australia are geared toward concise early reporting of suspected reactions, as a professional duty to be accepted by practitioners, as are other aspects of patient care.

Hospitals have unique advantages in the field of drug monitoring since they can provide facilities for the application of new methods of eliciting, recording, and handling clinical and laboratory data. Hospitals with *intensive monitoring* systems can make a useful contribution to national and international systems of drug monitoring because of their special capabilities and interests. Studies of the relative capabilities of voluntary and intensive monitoring systems can usefully be undertaken in the future.

The Activities of the WHO Drug Monitoring Center

Data essential to the development of the WHO project have been provided by 10 countries (Australia, Canada, Czechoslovakia, the Federal Republic of Germany, Ireland, Netherlands, New Zealand, Sweden, the United Kingdom, and the United States of America) which have established national drug monitoring centers and have agreed to participate by forwarding to the WHO Center case reports of adverse reactions to drugs.

Each center is required to transcribe information onto the WHO report form in the terminology of the reporting doctor and in the English language. The basic or minimum information comprises country code, case identification number, type of report (whether initial or followup), source of the report (e.g., hospital, general practitioner, specialist, dentist), age and sex of the patient, description of the adverse reaction, drugs administered and their dosage form, route and regimen. Additional information, such as outcome of the reaction, diagnosis or reason for the use of the drug(s), previous drug reaction history, and comments of the treating doctor and national center, has been provided for in the WHO reporting form.

The WHO Center was established in January 1968 in Virginia, U.S.A., utilizing premises and computer facilities provided under a grant from the United States Government. Since 1968, the WHO Center has been receiving case reports of adverse reactions recorded in the national centers. A uniform system acceptable to the 10 participating national centers has been developed for processing, recording, storing, linking, and retrieving such reports. Computer printouts containing recorded data in various forms have been forwarded to national centers on a trial basis. Up to September 1970, more than 34,000 case reports have been handled in this way.

The WHO Center has established, and the participating national centers have agreed on, classifications for drugs and terminologies designed for recording adverse reactions. Computer printouts have been forwarded to the participating centers with the following types of information: (a) frequency of reactions recorded for each drug; (b) frequency of reports on drugs associated with an adverse reaction, including cumulative totals for various periods; (c) condensed data for rapid reference; and (d) drug reference lists. Efforts have been directed toward developing *signalling programs* in order to increase the effectiveness of the system as an early warning device. The signalled reports include drugs, adverse reactions, and drug-adverse reaction associations (i) *new to the system* and (ii) reported at *an increased rate.*

Conclusions

After an experimental period of almost two years, representatives of national centers and independent experts recommended that the WHO system for the monitoring of adverse reactions to drugs was feasible and should be developed into an operational international program. The evaluation of the project had indicated that such an international drug monitoring program could yield substantial benefits to therapeutic medicine and public health, e.g., clinical pharmacology and therapeutics, drug safety control, drug dependence, congenital malformations and human genetics, international classification of diseases, etc., in addition to the development of monitoring methodologies at the national and international levels. Such benefits would not be limited to the countries directly associated with the program, but would extend to nonparticipating countries as well.

Subsequently, the World Health Assembly in May 1970 recommended that the activities of the project should be developed into a primary operational phase aimed at the establishment of an international system for monitoring adverse reactions to drugs with provision for alerting Member States in cases of urgency.

Thus, the responsibilities undertaken by WHO in international drug monitoring include the following areas:

1. Assistance in the establishment and development of national drug monitoring systems, both voluntary and intensive.

2. Assistance in the establishment of special monitoring centers in countries not in a position to develop national systems.

3. Coordination of national and special drug monitoring systems at the international level in the recording and processing of case reports of suspected adverse reactions, with feed-back of the data thus collected.

4. Development of guidelines for internationally acceptable terminology, classifications, and recording methods for drug monitoring.

5. Exploration of methods by which information derived from national drug monitoring centers can best be collected, integrated, and studied.

6. In collaboration with national and special centers, the study and development of methods by which appropriately evaluated information about drugs and their adverse reactions can be made available.

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THE INTERNATIONAL PHARMACOPOEIA

O. WALLÉN *

Introduction

Even though the wish to establish an international pharmacopoeia dates back to the seventeenth century, it was only in 1902 that a first attempt was made by several countries to set up such a pharmacopoeia under the Brussels Protocol. In that year an Agreement for the Unification of Formulae of Potent Drugs was prepared, and this was ratified by 19 countries in 1906.

The Brussels Agreement was drawn up in 1925 and ratified in 1929, with a provision that the League of Nations should assume part of the task of preparing an international pharmacopoeia.

In 1937 the Health Organization of the League of Nations set up a Technical Commission of Pharmacopoeial Experts, which in 1948 was succeeded by the WHO Expert Committee on the International Pharmacopoeia, and in 1951 by the members of the Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations.

The International Pharmacopoeia

The first edition of the International Pharmacopoeia was published in three volumes: 1951, 1955, and 1959. A second edition was published in 1967. It is available in the English, French, and Russian languages, and a Spanish edition is in press and expected to be available by the end of this year or early in 1971.

Specifications for 162 newer drugs were introduced in the second edition, while 114 monographs of the first edition were omitted, to give a total of 555 monographs with 69 appendices. The text was prepared in cooperation with members of the WHO Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations and a large number of other specialists from different countries. The analytical procedures given in the monographs and appendices have been tested in the laboratories of national pharmacopoeias, in national laboratories of a number of manufacturing firms, and in pharmaceutical and other institutions.

Modern analytical methods used in pharmaceutical quality control are described in the appendices; for example, infrared spectrophotometry, polarography, and chromatography (column, paper and thin-layer), and also methods for determining radioactivity.

Although some of the methods, such as polarography, have not been applied to the requirements of any particular monograph, it was thought that the International Pharmacopoeia should be representative of the best current practice in drug quality control and that they were a desirable addition.

An appendix has been included on the identification of substances based on the determination of melting point, eutectic temperature, and refractive index by the Kofler

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method using microscope or hot bar. Data for more than 200 substances are presented in two tables, which also give special remarks about the characteristic behavior of the substances during heating.

A provisional text of the second edition was sent on 9 March 1964 to members of the WHO Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations and a number of other specialists interested in this work, with a covering letter asking for comments, which were later examined for possible integration in the provisional text.

In October 1964 the revised provisional text was forwarded to Member States, inviting them to submit comments within three months.

These and further comments were integrated in the text of the second edition in order to adapt it to latest requirements.

The specifications of the International Pharmacopoeia constitute a collection of recommended specifications which are not intended to have legal status per se. Any Member State of WHO may include all or part of these provisions in its national requirements.

The present way of establishing the specifications of the International Pharmacopoeia can be criticized, especially from the viewpoint that the time between new editions is too long in relation to the speed with which new drugs are introduced onto the market and the relatively short lifetime of most modern drugs.

In 1967 the Twentieth World Health Assembly, in Resolution WHA20.34, requested the Director-General to "continue work on analytical control specifications for international acceptance to be published as they are completed." This phrasing expresses the urgency which the Assembly attaches to the wide and rapid distribution of specifications for drug control.

The Expert Committee on Specifications for Pharmaceutical Preparations has discussed two ways to achieve this goal:

a) To devise a scheme by which WHO, in cooperation with the producers of drugs, could issue analytical data on drugs very soon after they are introduced onto the market. Such specifications, even if not complete, but made available early, might contribute to the achievement of more uniform specifications throughout the world. Comments from interested parties would be invited and form the basis for revision of the specifications for eventual inclusion in the International Pharmacopoeia.

In order to be successful, such a scheme would, of course, require free cooperation between WHO, producers, pharmacopoeia commissions, and national control authorities.

The Expert Committee on Specifications for Pharmaceutical Preparations suggested proposals for such a scheme (*1*), but it must be realized that it would be a long-term project to put such a scheme into effect.

b) To continuously amend and revise the International Pharmacopoeia and to issue supplements reflecting the latest developments in quality control. The twenty-third WHO Expert Committee on Specifications for Pharmaceutical Preparations, which met in Geneva in November 1969, recommended that this procedure should be followed at present, but that at the same time attempts should be made to pursue the approach mentioned under (a). Even if it must be considered as a long-term project, the Committee stressed its potential importance for the future work of WHO on specifications for newer drugs.

Another approach to make specifications available as early as possible would be to

publish monographs as soon as they are provisionally adopted by an Expert Committee, with a view to including them later in the International Pharmacopoeia. Such a procedure could be expected to encourage comments at an early stage and thus make it possible to adopt the final text sooner.

Supplement to the International Pharmacopoeia

A Supplement to the second edition of the International Pharmacopoeia is now in its editorial stage. A draft text was finalized by the Expert Committee on Specifications for Pharmaceutical Preparations at its meeting in 1969; it was sent to WHO Member States and specialists concerned, in a similar way to the second edition; and with the assistance of consultants the comments received were considered for inclusion in the text.

The Supplement contains 20 new monographs, mainly antituberculosis drugs which were not included in the second edition of the International Pharmacopoeia but which are widely used in UNICEF/WHO-assisted field projects and radioactive pharmaceuticals. It also contains a number of amendments to monographs in the second edition and seven new or revised appendices. The appendices on radioactivity and chromatography have been substantially revised. The requirements for "Good Practices in the Manufacture and Quality Control of Drugs" have been appended to the Supplement, following the suggestion of the Expert Committee, since they constitute an integral part of the WHO program in the field of quality control of drugs.

Specifications for Reagents

During the work on the first edition of the International Pharmacopoeia it was felt that more detailed specifications for reagents used in conjunction with the assays and tests included therein should be drawn up.

Work on specifications for reagents, based on existing specifications and on collaborative work of experts, was later coordinated with the preparation of the second edition of the International Pharmacopoeia. In 1958 draft specifications for reagents became available and were widely distributed for comments, which were taken into consideration in the preparation of the final text by the Secretariat, assisted by specialists in the matter. The "Specifications for Reagents Mentioned in the International Pharmacopoeia" were published in English (1963) and in French (1966).

The specifications included in this volume also apply to the reagents required for the tests and assays of drugs described in the second edition of the International Pharmacopoeia and are quoted in the list of reagents and test solutions in that volume.

Chemical Reference Substances

In 1952 the WHO Expert Committee on Specifications for Pharmaceutical Preparations noted a recommendation from the Expert Committee on Biological Standardization that a collection of authentic chemicals be established, including a number of biological standards and chemicals required for some of the assays described in the International Pharmacopoeia or for biological research. One reason for this recommendation was that it had been decided not to replace the biological standard for vitamin A but that a standard was still needed as reference for the spectrophotometric determinations. Later the same year the proposal was discussed and its was agreed that there was a need for such a collection, which should include:

"a) Substances for which international

biological standards have been provided in the past but which can now be characterized entirely by chemical methods and for which no biological standards will be provided in the future;

b) Chemicals required as working standards for the assays and tests described in the International Pharmacopoeia;

c) Other chemicals required as reference standards for research purposes."

During the next few years the subject was further discussed and in 1956 a center was created at the Apotekens Kontrollaboratorium in accordance with an agreement between the Apotekarsocieteten, Stockholm, and the World Health Organization for the collection, storage, and distribution of chemical reference preparations. The collection included, apart from vitamin A, some discontinued biological standards such as estrone and progesterone and some new substances—for example, digitoxin and ergometrine maleate.

At the meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations in 1958, two suggestions were made to study the inclusion of substances: (1) for checking melting points; (2) for checking the absorption reading of spectrophotometers operating in the ultraviolet and visible part of the spectrum.

At a meeting of the aforementioned WHO Expert Committee in 1964 (*2*), the following guiding principles for the establishment of chemical reference substances were recommended.

For the second edition of the International Pharmacopoeia it was agreed that reference substances should be provided in the following cases:

a) When infrared identification is required;

b) When chromatographic tests and assays are given in the monographs;

c) When spectrophotometric or photometric methods are necessary for the determination of the substance.

If the substance itself can be analyzed by a "classical" method but, for example, tablets or injections are analyzed by spectrophotometric methods, it was considered permissible to use a substance which complied with the monograph as reference substance.

As for the evaluation of substances for their suitability as reference material, it was urged that an estimate be given of the content of total impurities. Such a figure was considered valuable even if not of high accuracy.

For the tests and assays of the second edition of the International Pharmacopoeia, about 40 International Chemical Reference Substances are available (*3*), mostly steroids, cardiac glucosides, and semisynthetic penicillins.

The appended table lists the reference substances of the second edition and also indicates for what purpose they are needed. The substances are available from the WHO Center for Chemical Reference Substances, Apotekens Centrallaboratorium, Box 333, 171 03 Solna, Sweden.

REFERENCES

(*1*) World Health Organization. *Expert Committee on Specifications for Pharmaceutical Preparations (22nd Report).* Technical Report Series *418,* Geneva, 1969.

(*2*) World Health Organization. *Expert Committee on Specifications for Pharmaceutical Preparations (21st Report).* Technical Report Series *307,* Geneva, 1965.

(*3*) World Health Organization. *Specifications for the Quality Control of Pharmaceutical Preparations*—Second edition of the *International Pharmacopoeia,* Appendix 22, Geneva, 1967.

Annex

TABLE RELATING TO USE OF CHEMICAL REFERENCE SUBSTANCES IN THE SECOND EDITION OF THE INTERNATIONAL PHARMACOPOEIA

Chemical Reference Substance	*Use*
a) Steroids	
Cortisone acetate	IR identification; colorimetric assay (blue tetrazolium)
Desoxycortone acetate	IR identification; colorimetric assay (blue tetrazolium)
Dexamethasone	IR identification; colorimetric assay (blue tetrazolium)
Dexamethasone acetate	IR identification; colorimetric assay (blue tetrazolium)
Estradiol benzoate	IR identification; colorimetric assay (Kober reaction)
Ethinylestradiol	IR identification; spectrophotometric assay (280 nm)
Ethisterone	IR identification; spectrophotometric assay (240 nm)
Hydrocortisone	IR identification; colorimetric assay (blue tetrazolium)
Hydrocortisone acetate	IR identification; colorimetric assay (blue tetrazolium)
Methyltestosterone	IR identification; spectrophotometric assay (240 nm); colorimetric assay (dinitrophenyl hydrazone)
Prednisolone	IR identification; colorimetric assay (blue tetrazolium)
Prednisolone acetate	IR identification; colorimetric assay (blue tetrazolium)
Prednisone	IR identification; colorimetric assay (blue tetrazolium)
Prednisone acetate	IR identification; colorimetric assay (blue tetrazolium)
Progesterone	IR identification; spectrophotometric assay (240 nm)
Testosterone propionate	IR identification; spectrophotometric assay (240 nm)

Chemical Reference Substance	*Use*
b) Cardiac glucosides	
Digitoxin	IR identification; colorimetric assay (Baljet)
Digoxin	IR identification; colorimetric assay (Baljet)
Lanatoside C	IR identification; colorimetric assay (Baljet)
Ouabain	IR identification; colorimetric assay (Baljet)
c) Semisynthetic Penicillins	
Ampicillin	IR identification; bio-assay
Ampicillin sodium	IR identification
Cloxacillin sodium	IR identification; bio-assay
Meticillin sodium	IR identification; spectrophotometric assay (280 nm)
Nafcillin sodium	IR identification; spectrophotometric assay (280 nm); bio-assay
Oxacillin sodium	IR identification; spectrophotometric assay (235 nm); bio-assay
Phenethicillin potassium	IR identification; spectrophotometric assay (268 nm)
Propicillin potassium	IR identification; iodimetric titration using the reference substance to determine the equivalent; spectrophotometric assay (268 nm)
d) Others	
Ergometrine maleate	Test for secondary alkaloids (paper chromatography); test for secondary alkaloids (thin-layer chromatography); colorimetric assay (Van Urk)
Ergotamine tartrate	Test for secondary alkaloids including semi-quantitative determination of ergotaminine (paper chromatography); colorimetric assay (Van Urk)
Folic acid	Colorimetric assay
Riboflavine	Spectrophotometric assay (267 nm); fluorimetric assay
Tubocurarine chloride	Bio-assay
Warfarin	Spectrophotometric assay (308 nm)

ORGANIZATION AND OPERATION OF A DRUG CONTROL LABORATORY

DR. JERÓNIMO AVERZA *

Introduction

A drug control laboratory is in a very delicate position; besides performing an immense social service by analyzing drug products in terms of public health, it regulates the pharmaceutical trade, a large business sector having an important impact on the national economy.

In general, criticism tends to be directed at measures that regulate activities previously outside the sphere of direct public control, such as the pharmaceutical trade in the great majority of our countries, and there is a certain resistance from sectors accustomed to operating in a manner which best serves their interests. Yet nearly all citizens and all important and well-known business concerns are in favor of setting up a control laboratory which can be kept up to date and acquire reliability and efficiency through the use of the latest and complete equipment, on the one hand, and of qualified staff, on the other. High costs and operating expenses make it difficult to assemble all the equipment needed for proper operation of such a laboratory, but it is still more difficult to gather the large nucleus of highly qualified scientists required by an agency of this type.

However, various agencies of this kind already exist in the Americas, including the U.S. Food and Drug Administration, the Canadian Food and Drug Directorate, the Specialized Analysis Laboratories at the University of Panama, those in Caracas, Buenos Aires, etc. The level of difficulty involved makes it particularly advisable to copy from these models, which are working demonstrations of the fact that such difficulties can be overcome by strong resolve and dedication.

The importance of a drug control laboratory goes without saying, given the present stage of development of our scientific and technological world in this post-industrial atomic age, which has changed us into what some writers call "the consumer society." Every industry, including pharmaceuticals, has to acquire most or all of its raw materials from other manufacturers, and experience shows that not all the buyers have adequate means for properly and continuously checking the materials bought and processed. Moreover, preparations are altered by passage of time and are affected by temperature, humidity, and transportation conditions; the most carefully prepared product may reach the consumer after having lost some of its therapeutic value, resulting in total or partial ineffectiveness with all the danger which this holds for the patient. Therefore, the activities of the Pan American Health Organization/World Health Organization designed to promote control of medicines in daily use deserve the highest praise. PAHO/WHO is making

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efforts in several Latin American countries to introduce laws and laboratories that can facilitate this noble task of protecting the health of our peoples.

Organizing a Drug Control Laboratory

There are various ways to set up a drug control laboratory. Some of these are very elaborate and complex, while others are simple through efficient. According to our way of thinking and from our experience, the institution should be organized in a way that facilitates basic operations and makes internal control easy and effective.

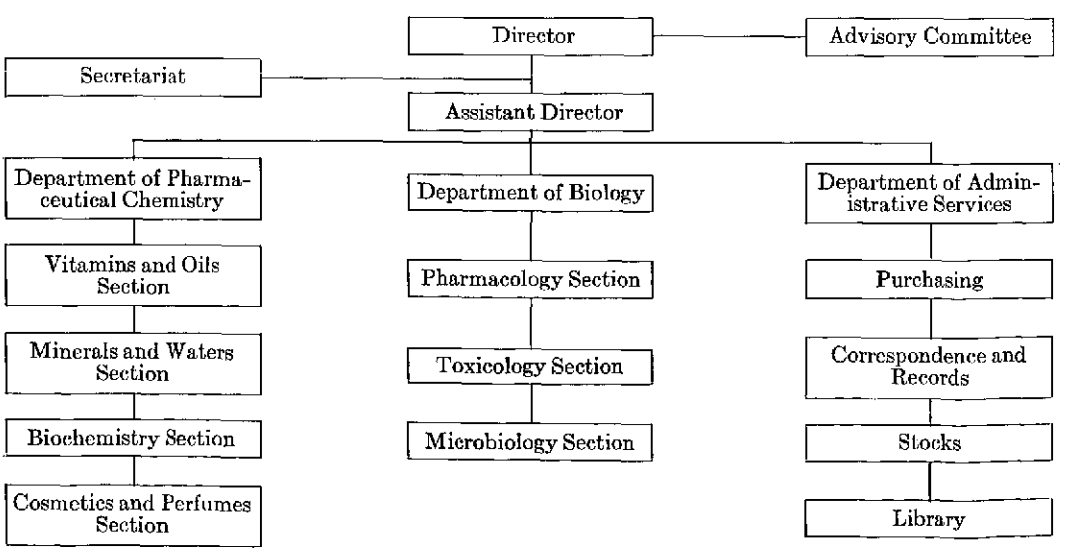
Organization of Personnel

The laboratory staff should perform the following tasks: (1) analysis of pharmaceutical preparations in order to check for purity, quality, potency, and sterility; (2) delivery of the results to the government drug control and registration office for action (approval, rejection, imposition of fines, or seizure and destruction, whatever the case may be); and (3) publication of the results of research.

a) All scientific staff of the laboratory should be university graduates; the Director, Assistant Director, and department and section heads should hold postgraduate degrees. University degrees are not required for subordinate personnel such as technicians and aides, but a secondary school diploma should be the minimum qualification.

b) The laboratory administrators should select various institutions of well-known academic standing to train its personnel, such as: the U.S. Food and Drug Administration and the Canadian Food and Drug Directorate, for those who have a command of English; the Adolfo Lutz Institute in São Paulo, Brazil, for Portuguese-speaking personnel; and the Specialized Analysis Lab-

LABORATORY ORGANIZATIONAL CHART



oratories of the University of Panama, for those speaking Spanish. When postgraduate training for a Master's degree or Doctorate is involved, universities may be selected in the United States of America and Europe. We understand that in Latin America a high-level instruction program in this field will soon be set up which can be utilized by those professionals who do not have a command of English.

c) No laboratory member should have any direct or indirect association, affiliation, or relationship with a private firm, company, corporation, or other concern dealing in the manufacture, preparation, or sale of pharmaceutical products; nor should any member accept favors, such as large gifts, special courtesies, etc., from companies or persons who might benefit economically or scientifically from his opinions. Violation of these regulations should result in immediate termination of employment.

d) Salaries offered should be comparable or superior to those paid by industry to persons with similar qualifications; other economic incentives such as periodic salary increases should also be provided.

e) Personnel should be immune from politics and should have a great deal of working experience (either in the administrative or the civil service areas), since highly qualified personnel are hard to find and their training is long and costly.

f) Laboratory employees should not engage in other activities which may affect their work; however, time should be allowed them to continue their education or to take refresher courses. They may also be granted a certain amount of time for teaching at the university level.

Equipment and Plant

The equipment and plant should be of high quality and should be adapted to the latest analytical methods.

a) They should be used only for their vital purpose, i.e., analysis of drugs.

b) The facility should have all necessary conveniences, including heating, air conditioning, and humidity control.

c) There should be adequate space for analyzing drugs as well as special storage spaces for reagents and refrigeration.

d) Besides common laboratory equipment (glassware, reagents, ovens, hot plates, shields, vacuum ovens, microbiology equipment, etc.), the facility should be able to rely on a modern pharmaceutical analysis laboratory with colorimeters; spectrophotometric equipment for visible, ultraviolet, and infrared light; paper, columnar, thin-layer, and gas chromatography equipment; a potentiometer; precision scales, etc.

Specimens and Internal Control

a) Inspectors of the government drug control office should establish a systematic sample pick-up schedule embodying the following:

- Programming of the weekly intake and analysis of specific categories of products, with total intake depending on the number of registered and patent medicines in a particular category. (For example, week 1—quality control of penicillin-type antibiotics; weeks 2 and 3—vitamins and multivitamins, B complex; week 4—modern sulfa drugs of the sulfadimethylpyridazine type; week 5—antimalaria synthetics; etc.)
- Establishment of a work schedule based on weekly sample quotas geared to the laboratory's maximum production capacity. The laboratory should never receive more samples than its facilities can handle, as this reduces the quality, accuracy, and efficiency of the work performed. Normal statistical rules should be applied.

b) An internal control program should be set up. Although this program may vary from laboratory to laboratory, one which we have found to give excellent results is the following:

- The person in charge of stocks receives the samples and catalogs them according to the laboratory's internal code.
- The Director distributes the samples to the department heads at the time analysis is to begin; this prevents anyone from knowing beforehand what product he will be analyzing.
- As a precautionary measure, the analysts perform a double analysis in each case.
- Whenever an analysis yields results deviating from established norms the analyst makes two additional double analyses, bringing the total number of operations to six. If the results are still deviant, the analyst will report such results to the Director.
- The Director then selects another laboratory analyst to repeat the same procedure, and if the results are still negative the product is rejected.

Analytical Standards and Specifications

a) A monographed control including all products scheduled for analysis should be printed on cards and distributed to all laboratory departments, accompanied by an adequate bibliography. The Pharmacopeia and the National Formulary of the United States (latest edition) are used by most Latin American countries as the official references for analytical standards of pharmaceutical products, and they should therefore be available in every laboratory.

With respect to other test series such as those dealing with antibiotics, tests designed by the U.S. Food and Drug Administration in Washington, D.C., are applied. In addition, sera, vaccines, and similar products are subject to official tests of the Biological Control Laboratory of the U.S. National Institutes of Health.

b) A form must be drawn up that enables each working analyst to detail all relevant information pertaining to the sample analyzed. This information is then recorded in an official log that is kept in the laboratory's head office and used to provide information to the ministry of health or other official agencies requesting the analysis.

Library

A high-quality library specializing in the field of analysis should be set up; it should contain the U.S. National Formulary; the U.S., International, British, and German Pharmacopoeias; the Codex Français; other pharmacopoeias; *Methods of Analysis* of the Association of Official Analytical Chemists (AOAC); journals of pharmacy and chemical societies; the *International Pharmaceutical Abstracts* of the American Society of Hospital Pharmacists; *Chemical Abstracts;* the *FDA By-Lines* of the U.S. Food and Drug Administration; the *Merck Index;* etc.

Legislation

This subject has purposely been left for the end of this study because it constitutes the keystone upon which all work accomplished by a drug control laboratory must depend. Without adequate and up-to-date legislation a laboratory is of little avail, since all of its efforts are lost in the bureaucracy of government administration.

Laws should be enacted to regulate the production, manufacture, processing, marketing, sale, and consumption of medicines. At the same time, a drug control and registration office should be established which employs inspectors trained for their scien-

tific surveillance duties in the health field, and who have professional qualifications in the areas of pharmacy, chemistry, general medicine, veterinary medicine, etc. A useful example of legislation in the drug area is Decree No. 92, of 12 February 1962, of the Republic of Panama.

Information

The following series of steps should be taken immediately upon passage of pharmaceutical control legislation in a given country.

a) An information and education campaign should be conducted by the drug analysis laboratory.

b) The head office of the laboratory should arrange for a series of meetings with personnel of government and independent agencies that have direct or indirect contact with the laboratory or may make use of its services, for the purpose of obtaining adequate cooperation.

c) The head office should also arrange a series of meetings with manufacturers and distributors of medicines, cosmetics, and similar items, in order to explain the activities carried out by the facility. Such meetings should help to demonstrate the benefits resulting from these activities, thus promoting industry cooperation in carrying them out.

d) Another series of meetings should be arranged with associations of physicians, dentists, pharmacists, veterinarians, and nurses, in order to gain the direct cooperation of professionals in the field of health for developing future laboratory programs.

Advisory Committee

On occasion, problems will arise which will require consultation with high-ranking experts in this field, sometimes on an urgent basis. Such experts, including both national and foreign specialists, will be chosen from outside the institution's staff and will serve as advisers to the laboratory's head office on matters concerning general policy and operations.

Conclusion

We have tried to be as objective as possible in discussing a matter of such vital importance in the health care of our peoples. From our point of view it is not possible to oppose creation of this drug control facility. The need for its establishment, organization, and operation in terms of protection of public health and promotion of scientific and technological progress in our countries is above all objections available to its opponents. My personal opinion is that a country without such an agency is not on a level with the post-industrial society which we so loudly acclaim.

DRUG TESTING EQUIPMENT
A SURVEY OF CURRENT USAGE

DANIEL BANES AND GEORGE SCHWARTZMAN *

Earlier this year, the Pan American Health Organization (PAHO), in collaboration with the U.S. Food and Drug Administration (FDA), instituted a concentrated course of study in advanced analytical training for pharmaceutical chemists from Western Hemisphere countries. The first of these intensive study sessions was concluded only three weeks ago. Scientists of the FDA delivered a series of lectures and demonstrations on the theory of instrumental systems useful in the analysis of drugs. The students then utilized these instrumental techniques to examine pharmaceutical preparations as they are actually encountered in the channels of commerce.

A brief listing of the subjects covered in the course of lectures and laboratory experiments indicates the wide range and variety of instrumental techniques currently employed in the testing laboratory to determine the identity, purity, and potency of drug products. They include: visible, ultraviolet, and infrared spectrophotometry; spectrophotofluorimetry; non-aqueous titrimetry; spectropolarimetry; polarography; differential thermal analysis; nuclear magnetic resonance spectrometry; radiochemistry; chromatographic separations (of the paper, thin-layer, gas-liquid, column partition, and ion-pairing varieties); mass spectrometry; and X-ray diffractometry. The mere recital of this catalog sounds both impressive and confounding. Many of the terms seem esoteric, and far removed from the day-to-day operations of the drug control laboratory. Nevertheless all of these instrumental techniques are now employed continually in drug examinations, and many of them are required in conducting the tests and assays included in current pharmacopoeia monographs. A brief bibliography on selected instrumental techniques is appended to the list of references.

As one might surmise from the lengthy titles, the equipment necessary to perform some of these analyses is usually expensive. Therefore, unless unlimited funds are available, it would be prudent to decide which equipment is essential to the vital functioning of the control laboratory, and which instruments might be considered specialized luxuries that make life easier and more pleasant but are not indispensable. Representative prices currently quoted for the various instruments are listed in Tables 1 and 2.

Among the instruments that may truly be said to be indispensable to the drug control laboratory are those which are the long familiar mainstays of gravimetric and volumetric analysis. Today, as in ancient times, the crucial apparatus for assuring reliability in evaluating drug materials is an accurate weighing balance and honest standards of measurement. To state the matter in Biblical terminology: "Do no

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TABLE 1—Approximate cost of absolutely essential equipment.

(In U.S. dollars)

Item	Cost
Analytical balance	$600 to $1,000
Calibrated glassware	500 to 2,000
Laboratory glassware (Averages $4.00 per piece of equipment)	1,000
Thin-layer chromatographic apparatus (spreaders, plates, special pipets, materials, etc. Prepared plates can now be purchased in the U.S.)	500
Ovens:	
Drying	200 to 750
Muffle	450 to 1,500
Vacuum	200 to 800
Ultraviolet-visible recording spectrophotometer	10,000 to 24,000
Infrared recording spectrophotometer	8,000 to 30,000
Gas-liquid chromatograph	3,000 to 12,000
Polarimeter	1,500 to 30,000
pH Meter	200 to 800

TABLE 2 — Approximate cost of less essential equipment.

Item	Cost
Radiopharmaceutical instrumentation	$8,000 to $30,000
Nuclear magnetic resonance spectrometer	25,000 to 100,000
Mass spectrometer	30,000 to 150,000
X-ray diffraction and fluorescence spectrometers	20,000 to 50,000
Polarographs	2,000 to 10,000
Spectrophotofluorimeter	6,000 to 14,000
Differential thermal calorimeter	8,000 to 20,000
Liquid-liquid chromatograph	12,000 to 30,000
Computers	50,000 to ∞

unrighteousness in judgment, in weight or in measure; just balances and just weights must you have," (*1*) for "a false balance is an abomination to the Lord, but a perfect weight is His delight" (*2*). The same principle holds for volumetric measurements.

Fortunately, adequate analytical balances and standard weights are readily available for modest prices, and so are accurately calibrated volumetric flasks, pipets, and burets. For convenience and speed in weighing large series of samples, the single-pan readout balance is popular (cost, about $1,000). However, it should be noted that the accuracy achieved by the more expensive instrument is of about the same order of accuracy as the old fashioned simple two-pan balance. Moreover, in our experience the single-pan balance cannot be as highly recommended for the precise measurement of specimens weighing less than 50 milligrams. The electrobalance, an ingenious device for weighing specimens in the range of micrograms to milligrams, sells for $600-$1,000 depending on the range. One must know the limitations of a single-pan balance, otherwise it can be less accurate than the two-pan balance. These comments also apply to the electro (Kahn) balance.

As recently as 1940, practically all of the assays conducted in the drug control laboratory could be accomplished with simple gravimetric and volumetric equipment, augmented with such appurtenances as beakers, flasks, funnels, separators, burners, ice-, steam-, oil-, and sand-baths, ovens, muffles, distillation apparatus, and a polarimeter. Color reactions were used chiefly in qualitative and limiting tests, and they could be performed more accurately by visual inspection than by use of the crude optical instruments then available.

The introduction of reliable spectrophotometers and chromatographic procedures about three decades ago initiated a technological revolution in drug analysis. Modern pharmaceutical examinations depend as much upon chromatography and visible, ultraviolet, and infrared spectrophotometry as upon the classical gravimetric and titrimetric methods. Therefore, the visible-ultraviolet spectrophotometer, the infrared recording spectrophotometer, and several types of chromatographic ap-

paratus must be added to the list of indispensable laboratory equipment.

The wide variation in the cost of spectrophotometers is even greater than the price range for automobiles. When first introduced, the finest manually operated visible-ultraviolet spectrophotometer cost less than $2,000, and reliable electronic colorimeters accurate down to 330 nanometers could be obtained for about $500. Current production emphasizes the recording visible-ultraviolet spectrophotometer at prices from about $10,000 up to about $25,000. The manually operated instrument at about $5,000 is suitable for most analytical purposes in the spectral range of 200-800 nanometers. For the more restricted ultraviolet visible region of 320-700 nanometers, a reliable instrument may be purchased for about $1,000. However, because of the valuable information which is given by the entire spectrum, the recording instrument is highly recommended.

Because the spectral range in the infrared is so extensive, and significant absorption peaks are so sharply defined, the infrared spectrophotometer cannot be used for analytical work continually without an automatic recording attachment. The price of the infrared recording spectrophotometer depends chiefly on the nature of the optics and the accessories. A high resolution diffraction grating infrared spectrophotometer for research may cost upward of $30,000 but excellent instruments suitable for the purposes of drug control laboratories may be purchased for $8,000.

Fluorimetry, which is another species of photometry, has been employed heretofore only occasionally in regulatory drug analysis. It should achieve more extensive use in the near future. For work of the highest accuracy a spectrophotofluorimeter is required. The price range of this instrument is $6,000-$14,000. The filter-type model, costing $3,000, is less reliable. When fluorimetry becomes more prevalent, the cost differential would seem to justify purchasing one of the moderately priced spectrophotofluorimeters.

Similar considerations apply to polarimetry. The polarimeter ($1,500 to $5,000) has been utilized for almost a century to check the identity and purity of optically active drug substances in solution. Almost invariably, the rotatory power of the solutions has been measured at a wavelength of 589.3 nanometers, the so-called sodium-D line. The more expensive models are now provided with a mercury lamp and attachments that isolate monochromatic light at the prominent mercury lines, permitting measurements at more favorable wavelengths. Spectropolarimeters providing for optical rotatory determinations at any wavelength in the near ultraviolet and visible range can now be obtained commercially at a price of $10,000 to $30,000.

The cost of chromatographic equipment is, in general, much more modest. Paper or thin-layer chromatography can be performed continuously for an expenditure of less than a dollar a day for equipment, and not much more for solvents and reagents. These analytical processes require only microgram quantities of drug substances, and they achieve separations that border on the miraculous. For example, the three mixed sulfonamides known as trisulfapyrimidines—sulfadiazine, sulfamerazine, and sulfamethazine—can be readily separated by paper or thin-layer chromatography. This partition is the basis of the U.S. Pharmacopeia assay for Trisulfapyrimidines Oral Suspension and Trisulfapyrimidines Tablets (*3*). However, it is difficult to adapt such procedures for convenient quantitation. The previously cited USP

assay for trisulfapyrimidines locates the spots in the developed chromatogram by viewing under short-wavelength ultraviolet radiation. The spots are then cut out of the paper sheet, dissolved in dilute hydrochloric acid, diazotized with nitrous acid, coupled with N-1-naphthyl-ethylenediamine (Bratton-Marshall reagent), and measured colorimetrically by comparison with appropriate standards. This method is capable of yielding accurate results, but it is laborious and requires exquisite technique and painstaking attention to details.

To obviate the need for removing the separated substances from paper or thin-layer chromatograms, various spot-sensing devices have been proposed. We are currently evaluating a densitometer ($12,000) which can measure the fluorescence, reflectance, or absorbance of the spots *in situ*, and thus affords a convenient but somewhat costly means for quantitative determinations without further manipulation of the chromatogram. If this apparatus performs only half as well as is hoped, the benefits will easily justify the expenditure.

Column partition chromatography and ion-pairing partition are powerful, versatile, and economical techniques for the quantitative separation of mixtures. These column procedures require only a glass tube, a tamping rod, some diatomaceous silica, and common chemicals. They yield reliable, reproducible chromatographic separations of drugs in either microgram or milligram amounts and the eluted fractions can be quantitated readily by colorimetric or spectrophotometric procedures. The FDA laboratories have utilized this approach extensively. An excellent review and many original papers on the subject have been published by Levine and his co-workers (*4*).

Automated high-pressure liquid-liquid chromatography is still in the developmental stages as an instrumentality for drug analysis. Gas-liquid chromatography has been applied to this purpose for over a decade. The present U.S. Pharmacopeia includes gas-liquid chromatographic assays for Atropine Sulfate Injection (*5*) and for several other preparations containing volatile alkaloids, and the National Formulary includes a gas-liquid chromatographic assay for codeine phosphate in codeine phosphate, aspirin, phenacetin and caffeine tablets (*6*). These methods have been validated in collaborative studies.

Experience with gas-liquid chromatography has demonstrated that it is simple in operation, achieves a high degree of resolution in its separations, requires only minute quantities of the drug substances, and affords both a qualitative identification and a quantitative determination. However, in actual performance it can be so beset with unexplained vagaries that even consecutive analyses under apparently identical conditions may yield erratic results. The investigator exploring GLC applications needs the patience of Job combined with the persistence and ingenuity of Satan. The technique, in theory at least, holds promise of tremendous success. Even in the present state of the art, the gas-liquid chromatograph must be considered an indispensable laboratory adjunct for qualitative analyses, for the assays already validated, and for the sake of its potentialities. The price of the instruments now available varies from $3,000 to $15,000.

Value judgments on the utility of any particular analytical instruments depend in part upon the prejudices of the critic. Our preference for column partition chromatography and our adverse remarks about gas-liquid chromatography are undoubtedly resultants of pleasant associations with the former and harrowing experiences with the

latter. This precautionary disclaimer applies similarly to our following unenthusiastic comments on polarography. With all due respect to the discoverers of this technique, to the theoreticians who have explicated it, and to practitioners who have employed it to accomplish noteworthy deeds, we have found the polarograph of limited intrinsic value for regulatory drug analysis. It does few things that cannot be done better and more reliably by other means.

Nuclear magnetic resonance spectroscopy is an extremely useful research technique in determining the structural configuration of organic compounds. It discriminates between "types" of protons in the compound and thus yields information unobtainable from any other source. As an analytical tool, the nuclear magnetic resonance instrument has been used successfully in FDA to determine dimethylsulfoxide (DMSO) quantitatively in mixtures; and one of our field districts has published an analytical procedure on this subject (7). However, it is an expensive tool for this purpose. It is anticipated that one of the manufacturers may soon come out with an instrument priced at $5,000. At present the price range for NMR instruments is from $20,000 to well over $100,000.

Two other instruments considered elegant adjuncts to the drug laboratory are the mass spectrometer and the X-ray diffraction spectrometer. The pattern of positively charged particles produced by a mass spectrometer is characteristic of the molecule treated. The spectrum obtained is most useful in positively identifying minute amounts of a substance. The price of these instruments ranges from about $30,000 to over $150,000. Since the mass spectra are voluminous, the data are usually processed by computers. This accessory generally increases the cost significantly (about $50,000 additional). We have used mass spectrometric data in our laboratories to determine molecular weights of drugs and their derivatives, and to confirm the identity of active ingredients in unknown tablets and capsules submitted to us for analysis.

Last year an unknown drug sample submitted to our laboratory was analyzed rapidly and simply by X-ray diffraction. Both the ultraviolet and infrared spectra gave inconclusive data. However, the X-ray diffraction patterns showed the material to be a mixture of two, or possibly three, sulfonamide drugs. Given this information, the sample was examined by thin-layer chromatography and it proved to be a mixture of three well-known sulfa drugs. The cost of X-ray diffraction spectrometers is in the vicinity of $45,000. It should be pointed out that eight monographs in the latest edition of the National Formulary (NF XIII) require X-ray patterns for identity tests.

Radio pharmaceuticals now play an important role in both the diagnosis and the treatment of disease. The quality control of these products is essential, and special methodology and handling are required for such materials. There are numerous devices for detecting and determining the radiation. Basically these consist of a detecting unit such as a Geiger Muller counter, scintillation detector, etc., and an amplifying and recording device to measure the radioactivity. Instrumentation for quality control analysis of radiopharmaceuticals ranges in price from $8,000 to $30,000. One must also consider the need for protection from radioactivity in the handling of these materials. Special rooms and protective equipment can add substantially to the cost for this type of program.

Automated analytical apparatus has been employed to examine large numbers of similar types of drug preparations in both industry and government control laboratories. Both the National Center for Antibiotic Analysis and the National Center for Drug Analysis are equipped with such automated systems. A set of modular apparatus for automated analysis costs about $20,000. Other systems may be more expensive. With increasing official requirements for individual tablet and capsule analysis, automated equipment is, or will soon become, indispensable for both quality control and regulatory analysis.

Finally, we believe that drug laboratories in the not-too-distant future will be computerized. The U.S. Food and Drug Administration now has the capability of searching through 95,000 infrared spectra. There is similar computer capability for searching X-ray diffraction spectra. Many laboratories now utilize small computers in their GLC operations, in sample record-keeping and in reporting analytical data. At present it is difficult to hazard a guess as to the price of the computers most useful for these purposes.

Obtaining the necessary instruments and securing the experts to utilize them are not the only prerequisites for operating a successful drug laboratory. Since most of the analytical tools previously described are complicated electro-optical contrivances, skilled specialists are required to maintain them in good working condition. Therefore, before purchasing these expensive instruments, it is absolutely essential to ensure that in case of misfunction they can be repaired within a reasonable time interval. Several searching questions require investigation. Does the firm selling the machine have service engineers within several hundred miles of the laboratory? How soon can they get to the laboratory if the instrument fails to operate properly? And does the firm have the needed spare parts? The answers to these questions must be forthcoming before money and time are invested in expensive and sophisticated instrumentation.

The drugs in use today are potent, complex substances, and the methods whereby we can determine whether they are satisfactory are also complex. Only by judicious selection of appropriate instrumentation operated by skilled analysts can we control and maintain their quality, and thus help to safeguard the health and welfare of the consuming public.

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RESEARCH NEEDS OF A DRUG TESTING LABORATORY

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General Considerations

From a beginning based on "folk" knowledge of drugs that were derived mainly from plants, modern methods of purification, identification, structural determination, and chemical synthesis, combined with advances in pharmacology and toxicology, have developed the enormous catalog of modern drugs that have today replaced the large majority of natural products.

This has been the result of scientific investigations, particularly in university and industrial laboratories, which have found practical application in the drug industry since the end of the last century.

Scientific research is absolutely essential to a country's intellectual and cultural progress. It is indispensable in the biomedical sciences and in the sciences providing experimental support to medicine. I refer here both to basic or fundamental and to applied research, and I believe that a control laboratory must engage in both these scientific activities, whether it is dealing simply with regulatory aspects of drug analysis methods or the obtaining of biological data on drugs, or whether it is studying the more basic aspects of the development of the sciences on which control work is based.

I also believe, however, that applied research has the higher priority within the functions of a control organization, and therefore ought to be given the greater stimulus, provided this does not impede the conduct of basic research.

Following this policy, our Institute of Pharmacology and Bromatology has undertaken a number of basic research projects in the fields of chemistry, biochemistry, and pharmacology, while also promoting and financing outside research through subsidies, agreements, fellowships, and research contracts.

But my purpose in this paper is to refer to certain specific apsects of research associated with the inspection or control functions of a drug testing laboratory.

A control laboratory can best be conceived, in my opinion, as an organization or institution established to provide scientific and technical support to the inspection activities of the health authorities. In other words, it must operate as a scientific organization endowed with regulatory powers over the pharmaceutical industry.

The relative importance of control versus research functions has been debated on many levels in recent years. Thus, it has been said that a testing laboratory should receive the same degree of support as other government laboratories more directly involved in research, and that research activities should be given some priority within the public health policy so that the staff of a drug testing laboratory will not be regarded as having a lower standing.

Obviously, this does not imply that the emphasis on the development of scientific work should lessen the importance of the

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control functions, which in every sense have a higher social priority, since protection of the consumer depends on the work of professionals in the control laboratory.

In this connection, it might be well to emphasize that if a drug testing laboratory performs its assigned functions vigorously—investigating and evaluating analytical methods, conducting experiments in toxicology or pharmacology, and testing the products sold to the public to see that they conform to established standards—it automatically arouses the opposition of all those who consider themselves affected by these measures. Paradoxically, this type of work is subject to criticism by university organizations and by the rest of the scientific community. It is for this reason that in Argentina we have sought to have our Institute operate in close relationship with the country's scientific community in order to ensure that our control activities have a sound scientific foundation, and thus enable us to obtain the support of the industry we regulate.

This dual perspective that regards a control organization as both a scientific institution and an agency with regulatory powers over the pharmaceutical industry results in certain internal contradictions.

The technicians and professionals working in such a laboratory find themselves in an environment where regulatory and research matters are discussed in accordance with apparently conflicting approaches.

Research activities appear at first glance more attractive and enlightening. There are two reasons, however, why this duality is not objectionable, just as teaching is not inconsistent with research in a university, nor research and the development of new products inconsistent with the production of goods for profit in industry.

In the first place, control and analysis are creative tasks if regarded as means for solving problems affecting the welfare of society, as has been shown, for example, by the thinking about modern drugs expressed during this Seminar.

In the second place, the scientific staff of a drug testing laboratory is bound to realize that the simultaneous undertaking of these two types of work is beneficial for their training and for the results of their work, provided that the laboratory administrators adopt a clear policy and define the roles and missions of the professionals.

The general ideas presented so far, which are derived mostly from our own experience, may be useful for medium-sized laboratories. As for the research activities that can be carried out by laboratories of this type, I believe that they should be directed toward bringing about a better knowledge of the characteristics of drugs and also toward the study of normal life processes and pathological or abnormal conditions in relation to the utilization of drugs.

Although, as already noted in this Seminar, the control agency is responsible for evaluating material submitted on the basis of clinical studies of drugs, it is evident that medical research per se is not directly within its sphere, except for promoting such research, especially in regard to the more basic aspects of clinical pharmacology.

On the other hand, basic sciences such as chemistry, biochemistry, molecular biology, and pharmacology—all of which have, in recent years, strongly influenced the biological aspects of the study of human health and disease—are directly related to the knowledge of modern drugs and are therefore within the scope of the research and control work of a drug testing laboratory. Applied sciences such as biostatistics, used in bio-assays, and analytical chemistry and drug toxicology should all be considered

relevant to a control laboratory's work.

In its day-to-day operations, the control laboratory encounters many problems whose solution requires research on varied aspects of the use of drugs—for example, the development of analytical methods applicable to special cases. In my earlier presentation,[1] for instance, I noted how the presence of extraneous components in ipecacuanha syrup (*1*) led to the development of a method suitable for analyzing the normal components of the extract.

Even the least developed and most poorly equipped laboratories frequently encounter problems which cannot be solved by the methods prescribed in the pharmacopoeia, or by official techniques or those published in specialized journals, and whose solution therefore requires the creative skills of an analyst.

Examples of Research Conducted in Argentina

Since I previously referred to some of the problems currently encountered in drug control work, I should like to briefly describe some of the studies being done at our Institute, as an example of the type of research done at a drug testing laboratory.

Studies on the stability of pharmaceutical preparations pose serious problems in the development of new products and in the interpretation of the analytical results of public health inspection. A significant source of error is lack of knowledge of the reactions involved in degradation. While it is not necessary to know the mechanism, it is desirable from an analytical and toxicological point of view to know the identity of the possible decomposition products. Corticosteroids such as dexamethasone, which have a 1,4-diene-3-one system and a lateral chain with oxygenated functions, are susceptible to photochemical decomposition. In a recent study of 16-nordexamethasone we found that a rather large number of compounds, depending on the reaction time and pharmaceutical form, resulted from decomposition; their structure is being studied and correlated with the decomposition occurring in various pharmaceutical forms.

A paper was recently published on the nuclear magnetic resonance analysis of synthetic corticosteroids having this unsaturated structure. This method makes it possible to analyze the active principles as such and as components of pharmaceutical preparations containing other very similar steroids. The method, which was developed in the laboratories of the Food and Drug Directorate of Canada, has given useful results in our work (*2*).

The methods in widest use for the assay of menadione sodium bisulfite are based on conversion into menadione and assay of the latter by colorimetry or cerimetric procedures or by polarography in non-aqueous solvents. The treatment to which the sample is submitted leads to a sure source of error. The work done at our Institute to improve upon available methods and also avoid the influence of interfering substances present in pharmaceutical formulations has included the study of electrochemical techniques. Direct polarography of hydrosoluble vitamin K in pharmaceutical products containing such other active principles as phthalylsulfathiazole and phthalylsulfacetimide, common components of antidiarrheal preparations, led to the development of a simple technique for use in drug testing laboratories (*3*).

Studies of other drug testing methods have been undertaken under similar circumstances. Modern physicochemical methods are increasingly pointing to the possibility of assaying microquantities of active prin-

[1] See p. 24.

ciples in relatively complex preparations by using either destructive or nondestructive analyses. The Institute is exploring, in addition to nuclear magnetic resonance, such techniques as radioactivation and determination of vitamins through isotopic dilution and the use of atomic absorption spectroscopy to investigate traces of certain elements in natural products.

These are examples of analytical research aimed at developing new techniques. There are other unsolved problems more directly related to drug inspection and control activities. Among them is the question of standardization, which entails the review of certain standards in order to propose modifications to facilitate the control work conducted either in the industry's laboratories or in our own.

There are many medicinal plants still in use as components of drugs. Their botanical and phytochemical description is incomplete, and to facilitate their proper identification our Pharmacobotanical Division has made anatomical studies of the principal parts of the plants and of the drugs prepared in powdered form from certain species not described in our Pharmacopoeia. This work must be supplemented by phytochemical and pharmacological studies.

The systematic standardization work being done includes pharmacotechnical testing of samples of suppositories taken by our inspection service. The purpose is to set limits for the control of homogeneity, softening and melting points, melting and liquefaction time, resistance to breaking, and pH of the aqueous solution. A proposed standard has thus been prepared and is under final study. Similar work has been done in regard to the list of authorized drug coloring agents and the analytical methods used for a number of stupefactive alkaloids. We should like to make it clear that these studies have been done in cooperation with the associations of professionals working in the pharmaceutical industry.

As part of its control work, our Institute does testing for safety limits as required by the Pharmacopoeia. A classical example is the determination of the safety level of antibiotics in mice. A study was made to record the reactions of different strains of mice (purebred, inbred, closed colony, etc.) to different antibiotics. Although the work has not been completed, important variations have been observed in the determination of the LD_{50}, but not in the assays for safety.

In assembling information on adverse effects in hospital practice, we have gathered some data that can serve as a useful basis for toxicity studies. The undesirable effects can be attributed to the pharmaceutical quality of the drug in terms of physiological availability, to a metabolic failing, or to incorrect dosage.

Metoclopramide in pediatric use can provoke extrapyramidal symptoms such as difficulty in swallowing and speaking, strabismus, etc., as observed recently in hospitals in Buenos Aires. Because of the experience with this drug, the Institute undertook a study in collaboration with clinical physicians to determine the factors causing the adverse effects, identify the action mechanisms, and review the therapeutic doses. The clinical picture prior to administration of the drug was reproduced in experimental animals, and studies were made of acute toxicity, effective doses, and levels in plasma and tissues. The results of this work, and the clinical observations being made concurrently in the Toxicity Center of the Children's Hospital, should enable us to adopt appropriate health safeguards and regulations.

Diphenylhydantoin is the preferred drug for the treatment of certain cases of epi-

lepsy. Its more common adverse effects in adults are known, as is the relationship between the dose and its therapeutic action. The same is not true in the case of children, particularly infants. Experiments have been undertaken in our laboratory to determine the relationship between doses and effects and blood levels.

In Argentina there is a very marked trend toward the development of slow-acting forms of pharmaceutical preparations. In my earlier paper I referred to the problems involved in regard to bioavailability of active principles. An attempt has been made to establish correlations between assays *in vitro* and studies *in vivo*, but methodological limitations may be anticipated because of the difficulty, on the one hand, of reproducing the internal medium in artificial systems and, on the other hand, of extrapolating to man the results obtained in experimental animals. The subject is of sufficient interest to warrant continuation of the studies, and the results should be of enormous importance to industry.

Final Comments

I have already referred to the support which government drug control laboratories must have if they are to perform research conducive to more effective health inspection. It is important that all planning of research work give due regard to the human protagonist, who in this case is in a field which is undergoing an irreversible process of change.

If the production of drugs is today almost entirely within the province of sophisticated industrial establishments, and if the development of new drugs requires the participation of scientific and technical personnel from a wide variety of disciplines, it is no less true that the government laboratory must be assisted by a highly skilled team of pharmacists, biochemists, pharmacologists, chemists, etc., working toward the solution of the problems posed by the daily and massive use of drug products. This places an obligation upon our universities: "The training of professionals and scientists properly prepared for and dedicated to the solution of public health problems, possessing the necessary ability, attitude, and interest to aid in the advancement of their special field, in the improvement of techniques, and in the search for new courses of action.

"These are qualities which are acquired in the methodical and orderly practice of scientific research and in the constant use of the scientific method. What is needed today is a professional with originality, creativity, and the ability to bring about advances in his particular field, or at least the ability to interpret boldly, and with creative freedom, rising above the consequences of an all-absorbing routine." (*4*)

I realize that these qualities are preeminently important in research, but they are no less desirable in a task that has changed so radically in recent years that we now have a theory of drug analysis and control, as has been expressed at many national, regional, and international meetings and seminars, in existing or proposed legislation, and in many technical reports of the World Health Organization.

Without technical and professional personnel who possess the qualities and abilities we have described, it will not be possible to perform a function whose aim, above and beyond the performance of routine controls and analyses, should be to open up new paths to progress. I believe that the ultimate objective is the preservation and improvement of public health through technical improvement of the drug industry.

An essential factor in the achievement of these purposes is to provide the professionals

and technicians with a suitable work environment and appropriate incentives, together with the means of bringing their knowledge up to date and keeping abreast of the latest scientific developments, so that they may maintain their scientific skill and thus ensure the highest level of performance.

The creation of this suitable climate is furthered by the performance of research such as that described (and even more, by the active promotion of such research), and by facilitating continuous improvement through attendance at scientific meetings and seminars and participation in courses such as the one recently held by the Food and Drug Administration in Washington. Continuing relationships with other similar centers also help to make the control laboratory a stimulating and active organization.

Finally, I wish to underscore how important it is that all personnel be sufficiently informed of the latest activities and trends in the field of drug control and analysis. For this purpose, a good documentation and information center, a library, and a well-stocked collection of journals are indispensable. In a word, a drug testing laboratory must be aware of all scientific advances and endeavor to put them to immediate use, keeping abreast of drug control activities throughout the world.

Another point to keep in mind is that government authorities must recognize the tremendous influence of science and technology on economic development, social progress, and individual and collective well-being. The work of a government laboratory devoted to drug control and analysis contributes to the achievement of these objectives. Support of research and scientific training in the field of public health will make it possible to obtain the benefits deriving from utilization of the most advanced techniques and methods.

Methodological research, including that which concerns the regulatory and official control aspects, of which we have given some examples, should be done in collaboration and communication with the pharmaceutical industry because this will help to raise scientific and technological levels, an objective of prime importance that cannot be overlooked by the health authorities of developing countries.

At the present stage of technological development of modern drugs, the essential goal is to ensure that their production is responsive to current health needs and therefore that they have been formulated and manufactured in accordance with the latest scientific advances. By the same token, public health will be better protected if the official control is exercised in the light of the data supplied by research, a complex and arduous but also stimulating and beneficial task.

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RESTRICTING DRUGS TO DISPENSING ON PRESCRIPTION

ROBERT S. ROE *

A few decades ago, the list of available drugs did not include very many substances that were likely to cause injury when used by the general public for self-medication, and at that time there were only a few drugs, such as the narcotics, that were abused by people who employed such substances for self-gratification. The picture today, however, is quite different because the drugs now available include a considerable number of new compounds that are very potent and for which there is only a small margin between the effective dose and the toxic dose.

Moreover, some of the new products of the drug manufacturing industry have turned out to be subject to great abuse by people who consume them as stimulants, as depressants, as hallucinogens, or for other psychotropic effects that may provide a temporary escape from the ordinary worries of everyday life. The problem of drug abuse has become very widespread so that in practically all parts of the world, in addition to the narcotics problem, there are growing problems of misuse of the amphetamines, the barbiturates, and hallucinogenic substances such as LSD.

The serious harm resulting from self-administration of modern potent drugs by the general public, and the deliberate abuse of some of these new substances for self-gratification have lead to new developments in the field of drug control. It may be useful to consider briefly the history of this process in the United States of America.

The first U.S. law regulating drugs generally was the Federal Food and Drugs Act of 1906. This early law contained no provision whatever for restricting the sale of any drug and it was left entirely to the drug industry to decide which drugs could be advertised for sale directly to the public and which should be promoted only to the medical profession. In fact, it was not until 1914 that the Congress enacted a law for restricting the dispensing of narcotic drugs to doctors' prescriptions.

In 1938 the Congress enacted the Federal Food, Drug and Cosmetic Act to replace the outdated 1906 Act. However, the 1938 Act contained no provision specifically restricting any class of drugs to dispensing on prescription. It did not mention prescription drugs except in one brief clause which exempted a drug from bearing certain otherwise required label information when the drug was removed from the manufacturer's bottle and dispensed to the patient on the written prescription of a physician.

Because the law was silent on the subject, there was no uniformity among U.S. drug manufacturers as to which drugs should be restricted to prescription dispensing. As a result, a particular drug would frequently be available on the druggists' shelves labeled by one manufacturer as a prescription drug, and by another as for sale directly to the public. This situation was confusing to pharmacists and the public alike.

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In 1951 the Congress took action to clarify the situation, enacting an amendment to the Federal Food, Drug and Cosmetic Act which provided that a drug must be restricted to dispensing on medical prescription if:

1. It is a habit-forming drug; or
2. Because of its toxicity or other potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use, the drug is not safe for use except under the supervision of a physician licensed by law to administer such drug; or
3. It is limited by an approved new drug application to use under the professional supervision of a physician licensed by law to administer such drug.

The twofold purpose of the 1951 amendment, as stated in the report of the Congressional Committee which sponsored the amendment, was

1. To protect the public from abuses in the
2. To relieve pharmacists and the public from sale of potent drugs; and
burdensome and unnecessary restrictions on the dispensing of drugs that are safe for use without medical prescription.

It is clearly not the intent of the United States law to prohibit self-medication. Rather, the law has been developed to require that drugs which are safe for self-use by the public should be permitted to be sold to the public, while drugs which cannot be safely used except under the supervision of the physician should be dispensed only on prescription. Further, the law requires that a drug which is suitable for self-use by the general public be labeled with adequate directions for such self-use, plus such warnings as may be necessary to assure safe and effective use by the public. Turning this proposition around, it is clear that the U.S. law intends that a drug for which adequate directions for safe and effective self-use cannot be developed should be restricted to dispensing only on the prescription of a physician.

We have already mentioned the growing problem of abuse of the amphetamines and barbiturates and psychotropic drugs. In 1965 the U.S. Congress enacted a law to amend the Federal Food, Drug and Cosmetic Act to provide greater controls over such drugs. This law, known as the Drug Abuse Control Amendments of 1965, imposed the following requirements:

1. That all wholesalers, jobbers, and manufacturers of controlled drugs must register annually with the federal enforcement agency and keep exact records of their handling of controlled drugs.
2. That pharmacists, hospitals, and doctors must keep records of all transactions involving the controlled drugs.
3. That the controlled drugs may be distributed only to persons and firms legally authorized to deal in such drugs; and
4. That a prescription for a controlled drug may not be refilled more than five times, or later than six months after the prescription was originally written.

The term "controlled drugs" refers to the list of drugs which the enforcement agency has by regulation designated as having "a potential for abuse because of (their) depressant or stimulant effect on the central nervous system or (their) hallucinogenic effects."

In 1968 the Congress transferred the authority over "controlled drugs" from the Food and Drug Administration to the U.S. Department of Justice, where the enforcement is carried out by the same agency that enforces the narcotics law. This is an indication that Congress regards the problem of social harm resulting from misuse of the amphetamines, barbiturates, and hallucinogenic drugs as having a degree of seriousness comparable to that of the problem of misuse of heroin and other narcotic drugs.

The recent upsurge in the problem of abuse of drugs is of course not confined to the United States; it is a worldwide problem. In fact, some countries have gone

further than the U.S. Government in their laws dealing with drug abuse. For example, the Government of Sweden decided that the problem of misuse of the amphetamine drugs was so serious that it enacted a law forbidding the distribution of amphetamines in Sweden for any purpose; even the physicians do not have access to those drugs.

At many meetings sponsored by the World Health Organization, the problem of restricting distribution of potent and dangerous drugs has been discussed. This problem is mentioned in a number of the WHO series of Technical Reports. For example, the report of a study group meeting in 1956 in Geneva refers to the creation of a new problem with the advent of drugs such as the sulfonamides and antibiotics which merited restriction to prescription, and urged that: "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."[1]

Considerable attention was devoted to this subject at the WHO European Technical Meeting held in Warsaw in 1961. Of special interest in the report of that meeting are the sections and the annex dealing with "Classification of Pharmaceutical Preparations in Relation to Restrictions on Sale." The report includes the following statements:[2]

. . . 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 [restricting drugs to prescription dispensing] 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. . . .

The Eighteenth World Health Assembly (1965), in Resolution WHA18.47, stated its views as follows:[3]

. . . Noting with great concern the increasing frequency of abuse of sedatives or stimulants not classified internationally as narcotic drugs, . . . and being aware of the epidemic-like spreading of this abuse, particularly among young persons in certain countries;

Referring to the repeated recommendations of the WHO Expert Committee on Dependence-Producing Drugs concerning the need for control of certain sedatives and stimulants; . . .

1. Concludes that control of widely abused sedatives and stimulants, such as barbiturates, tranquilizers, and amphetamines, is desirable;

2. Recommends that Member States which have not already done so place such drugs on medical prescription . . .

The Twentieth World Health Assembly (1967), in Resolution WHA20.43, repeated the views expressed in the earlier resolution and added the following:[4]

2. Recommends that Member States provide, in regard to those drugs, for (i) supervision of transactions from production to retail trade; (ii) licensing of all producers; (iii) limitation of trade to authorized persons; (iv) prohibition of possession without authorization . . .

Resolution WHA20.42 of the same Assembly stated the following:[5]

. . . Noting the resolution on LSD and similar substances recommended by the United Nations Commission on Narcotic Drugs for adoption by the Economic and Social Council; and

Recalling the recommendations of the WHO

[1] *Wld Hlth Org. tech. Rep. Ser. 138* (1957), 20.
[2] *Wld Hlth Org. tech. Rep. Ser. 249* (1962), 30.
[3] *Off. Rec. Wld Hlth Org. 143* (1965), 31.
[4] *Off. Rec. Wld Hlth Org. 160* (1967), 26–27.
[5] *Ibid.*, p. 26.

Expert Committee on Addiction-Producing Drugs,

1. Considers that the increasing abuse of LSD and related hallucinogenic substances with their inherent risk to the health of the individual and society calls for effective countermeasures;

2. Urges Member States: (i) to restrict the use of these substances to scientific and special medical purposes; (ii) to provide for the supervision, by competent health authorities, of the production, distribution, and conditions of use of these substances . . .

Similar comments and recommendations were repeated at the Twenty-First World Health Assembly in May 1968 and again at the Twenty-Third Assembly in May 1970, but with an indication of a growing feeling of urgency on the part of the Assembly members.

From a realistic point of view, it must be recognized that in many countries it has not been feasible to adopt or enforce prescription restrictions in the sale of drugs other than narcotics that are subject to the restrictions and procedures of the Geneva convention. Most drugs, including modern preparations such as antibiotics and steroids, are available in those countries "over the counter," at least in small quantities such as two or three capsules or tablets.

This custom, of course, has developed in part as a reflection of a practical situation: the unavailability of medical personnel for large numbers of people in some areas of these countries. It has seemed to the authorities that restricting these drugs to prescription dispensing would simply serve to deprive many people of their benefit rather than ensure the safe and effective use of the drugs. However, in view of the serious social problems arising from widespread misuse of dangerous drugs, and the potential harmful effects of modern potent drugs when not properly administered, the need for adequate government controls now appears to be fully justified.

It is recognized that extensive changes in long-established customs cannot be brought about quickly. However it is suggested that each country should undertake an evaluation of its own situation as regards control of potent drugs and develop a planned program of controls along the lines recommended by the several World Health Assemblies.

Action could be taken now to restrict the psychotropic drugs to dispensing on prescription. This could be followed by action to restrict the dispensing of drugs that require very carefully regulated dosage and medical supervision for safe and effective use. As the country's medical treatment facilities and programs are expanded and improved, the government program for restricting such drugs to prescription dispensing would be readily accepted by the public.

APPENDICES

Appendix 1

THE DRUG CONTROL SITUATION IN THE COUNTRIES OF THE AMERICAS

This statement of the drug control situation in the countries of the Americas was prepared by the Pan American Health Organization using data obtained largely by means of a questionnaire sent to the countries of the Region in August 1970. The statement describes in brief form the drug control system in each country and provides information regarding the volume of drugs consumed and the Governments' expenditures for drug control.

ARGENTINA

Drug registration is conducted by the Pharmaceutical and Food Industries Control Department (Departamento de Contralor de Industrias Farmacéuticas y Alimentarias), while factory inspection, sample collection, and drug testing are conducted by the National Institute of Pharmacology and Bromatology (Instituto Nacional de Farmacología y Bromatología). These two agencies are units of the Secretariat of State for Public Health.

All drugs require registration and registration must be renewed every five years.

The Pharmaceutical and Food Industries Control Department has an advisory group (composed of physicians, pharmacists, and biochemists) for evaluating drug registration applications. This advisory group studies the information in the application and takes into account a report prepared by the National Institute of Pharmacology and Bromatology on the chemical, toxicological, and pharmacological aspects of the registration application.

BARBADOS

At the present time, no specific arrangements exist for the control of drugs except those which fall under the Dangerous Drugs Act and the Therapeutic Substances Act. However, the Government will soon put into effect a new "Control of Drugs Regulation" and will have drug inspectors who will collect samples for testing purposes.

BOLIVIA

Drug registration and factory inspection are conducted by the National Pharmacy Department (Dirección General de Farmacias). Samples submitted with drug registration applications are tested by the Drug Analysis Laboratory (Laboratorio de Análisis de Medicamentos). These two agencies are units of the Ministry of Social Welfare and Public Health.

All pharmaceutical products must be registered. Registration must be renewed every 10 years in the case of a product manufactured in Bolivia and every five years in the case of an imported drug product.

At the present time, there is no medical advisory group with specific responsibility for evaluating registration applications.

BRAZIL

Drug registration is conducted by the National Medical and Pharmaceutical Products Control Service (Serviço Nacional de Fiscalização da Medicina e Farmácia), a unit of the national Ministry of Health.

Factory inspection and sample collection are conducted by state employees. The state governments that are active in this regard are Guanabara (includes the city of Rio de Janeiro) and São Paulo (includes the city of São Paulo). More than 90 per cent of the drugs produced in Brazil are manufactured by firms located in those two states.

Drug testing is conducted by the Central Food and Drug Control Laboratory (Laboratório Central de Contrôle de Drogas, Medicamentos e Alimentos), a unit of the national Ministry of Health, and by the Adolfo Lutz Institute, a unit of the São Paulo State Government.

All drugs require registration, and registration must be renewed every 10 years.

Registration applications are reviewed by the Biopharmacy Commission (Commissão de Biofarmacia), a unit of the National Medical and Pharmaceutical Products Control Service. The Commission is composed of physicians, pharmacists, and other professional experts.

CANADA

Drug registration, factory inspection, sample collection, and drug testing are conducted by the Food and Drug Directorate, a unit of the Canadian Department of National Health and Welfare.

Applications for permission to sell new drugs are submitted to the Food and Drug Directorate, where they are evaluated by a medical review board composed of physicians, pharmacologists, pharmacists, etc. However, initial requests for certification of antibiotics are reviewed by a different unit of the Department of National Health and Welfare.

Manufacturers of vaccines, sera and analogous drugs, insulin preparations, antibiotics for injection use, and certain other drugs must obtain a license from the Department of National Health and Welfare before distributing such "Schedule C and D Drugs."

CHILE

Drug registration is conducted by the Drug Registration Service (Servicio de Registro de Medicamentos); sampling of drugs in distribution channels is conducted by the Pharmacy Section (Sección de Farmacia); and drug testing is conducted by the Cosmetic and Pharmaceutical Products Quality Control Department (Departamento de Control de Calidad de Productos Farmacéuticos y Cosméticos). These agencies are units of the National Health Service.

All drugs require registration, and registration must be renewed every three years.

Registration applications are studied by an *ad hoc* commission consisting of a physician, the chief of the Pharmacy Section, two pharmacists, and the chief of the Cosmetic and Pharmaceutical Products Quality Control Department. In the case of a "new drug," this commission transmits the application to the National Formulary Commission (Comisión del Formulario Nacional) for review.

Every batch of those products designated as biologicals or biochemicals must be tested and approved by the Cosmetic and Pharmaceutical Products Quality Control Department before it is distributed.

COLOMBIA

Drug registration is conducted by the Drug Control Office (Oficina de Control de Drogas) and by the Juridical Office (Oficina Jurídica), both of which are units of the Ministry of Public Health.

Factory inspection and sample collection are conducted on occasion by members of the departmental and municipal public health bureaus.

Drug testing is conducted by the National Health Laboratory (Laboratorio Nacional de Salud), a government agency which has some degree of autonomy.

All drugs require registration, and registration must be renewed every 10 years.

The registration applications are submitted to the Ministry of Public Health. The samples submitted as part of the registration application are analyzed in the National Health Laboratory, and on the basis of the reports submitted by that agency the Ministry of Public Health determines whether or not the registration application is acceptable. There is no medical advisory group with responsibility for evaluating registration applications.

COSTA RICA

Registration of pharmaceutical specialties and drug factory inspection are conducted by Costa Rica's Pharmaceutical Society (Colegio de Farmacéuticos).

Registration of generic drugs is conducted by the Generic Drugs Registration Office (Oficina de Inscripción de Productos Farmacéuticos Genéricos), a unit of the Ministry of Public Health.

Costa Rica has no agency specifically designated for testing drugs.

Each of the two drug registration agencies has its own medical advisory group for reviewing drug registration applications.

Drug registration applications approved by the Pharmaceutical Society are valid for 15 years, while drug registration applications approved by the Ministry of Public Health are valid for five years before renewal of registration is required.

DOMINICAN REPUBLIC

Drug registration, factory inspection, and sample collection are conducted by the Division of Pharmaceutical Products and Narcotic Drugs Control (División de Productos Farmacéuticos y Control de Drogas Narcóticas). Drug testing is conducted by the National Public Health Laboratory. These two agencies are units of the Ministry of Public Health and Social Welfare.

All drugs except articles intended for certain veterinary uses require registration. The proposed labeling and literature are reviewed by a commission made up of three physicians from the Ministry.

An approved registration is valid for five years.

ECUADOR

Drug registration, sample collection, and drug testing are conducted by the National Institute of Hygiene (Instituto Nacional de Higiene), a unit of the Ministry of Public Health.

All drugs require registration, and registration must be renewed after seven years.

There is no medical advisory group specifically designated to evaluate registration applications.

EL SALVADOR

Drug control in El Salvador is conducted by the Superior Public Health Council (Consejo Superior de Salud Pública), the Medical Profession Surveillance Board (Junta de Vigilancia de la Profesión Médica), the Pharmaceutical Profession Surveillance Board (Junta de Vigilancia de la Profesión Farmacéutica), and the Dental Profession Surveillance Board (Junta de Vigilancia de la Profesión Odontológica). The Superior Public Health Council and the three Boards are autonomous but operate in conjunction with the Government's Ministry of Public Health and Social Welfare.

Factory inspection and drug testing are conducted by the Pharmaceutical Profession Surveillance Board.

All drug products require registration.

Registration applications are reviewed by the Pharmaceutical Profession Surveillance Board and the Medical Profession Surveillance Board, except that if the product is intended for dental use it is reviewed by the Dental Profession Surveillance Board in conjunction with the Pharmaceutical Board.

An approved registration is valid without time limit but a fee must be paid annually.

GUATEMALA

Drug registration and factory inspection are conducted by the National Pharmaceutical and Drug Inspection Office (Inspección General de Farmacias y Estupefacientes), a unit of the Ministry of Public Health and Social Welfare.

All drugs require registration. An approved registration is valid without time limit.

Registration applications for products manufactured in Guatemala are reviewed by a committee composed of two physicians and one pharmacist.

GUYANA

The Government is considering the adoption of a modern drug control law, but at the present time there is no drug registration requirement.

Drug quality control is at present conducted in connection with enforcement of the Pharmacy and Poisons Ordinance, the Dangerous Drugs Ordinance, the Antibiotics Ordinance, and the Food and Drugs Ordinance.

Inspectional activities are assigned to an inspector who is attached to the Pharmacy and Poisons Board.

The Government Analyst is charged with analysis of drug samples submitted by officers authorized under the Ordinances on pharmacy and poisons, dangerous drugs, antibiotics, and food and drugs.

HONDURAS

Drug registration and factory inspection are conducted by the Society of Chemists-Pharmacists (Colegio de Químico-Farmacéuticos) of Honduras. On occasion, the Society sends drug samples for analysis to the National University.

There is no specifically designated medical group for studying drug registration applications. An approved registration is valid for one year, after which it must be renewed.

JAMAICA

All imported drugs must be registered and all drug manufacturing in Jamaica must

be licensed. These activities, as well as factory inspection activities, are conducted by the Drugs and Poisons Board.

Applications for registration of imported drugs and licensing of domestic drugs are reviewed by a medical advisory group. Applications pertaining to antibiotic products are reviewed by a specially constituted Board.

Approved registrations for imported drugs are valid without time limit. Licenses issued for drugs manufactured domestically must be renewed annually.

Drug testing is conducted by the Government Chemist's Department. At the present time, such testing is confined almost exclusively to samples of domestically produced products.

MEXICO

Registration of drugs for human use is conducted by the Drug Control Department (Dirección de Control de Medicamentos). Registration applications are reviewed by specialized groups, each group containing physicians and chemists.

An approved registration is valid for one year and must be renewed annually.

Factory inspection activities are the responsibility of the Drug Control Department. Employees of this agency conduct factory inspections within the Federal District and utilize employees of the Coordinated Services for States and Territories in carrying out inspectional activities in the states and territories.

Drug testing is conducted by the National Health Laboratory (Laboratorio Nacional de Salubridad) and by the National Virology Institute (Instituto Nacional de Virología).

The Drug Control Department and the aforementioned Laboratory and Institute are units of the Ministry of Health and Welfare.

Drugs for veterinary use are controlled by the Ministry of Agriculture and Livestock through that agency's Drug Department.

NICARAGUA

Drug registration and factory inspection are conducted by the Pharmaceuticals, Drugs, and Food Division (División de Farmacias, Drogas y Alimentos). Drug testing is conducted by the Chemistry-Biomatology Laboratory (Laboratorio Químico-Bromatológico), both of which are units of the Ministry of Public Health.

All drugs require registration and approved drug registrations must be renewed annually.

There is no medical advisory group specifically designated for reviewing drug registration applications.

PANAMA

Registration of all drugs, for human or veterinary use, is conducted by the Pharmacy, Drugs, and Food Department (Dirección de Farmacia, Drogas y Alimentos), a unit of the Ministry of Health. The inspector-technicians of this unit make factory and establishment inspections and are authorized to collect control samples.

Drug testing is conducted by the Specialized Analysis Laboratories (Laboratorios Especializados de Análisis—LEA). LEA is located on the premises of the University of Panama and operates in coordination with the Pharmacy, Drugs, and Food Department.

All drugs require registration. Plans are being drafted for a new Health Code which would create a National Therapeutics Committee (Comité Nacional de Terapéutica), composed of physicians, pharmacologists, pharmacists, a veterinarian, and the legal adviser of the Ministry of Health, to study and determine the therapeutic actions of medicinal products for human or veterinary use and submit their views to the Ministry for consideration.

Approved registrations are valid for five years.

PARAGUAY

Drug registration and factory inspection activities are conducted by the Chemistry and Pharmacy Department (Departamento de Química y Farmacia), a unit of the Ministry of Public Health and Social Welfare. There is no governmental unit for testing drugs.

All drugs require registration. Approved registrations are valid for 10 years, after which renewal of the registration is required.

Registration applications are reviewed by pharmacists in the Chemistry and Pharmacy Department.

PERU

Drug registration and factory inspection are conducted by the Pharmacy Department (Dirección de Farmacia), a unit of the Ministry of Health. Drug testing is conducted by the Biological Products and Drug Control Center (Centro de Control de Productos Biológicos y Medicamentos), a unit of the National Institutes of Health.

All drugs require registration. Registration applications are reviewed by a committee composed of physicians, pharmacists, and other professional personnel.

An approved registration is valid for three years.

TRINIDAD AND TOBAGO

The Drug Inspectorate conducts registration and inspection activities involving antibiotic preparations, while the Food and Drugs Division (a part of the Government Chemist Agency) conducts registration and inspection activities involving all other types of drugs. Both these agencies are units of the Ministry of Health.

All drug testing is the responsibility of the Food and Drugs Division.

Registration applications involving antibiotic preparations are reviewed by the Antibiotics Control Committee, composed of practicing physicians. Registration applications for other types of drugs are reviewed by a committee composed of physicians, chemists, and other professionals.

An approved registration is valid without time limit unless a change is made in the composition of the drug or in its labeling, etc.

UNITED STATES OF AMERICA

The major drug control agency of the Federal Government is the Food and Drug Administration. This agency has a registration-like authority over new drugs, and is responsible for factory inspection, sample collection, and testing with respect to most of the drugs used in the U.S.A. However, licensing control of vaccines and serums, etc. (biological products) for human use is exercised by a different agency, the Division

of Biologics Standards. Both the Food and Drug Administration and the Division of Biologics Standards are units of the Department of Health, Education, and Welfare.

Control over biological products intended for use in animals is exercised by the Department of Agriculture.

Control over the sale of narcotics and other dangerous drugs that may cause dependence is exercised by the Bureau of Narcotics and Dangerous Drugs, a unit of the Department of Justice.

URUGUAY

Drug registration and drug testing are conducted by the Central Chemistry Laboratory (Laboratorio Central de Química). Factory inspection activities are conducted by the General Chemistry, Pharmacy, and Drugs Inspection Office (Inspección General de Química, Farmacia y Drogas). Both agencies are units of the Ministry of Public Health.

All drugs require registration. Renewal of registration is required every five years.

There is no medical body specifically charged with evaluating the registration applications.

VENEZUELA

Drug registration, factory inspection, and sample collection are conducted by the Pharmacy Division (División de Farmacia) and drug testing is conducted by the National Institute of Hygiene (Instituto Nacional de Higiene). Both agencies are units of the Ministry of Health and Social Welfare.

All drugs require registration. There is no specified period after which registration must be renewed, but the registration unit constantly surveys the situation and may require changes in a product or its labeling, etc., if the circumstances warrant such change.

Registration applications are evaluated by government pharmacologists and other professionals and a decision is then made by the Review Board (Junta Revisora), composed of physicians and pharmacists, as to whether the application should be approved or denied.

Drug Consumption, Drug Manufacturing Establishments, and Drug Control Situation in 24 Countries of the Americas.

Country	Estimated retail cost of drugs consumed per year (in US$)	Number of drug manufacturing establishments	Government expenditure for drug control per year (in US$)	Total number of government drug control personnel	Number of government drug inspectors	Number of scientists testing drugs for Government	Government drug control expenditure per $1,000 of drugs consumed
Argentina	340,000,000	200	1,193,000	223	17	82	$3.5
Barbados	2,300,000	2		0	0	0	
Bolivia	11,000,000	7	20,000	13 [a]	3 [a]	3	1.8
Brazil	560,000,000	450	300,000 [b]	210 [a, b]	13 [b]	41 [b]	0.5 [b]
Canada	655,000,000	670	3,840,000	309	64	26	5.9
Chile	60,000,000	40	200,000	23	2	17	3.3
Colombia	200,000,000	82	120,000	30	4	13	0.6
Costa Rica	15,000,000	15	35,000 [c]	7 [c]	2 [c]	0	2.3 [c]
Dominican Republic	20,000,000	7	60,000	30 [a]	6 [a]	13	3.0
Ecuador	27,000,000	9	100,000	43 [a]	1	21	3.7
El Salvador	16,000,000	16	17,000 [d]	43 [a, d]	3 [a, d]	2 [d]	1.0 [d]
Guatemala	29,000,000	26	5,000	8 [a]	3 [a]	0	0.2
Guyana	5,500,000	1	7,500	5 [a]	1 [a]	1	1.4
Honduras	14,000,000	15	15,000 [e]	10 [a, e]	1 [a, e]	6 [a, e]	1.0 [e]
Jamaica	11,000,000	6	23,000	12 [a]	4 [a]	3	2.1
Mexico	315,000,000	750	618,000	294 [a]	140 [a]	28	2.0
Nicaragua	22,000,000	18	23,000	18 [a]	9 [a]	1	1.0
Panama	12,000,000	5	92,000 [f]	52 [a]	9 [a]	30 [a]	7.7 [f]
Paraguay	9,000,000	5	4,000	12 [a]	4 [a]	0	0.4
Peru	75,000,000	130	114,000	76 [a]	8 [a]	15	1.5
Trinidad and Tobago	8,000,000	5	20,000	17 [a]	9 [a]	4	2.5
United States of America	7,500,000,000	5,000	36,000,000 [g]	2,035 [a]	655 [a]	356	4.8 [g]
Uruguay	26,000,000	85	24,000	18 [a]	7 [a]	8	1.0
Venezuela	170,000,000	77	381,000	48	4	26	2.2

NOTES:
[a] Some of these personnel work part time or have other duties in addition to drug control.
[b] These figures include state and national personnel and expenditures for drug control.
[c] These data refer to drug control activities conducted by the Pharmaceutical Society of Costa Rica.
[d] These data refer to drug control activities conducted by the Pharmaceutical, Medical, and Dental Surveillance Boards and the Superior Public Health Council. These units are autonomous but depend economically on the National Government of El Salvador. They are related to the Government through the Ministry of Public Health and Social Welfare.
[e] These data refer to drug control activities conducted by the Society of Chemists-Pharmacists of Honduras (analyses are conducted by the National University).
[f] Of the US$92,000 listed as Panama's annual expenditure for drug control, $75,000 relate to that portion of the budget of Panama's Specialized Analysis Laboratories (LEA) attributable to testing drug samples submitted by firms wishing to sell drugs in the country. LEA performs such registration analyses on a fee basis and is self-financing.
[g] These data refer only to drug control activities carried out by the U.S. Food and Drug Administration.

Appendix 2

MODEL OF NATIONAL DRUG CONTROL LAW

This model "National Drug Control Law" was prepared by Mr. Robert S. Roe, consultant to the Pan American Health Organization, to serve as a guide for consideration by the authorities of countries that do not have a modern law on this subject. This model law embodies a group of basic principles that should be included in the legislative enactments, but its form and wording can readily be adapted to conform with the prevailing customs and legal procedures of the individual countries.

Article 1

This law may be cited as The National Drug Control Law.

Article 2

The purpose of this law is to ensure that drugs imported into, or manufactured, repacked, relabeled, stored, distributed, or sold in _____ are safe and effective for the intended uses and possess the proper identity, strength, quality, and purity. All regulations adopted under this law and all interpretations of the wording of this law shall be made in such manner as to carry out effectively the purpose of the law as stated in this Article.

Article 3

a) A drug may not be imported, manufactured, repacked, relabeled, stored, distributed, or sold unless there has been filed with the Minister an application for registration of the drug and such application has been approved by the Minister.

b) (1) The Minister shall issue regulations specifying the information required to be contained in the application for registration of the drug in order to establish that it is safe and effective for the intended uses and that it will have the proper identity, strength, quality, and purity.

(2) The kind and amount of safety and efficacy data required by the Minister in a registration application shall depend upon the composition and proposed uses of the drug so that a minimum amount of such information shall be required in the case of a well-known drug offered for its recognized uses while a maximum amount of such information shall be required in the case of a new drug.

c) (1) The Minister shall make his decision regarding approval or denial of registration on the basis of the information contained in the application and any other valid information known to him regarding the drug.

(2) The registration application and any other available pertinent information regarding the drug shall be reviewed by a scientific advisory committee appointed by the Minister, and the Minister shall give due consideration to the recommendation of such committee in determining whether to approve or deny the registration application.

(3) The scientific advisory committee shall have such composition as the Minister shall determine but in no event shall it consist of less than three members, including a physician, a pharmacologist, and a pharmacist.

(4) Registration applications shall be processed expeditiously and the Minister's decision shall be made known to the applicant not later than 180 days after the date of filing the registration application.

d) An approved registration shall be valid for a period of five years. Renewal of the registration must be obtained at five-year intervals in order to continue the importation, manufacture, repacking, relabeling, storage, distribution, or sale of the drug.

e) An approved drug registration shall cease to be valid if any significant change is made in the composition of the drug, the dosage form, the conditions of its manufacture, its labeling, or the purposes and conditions for which it is represented in its labeling or advertising, without prior approval by the Minister of such change.

f) Whenever new information not previously available indicates that a registered drug may not be safe or effective when used in the manner and for the purposes approved in the registration, the Minister:

(1) May require such revisions in the composition of the drug, its packaging, labeling, or advertising as may be necessary to ensure safety and effectiveness; or

(2) May revoke the registration.

g) The Minister may issue an exemption from the registration requirement to permit importation, manufacture, and distribution of a new drug intended solely for experimental use but such exemption shall end after three years unless the Minister, upon a showing of the need thereof, extends the exemption for an additional period of not more than one year.

h) (1) A drug that is being marketed on the date of enactment of this law shall be temporarily exempt from action under this Article provided the sponsor of the drug files an application for registration within six months after the date of enactment.

(2) Such temporary exemption shall cease when the Minister has rendered his decision approving or denying registration, or two years after the date of enactment, whichever comes sooner.

Article 4

a) (1) No drug shall be manufactured, repacked, or relabeled in a domestic establishment that is not licensed by the Minister for such purpose.

(2) A license shall be issued by the Minister if the person responsible for the establishment provides adequate evidence that the premises, equipment, and personnel are satisfactory for the intended purpose and that the establishment will be operated in accordance with applicable standards of good practices in the manufacture and quality control of drugs.

(3) The Minister shall issue regulations specifying the information that must be submitted by the person seeking a license under this Article.

b) A license issued under this Article shall be valid for a period of one year and must be renewed annually for continued operation of the establishment.

c) The Minister may at any time revoke a license granted under this Article:

(1) If he concludes, on the basis of convincing evidence, that the establishment

lacks any of the elements necessary to satisfy the requirements of current good practices in the manufacture and quality control of drugs; or

(2) If his authorized agents are refused permission to inspect the establishment at a reasonable time; or

(3) If the operator of the establishment refuses to provide such information as may be requested by the authorized agents of the Minister concerning any pertinent aspects of the manufacture, repacking, or relabeling of drugs at the establishment.

Article 5

a) The Minister shall publish a list of drugs which must be restricted to dispensing on prescription because they are habit-forming or are otherwise unsafe for use by the public except under the supervision of a licensed physician. Such drugs shall be labeled with the legend "Caution—this drug may not be dispensed except on the prescription of a licensed physician."

b) (1) The container of a prescription drug must bear a label which, in addition to the above-quoted prescription legend, states the name and quantity of each active ingredient, the recommended or usual dosage, the route of administration if the drug is not for oral use, the quantity of contents in the package, the name and place of business of the manufacturer, packer or distributor, and the lot number.

(2) The label or package labeling must bear adequate directions for use of the drug by physicians and any relevant warning information concerning its hazards, contraindications, and side-effects.

c) An advertisement for a prescription drug shall include:

(1) The name and quantity of each active ingredient; and

(2) A brief summary of information concerning its effective use and the precautions that must be observed in connection with its use.

d) Advertisements for prescription drugs shall be disseminated only to physicians or other medical professionals authorized to prescribe or administer such drugs.

e) The Minister shall issue such regulations as are necessary for carrying out the purpose of this Article. The Minister may impose additional labeling and advertising requirements that he concludes are necessary in particular cases, or he may provide exemptions in those instances in which it is not practicable to comply fully with the specified requirements of this Article because of inadequate label space or other particular circumstances.

Article 6

a) (1) In the case of a drug which is suitable for use by the public without the supervision of a physician, the container must bear a label which states the name and quantity of each active ingredient, the recommended dose, such warnings as may be necessary, the quantity of contents in the package, the name and place of business of manufacturer, packer or distributor, and the lot number.

(2) The label or package labeling must state the conditions for which the article is to be used, the dosage instructions for each particular use, and such other relevant information, including warnings, as may be necessary for safe and effective use of the drug by members of the general public.

b) The Minister shall issue such regulations as are necessary for carrying out the purpose of this Article. The Minister may impose additional labeling and advertising requirements that he concludes are necessary in particular cases, or he may provide exemptions in those instances in which it is not practicable to comply fully with the specified requirements of this Article because of inadequate label space or other particular circumstances.

Article 7

When a drug is dispensed on the prescription of a physician, the dispensed portion shall become exempt from the requirements of Articles 5 and 6 but the package as dispensed for the patient must bear a label stating the name and location of the dispenser, the name of the patient, the name of the physician, the date, the prescription serial number, the physician's instructions for using the drug, and any other information specified by the physician.

Article 8

a) The Minister shall publish a list of diseases, disorders, abnormal physical states, or the symptoms thereof, which cannot be treated successfully without the supervision of a physician and for which drugs may not be promoted in labeling or advertising directed to the public.

b) The regulations issued by the Minister under this Article may provide exemptions from section (a) of this Article in particular cases.

Article 9

a) The name used on the label, in the labeling, and in the advertising of a drug to designate an ingredient shall be the non-proprietary name that is commonly or usually employed for designating that substance.

b) If the drug as a whole is commonly referred to by a non-proprietary name, the label, labeling, and advertising must bear such name as the identifying name for the product as a whole.

c) The Minister is authorized to determine the non-proprietary name that must be used for a particular drug or ingredient if confusion has arisen because two or more non-proprietary names have been used to designate the particular drug or ingredient. Such decisions shall be published by the Minister in the form of a regulation.

d) Proprietary names may be used in addition to the non-proprietary names required under sections (a) and (b) of this Article provided that use of the proprietary names is in conjunction with the corresponding non-proprietary name and further provided that use of the proprietary name does not create a misleading impression concerning the identity or composition of the drug.

Article 10

A drug shall be deemed to be adulterated:

a) If it is represented as an article listed in a recognized pharmacopoeia or formulary and its identity or strength differs from, or its quality or purity falls below, the standard set forth in the pharmacopoeia or formulary; or

b) If it is not represented as an article listed in a recognized pharmacopoeia or formulary and its identity or strength differs from or its quality or purity falls below that which it purports to possess; or

c) If it consists in whole or in part of any filthy, putrid, or decomposed substance; or

d) If it has been prepared, packed, or held under insanitary conditions; or

e) If it has been manufactured, processed, packed, or held in premises or equipment, or under conditions that are not in conformity with current good manufacturing practices; or

f) If it contains for purposes of coloring a substance which is not generally recognized as safe for coloring the particular type of drug; or

g) If it is packed in a container which introduces harmful substances into the drug or otherwise reacts with the drug in a manner which significantly alters the properties of the drug.

Article 11

A drug shall be deemed to be misbranded:

a) If its labeling or advertising is false, misleading, or deceptive, or is likely to create an erroneous impression regarding its identity, composition, quantity, usefulness, or safety; or

b) If its labeling or advertising fails to conform with the requirements of Articles 5, 6, 7, 8, or 9; or

c) If it is represented as an article listed in a recognized pharmacopoeia or formulary which specifies a particular form of packaging and the article is not packaged in the specified form.

Article 12

For the purposes of this law:

a) The term "Minister" means the Minister of Health.

b) The term "drug" means:

(1) Any substance or mixture of substances represented for or intended for use in the diagnosis, treatment, mitigation, cure, or prevention of a disease, disorder, abnormal physical state, or the symptoms thereof, in man or animals; or

(2) Any substance or mixture of substances (other than food) intended to affect the structure or any function of the body of man or animals; or

(3) Any article listed in a recognized pharmacopoeia or formulary.

c) The term "new drug" means any drug which is not generally recognized by qualified experts as safe and effective for the purposes for which the drug is intended to be used.

d) The term "label" means a display of written, printed, or graphic matter upon the immediate container of a drug, or upon the carton or similar container (if such there be) in which the immediate container of drug is packaged.

e) The term "labeling" means all container labels, carton labels, circulars, or any other written, printed, or graphic matter physically associated with the container of the drug.

f) The term "advertisement" means any representation conveyed by any means whatever for the purpose of promoting directly or indirectly the distribution or sale of any drug.

g) The term "person" includes individual, partnership, corporation, and association.

Article 13

The following acts or the causing thereof are prohibited:

a) The importation, manufacture, storage, transportation, distribution, or sale of any drug that:

(1) Is in violation of the registration provisions of Article 3; or

(2) Is adulterated as defined by Article 10; or

(3) Is misbranded as defined by Article 11.

b) The manufacture, repacking, or relabeling of any drug in a domestic establishment not licensed as required by Article 4, or the storing, transport, distribution, or sale of such drug.

c) The use of any representation in labeling or in advertising which is inconsistent with the therapeutic representations, conditions of use, warning information, or any similar information that was contained in the labeling accepted by the Minister under the terms of the approved drug registration applicable to the product.

d) (1) The refusal to permit authorized agents of the Minister to inspect premises where drugs are manufactured, stored, packaged, repackaged, labeled, held, or offered for sale; or

(2) Refusal to permit inspection by authorized agents of the Minister of the records, facilities, equipment, raw materials, and processing used in any such establishment in connection with the manufacture, repacking, labeling, or holding of the drug.

e) The refusal to provide to authorized agents of the Minister information which is pertinent, with respect to determining whether the drug is in violation of any of the applicable Articles of this law.

f) The using by any person to his own advantage, or revealing other than to the Minister or officers or employees of the Ministry, or to the courts when relevant in any judicial proceeding under this law, of any information acquired in the course of administering or enforcing this law with respect to any method or process or other information concerning an individual business that is entitled to confidentiality.

Article 14

a) The Minister is authorized to issue notice of embargo with respect to any stock or shipment of any drug concerning which he has reasonable cause to believe is adulterated or misbranded, or not covered by an approved registration under Article 3, or is from a domestic establishment not licensed as required by Article 4. By court order, any such stock or shipment of a drug that is shown by proper evidence to be in violation of this law shall be destroyed or otherwise disposed of as the court may direct.

b) Any person who violates any of the provisions of this law shall on conviction thereof by a court of appropriate jurisdiction be sentenced to pay a fine of not more than _____ or to imprisonment for not more than _____ months, or both such fine and imprisonment.

Article 15

The Minister is authorized to provide quarters, facilities, equipment, and staff necessary to carry out the provisions of this law. The Minister is authorized to delegate to the appropriate members of the staff any or all of the powers granted to the Minister under the terms of this law.

Article 16

The Minister is authorized to establish and collect reasonable fees for drug registration under Article 3 and for establishment licensing under Article 4.

Article 17

In addition to the specific authority for regulation-making provided for in Articles 3, 4, 5, 6, 8, and 9, the Minister is hereby given general authority to promulgate regulations giving effect to or interpreting the purposes and provisions of this law.

REGULATIONS

Registration of Drugs

An application for registration of a drug must provide the following:

1. Name and address of applicant.
2. If applicant is a foreigner, the name and address of a local resident authorized to represent him.
3. A description of the product as to form and composition, including a complete listing of the name and quantity of each ingredient, whether active or not, contained in each dosage unit.
4. A batch formula representative of that to be used for the manufacture of the dosage form (all substances used for manufacturing the batch should be listed in the batch formula, whether or not they appear in the finished product).
5. A complete step-by-step description of the method of producing the batch.
6. A statement of the precautions used to assure proper identity, strength, quality, and purity of the raw materials used for manufacturing the drug.
7. A full description of the in-process control procedures during manufacture, including details of procedures used in testing the finished product.
8. Data regarding stability of the product; if the data do not show prolonged stability, the applicant should propose an expiration period to be stated on the label.
9. A description of the buildings, equipment, and any other physical facilities important in connection with the manufacturing, processing, packaging, labeling, and testing of the product.
10. A declaration that the product will be manufactured in accordance with standards of current good manufacturing practices comparable to the WHO recommendations contained in Resolution WHA22.50 of the World Health Assembly.

11. Adequate information to demonstrate that the product is safe and effective when used for the purposes and in the manner recommended in the labeling and other promotional material relating to the product. (If it is a new product, or recommended for new uses for which it is not generally recognized by medical scientists as safe and effective, complete reports of all clinical investigations and animal tests should be included.)

12. If the product is imported, a certificate from appropriate health officials in the country of origin (a) stating that the product has been approved for sale in the country of origin and (b) attaching labeling used with the product in the country of origin.

13. Specimens of proposed package labels and circulars, pamphlets, or other labeling.

14. Specimens of proposed advertisements and other proposed promotional materials.

15. A sample of the product.

Appendix 3

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Dr. Antonio Conti, Chamber of the Venezuelan Pharmaceutical Industry

Dr. Héctor De Lima, Chief, Vitamins Subsection, National Institute of Hygiene

Dr. Ernesto Díaz Montes, Venezuelan Pharmaceutical Federation

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Dr. Alfonso Müller, Member of the Pharmaceutical Specialties Review Board

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Dr. Julia Salas de Vegas, Pharmacology Section, National Institute of Hygiene

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Appendix 4

OFFICERS AND WORKING GROUPS OF THE SEMINAR

President:	**DR. RAFAEL DARIO BERTI**	Venezuela
Vice-President:	**DR. LILA LEE LUQUE**	Panama
Rapporteur:	**DR. RICARDO PICO NAVARRO**	Mexico
Secretary:	**MR. MORRIS L. YAKOWITZ**	Pan American Sanitary Bureau

WORKING GROUP NO. 1

Drug Registration Procedures
Possible Joint Action by the Countries

Participants

Dr. Elena de Cárdenas
Dr. Alton Ellington
Dr. Siegbert Holz
Dr. Mario Ibañez
Dr. Lila Lee Luque
Dr. Alberto Lezerovich (*Rapporteur*)
Dr. Michael Lines
Dr. Eduardo López Avila
Dr. Sebastião Marques da Fonseca
Dr. Graciela Pérez Herrera (*Moderator*)
Dr. Dixiana de Vásquez

Consultants

Dr. Jerónimo Averza
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WORKING GROUP NO. 2

Control of Biological Products
Organization of a National Drug Control Agency

Participants

Dr. Consuelo E. Agrelo (*Moderator*)
Dr. Rafael D. Berti
Dr. Denys Cook (*Rapporteur*)
Dr. Margarita L. de Cornejo
Dr. Mauricio Pallais
Dr. Ricardo Pico Navarro
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Dr. L. Greenberg
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WORKING GROUP NO. 3

Immediate and Long-Term Needs of the National Drug Control Agencies PAHO's Role in Helping the Countries

Participants

Dr. Sheila Bayley
Dr. Alfonso Bouroncle
Dr. Fernando Cháves Molina
Dr. Joseph J. DiLorenzo (*Moderator*)
Dr. Luis Espinoza (*Rapporteur*)
Dr. Haydée Frómeta de Montás
Dr. Ercilia Oneto
Dr. Carlos Ovalle B.
Dr. Milton Schmidt
Dr. Rogelio Valdés Benegas

Consultants

Dr. José Luis García Gutiérrez
Dr. Solón Suárez
Mr. Olle Wallén

Recent Scientific Publications of PAHO in English

		Price US $
No. 227	Facts on Health Progress. 1971 (70 pp.)	1.00
No. 226	International Conference on the Application of Vaccines against Viral, Rickettsial, and Bacterial Diseases of Man. 1971 *(in press)*.	
No. 223	Reported Cases of Notifiable Diseases in the Americas, 1968. 1971 (72 pp.)	0.50
No. 222	Metabolic Adaptation and Nutrition. 1971 (150 pp.)	2.50
No. 219	Descriptive Methods of Nursing. 1971 *(in press)*	
No. 218	III Inter-American Meeting on Foot-and-Mouth Disease and Zoonoses Control. 1971 (161 pp.)	2.00
No. 217	Guidelines to Young Child Feeding in the Contemporary Caribbean. 1970 (22 pp.)	0.50
No. 216	Health Agenda for the Americas, by Dr. Abraham Horwitz. 1970 (24 pp.)	*Gratis*
No. 211	Regional Advisory Committee on Computers in Health—First Meeting. 1970 (33 pp.)	0.75
No. 208	Financing of the Health Sector—Technical Discussions at the XIX Meeting of the Directing Council of PAHO. 1970 (34 pp.)	1.25
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No. 204	Maternal Nutrition and Family Planning in the Americas—Report of a PAHO Technical Group Meeting. 1970 (53 pp.)	1.00
No. 201	Study Group on the Coordination of Medical Care. 1970 (94 pp.)	2.00
No. 198	Hypovitaminosis A in the Americas—Report of a PAHO Technical Group Meeting. 1970 (33 pp.)	0.50
No. 196	II Inter-American Meeting on Foot-and-Mouth Disease and Zoonoses Control. 1970 (154 pp.)	2.00