CURRENT PROBLEMS IN DRUG CONTROL[1]

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The author discusses in detail some of the more recent technical problems involved in drug quality control, and singles out the gradual move toward the internationalization of concepts and standards. Emphasis is placed on the responsibilities of both official drug control agencies and the pharmaceutical industry for ensuring the effectiveness, safety, and stability of the products distributed.

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)[3] 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."

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

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

in the many recommendations and technical reports of the World Health 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.[4]

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

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 necessitate 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 incompatibilities. Although it has long been known that ascorbic acid, vitamin B_{12} and ferrous iron 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 physiological 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 for 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 ascertaining the usefulness of a sterilization process* and 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 because of the need to prevent delays in the introduction of promising pharmaceutical products and facilitate the withdrawal of dangerous products.

This is a problem to which the World Health Organization has given increasing attention.

Summary and Conclusions

Without attempting to deal in detail with all the problems currently confronting drug control, the paper discusses 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. It is to be hoped 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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