Relations between sales authorisation and pharmacopoeia

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At a time when the production and distribution of drugs and drug products is no longer confined within the national boundaries of particular countries, many thoughtful people are concerning themselves with the idea of standardisation of quality control procedures and specifications.

It is apparent that success in the economic production of drugs requires careful attention to regional, if not international, markets. The pace of merger and consolidation in the pharmaceutical industry is quickening, and one authority (1) has predicted that by 1985 the industry will be dominated by the big twelve international giants.

In the light of this trend, and even under present-day conditions, it is relevant to ask the question: for medicines currently marketed in different countries, is there a rational basis for the existence of multiple standards and specifications for both raw materials and finished products? It is fashionable to say that such a plethora comes from the old days of uncoordinated activities, which will disappear when plans for the regionalisation of drug standards and specifications have been put into operation. Realistic estimates of the situation however agree that such progress, for currently marketed drugs and dosage forms, will be measured and dignified.

Examples abound of drug monographs in different compendia, where, for the same chemical, or its dosage form, profound differences exist in the specifications described and in the methodology to be used to test compliance of marketed products.

In my own country, where national legislation permits some choice of pharmacopeial allegiance, which may be related to the historical background of our country, or to the trading preferences of our industry, quite different specifications for the same drug can be acceptable. My laboratories have been taking note of these differences for many years, and have recently been documenting on an individual basis, the similarities and differences (2). The Pharmaceuticals Unit of the WHO is also engaged in a similar task, and I am pleased to be able to inform you of a very cordial cooperation in this endeavour between our two organisations.

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It is quite true that in some specifications in some of the articles there are very important scientific and commercial reasons why differences should exist — one example may be the need for tests for selenium in sulphur-containing drugs, necessary in some parts of the world where different raw material manufacturing processes introduce an additional healt concern.

However, in many other specifications there seem to be no apparent reason why there should be such differences. The limits for drug content can vary by several percentage points in a dosage form requirement; a test for an impurity can be missing from one compendia, or appear in another with a different degree of stringency; identity tests may have the guileless simplicity of a colour reaction, or the rigid monolithic specificity of some of the spectroscopic tests (ultraviolet absorption spectroscopy excluded); content uniformity tests, absent from some compendia, may be widely used for low drug content dose forms in others; disintegration times vary widely, with great variability in the apparatus used to determine them, and all solid oral dosage forms are not treated alike; dissolution time specifications and methodology exist in some compendia but not in others.

Can we infer any potential consequences from this variability of specification? Can we aver that the population of country X receives inferior medication than country Y because of slightly less stringent specifications? Can we deduce from this that their health care is less effective? Can we suspect that dosage forms found defective in one country might be shipped under a different standard with different labelling into another country, yet meeting all the requirements of the importing country?. Answers to these questions may be in the affirmative and the negative, and we are thus left with the uneasy feeling that a good deal of unnecessary duplication may be going on.

Not only is there the question of differing specifications, there is also the very real problem of the robustness of the methodology which occurs in different compendia and the testing of analytical methods to remove inadequate aspects.

It is not my intention to dwell on the past nor to take to task those who have worked long and arduously in the vineyard. But to ensure that the message is driven home one might mention only a few samples:

Ipecac (adulteration with ephedrine).

In October 1971 the text of the USP monograph for Ipecac and its preparations was revised to incorporate a more specific assay for the two chief alkaloids contained therein, emetine and cephaeline. Column chromatography followed by quantitation using ultraviolet absorption spectrometry rendered the assay much more specific, and enabled a much more robust test (compared to the former titrimetric method) that permitted rejection of material adulterated with ephedrine.

It is interesting that BP 1973 retains the titrimetric method for quantitation; but carries an identification test based on acid–base shakeout separations of the alkaloids and subsequent colour tests.

Warfarin sodium (solvent of crystallisation).

In USP XVII (1965) sodium warfarin was described as an amorphous solid, or a crystalline clathrate consisting of isopropyl alcohol and sodium warfarin. In USP XVI (1960) no reference was made to the clathrate, and in USP XVIII (1970) there is greater detail concerning the varying ratios of drug, isopropanol and water, and the addition of a test for isopropanol. The assay is based on ultraviolet absorption spectrometry utilizing a peak at 308 nm.

The realisation that the preparation of warfarin sodium using isopropanol as solvent could lead to a clathrate formation involving varying molar equivalents of isopropanol, permitted the more precise analysis of warfarin sodium-products without the ambiguity of solvent of crystallisation. These improvements in methodology permitted the resolution of a distressing regulatory-analytical problem.

Phenytoin sodium (presence of benzophenone).

The presence of benzophenone in phenytoin sodium products and raw material has been recently demonstrated. Although one synthetic process for its manufacture requires benzophenone as a starting material no limit tests are described in any of the major pharmacopoeias, except for the IP II where a colour test (conc. NaOH) is described for foreign organic substances.

The very breadth of the problem, with 2309 entries in the North American Pharmacopoeia, and hundreds of counterparts existing in the compendia of European, Asian, and Far Eastern countries suggest that this kind of harmonisation, even given the will, may be slow. And in many cases there seem to be intractable areas of philosophical disagreement.

In one area, it seems to me, there may be greater optimism in looking forward to the possibility of earlier action in reaching agreement on adequate specifications. The process of registration of a new drug substance for the first time presents an opportunity to make known to drug regulation authorities, to academic and industrial pharmaceutical specialists, and other interested parties, the qualities and characteristics of the newly proposed agent and its dosage forms.

We shall need to ask many probing questions concerning the amount of information required, and the manner in which, and by whom, this information might be used. Let me talk first about the second point.

It will seem obvious to the initiated that the life expectancy of a newly delivered drug will be governed by many factors:

– its heredity; does it come from a long line of decaying antecedents, or is it a vigorous new progeny, blessed by some new vital spark?

– its nurture; has it been thoroughly cared for during its gestation. with the objective of verification of all its superior points?

– its peri–natal period; was it blessed with wise and experienced obstetrical and pediatric care in its first exposure to the harsh outside world?

– its siblings; does it have to fight aggressively for sustenance in the face of many established older relatives?

All of these factors and possibly many others will play a part in determining what share of the prescriber's attention the product ultimately gets. And the size of this share will govern the need, nationally and internationally, for a single unique standard for the raw material, and the dose form most favoured by local use.

As a working hypothesis, it will be appropriate that the health authority in the country of initial registration (sales authorisation) will have approved the specification and supporting methodology. And it would seem appropriate at this stage to initiate steps to make as much of this knowledge as is feasible, and appropriate, available to some central authority, fitted to act as both repository and disseminator. I know of no other agency, which by virtue of its mandate, its capability, and its inclination, that is more suitable to this purpose than the WHO. Some ideas are circulating that it would be useful to lay down a data base on pharmacological, toxicological and clinical data for certain drugs, and it would certainly be entirely appropriate at the same time to consider pharmaceutical, chemical, physicochemical, biological, immunological and other data.

How would we draw up a balance sheet of the *pros* and *cons* of this suggestion?

The advantages at present are mainly in the area of preventing duplication of effort in different countries when laying down legally enforceable specifications for drugs which may be marketed on a worldwide scale. There may also be a benefit in the cost of drug production when a single unique specification applies.

The disadvantages may be associated with real or imagined reasons for requiring different specifications in different countries because of:

a) differences in the supply of raw materials in different regions (e. g. the selenium in sulphur–containing drugs may be an example of this);

b) differences in medical practice in various parts of the world (e. g. greater reliance in some areas on botanical drugs; the use of different routes of administration of drugs in some countries (e. g. rectal *vs* oral administration);

c) differences in administrative practices (e. g. the different approaches to sales authorisation in different countries, leading to slower acceptance of new therapeutic agents);

d) differences in synthetic route for the active ingredient raw material, possibly because of patent rights, may lead to different impurity limit specifications in different regions.

A wide range of information will be needed on the chemical, physical, biological and physicochemical properties of the dosage forms as well as the raw materials of the active and inactive ingredients. Many of these requirements have already been described (3).

As a result of a meeting of an Expert Committee on Pharmaceutical Preparations a WHO report (3) described the following data as being relevant to the goal of delineating adequate specifications:

1) name and address of organisation;

2) details and dates of approval of the drug;

3) name of the drug (international non-proprietary name, where available); trade name; chemical name; molecular formula and molecular weight; graphic formula;

4) description, including physical form, colour, odour, taste, etc.;

5) solubility in grams per 100 ml of water, ethanol, ether, chloroform, and other solvents, at a stated temperature;

6) physical data, including: (*a*) melting range; (*b*) freezing point and congealing point; (*c*) boiling range; (*d*) refractive index; (*e*) optical rotation (sodium light, mercury light); (*f*) density in g/ml at a stated temperature; (*g*) spectral absorption (ultraviolet, infrared, nuclear magnetic resonance); (*h*) viscosity; and (*i*) pKa;

7) pH of a solution;

8) chemical reactions suitable for identification;

9) water content: loss of weight on drying, etc.;

10) residue on ignition;

11) description of assay method;

12) results of purity tests;

13) any other information that may be necessary for characterization of the drug and for its safe and effective use in pharmaceutical preparations (e. g. biological tests such as toxicity tests);

14) conditions recommended for storage of the drug.

Since this Technical Report was issued newer scientific discoveries have revealed the need to have available information on many other attributes of the drug and its dosage forms. These include mass spectrometry, x-ray diffraction patterns when polymorphism or crystal habit is a concern. Much

greater attention is being paid to the stability both of the raw materials, finished dose forms, and the impact of the container under recommended conditions of storage.

Toxicological data may be required on degradation products found, or impurities unavoidably carried over from the synthesis or purification steps, where there is doubt that these have been adequately documented.

It is likely that the relative bioavailability of a few dosage forms will have been measured during the final development stages, which may have been compared to the absolute bioavailability of an intravenous solution, provided this is a feasible safe method of administration. Physicochemical stability is required to guarantee long term consistency of biological effect, and both disintegration and dissolution will be tests of obvious value in assuring this. In addition, a dissolution test may also be an invaluable indicator of consistent formulation of the final product, even though the link to biological performance may still be somewhat tenuous.

While all, or nearly all of the above information can be assembled for most synthetic chemicals, for certain complex mixtures, or for antibiotics, or for hormonal substances or others of biological origin, such precise definition may not be possible. Adequate data to assure identity, consistency, and homogeneity of the material would be required.

Let me address myself for a moment to a very important aspect of disclosure of information concerning drug specifications. Divulging information can be a two-edged sword: in one sense disclosure can publicly reveal a high quality standard having stringent specifications which would clearly then set the tone for all subsequent products, whether on patent expiry, or by compulsory or voluntary license; on the other hand there is a risk that some detail of a specification, for it to be meaningful, might point to, or suggest, an aspect of the drug or its dosage form that could be considered a trade secret, or part of the confidential knowhow of the manufacturer.

How valid is the logic behind this last point? In some countries (and Canada is one of these), there are certain basic differences between the New Drug Specifications and compendial specifications. New Drug Specifications are written for each individual drug and formulation of a particular manufacturer, and are regarded as primarily concerned with providing a basis for the legal enforcement of drug regulations. They may not be changed without mutual agreement between manufacturer and the health authority. They are regarded as confidential, in Canada, and have not been shared, except by prior agreement, with other parties. We are aware that some of these attitudes are now changing, and there is a greater spirit of willingness to share information submitted at the time of registration. Great progress has been made in finding common agreement, in an overwhelming number of cases, on non-proprietary names, whether these be INN, USAN, or

Approved Names. In Canada, we refer to them as common names, because there is a common understanding of their significance, and a wish that they become more common throughout the world!

It is time that this inclination towards sharing be extended towards information on drug specifications at or around the time of registration.

In this connection it is appropriate to examine the proposals of an agency of one country that has attempted to define to what extent information can be shared. The country has been chosen because the information is easily available to me, and is current. The FDA proposed in the Federal Register of 24 Dec. 1974 a complex and voluminous set of regulations dealing with Freedom of Information.

Part of the information described in the Code of Federal Regulations referring to the Freedom of Information situation read as follows:

« The following data and information submitted voluntarily to FDA are available for public disclosure unless extraordinary circumstances are shown »; [4. 111. (c)].

« An assay method or other analytical method, unless it serves no regulatory or compliance purpose and is shown to fall within the exemption established † 4. 61. ». [4. 111. (c) (5)].

This seems to establish clearly that analytical methodology is intended to be included as disclosable material.

The regulations then proceed to define cases where information is *not* available for public disclosure and reads as follows:

« The following data and information submitted voluntarily to FDA are not available for public disclosure unless they have been previously disclosed to the public as defined in † 4. 81 or they relate to a product or ingredient that has been abandoned and they no longer represent a trade secret or confidential commercial or financial information as defined in † 4. 61 »: [4. 111. (d)].

« All safety, effectiveness, and functionality data and information for a developmental ingredient or product that has not previously been disclosed to the public as defined in † 4. 81 ». [4. 111. (d)] (1).

This information is then amplified to describe more specifically what is intended by the terms safety, effectiveness, and functionality as follows:

« For purposes of this regulation, safety, effectiveness, and functionality data include all studies and tests of an ingredient or a product on animals and humans and all studies and tests on the ingredient or product for identity, stability, purity, potency, bioavailability, performance, and usefulness ». [4. 111. (e)].

You will notice that there is an exception in one regulation († 4. 81) which deals with the authority to divulge non-disclosable information if

there has been previous public disclosure of that information. It would be of interest to know whether the information concerning assay methods. identity, stability, purity, potency, bioavailability, etc. would be considered public disclosure when made available to the non-governmental compendial authorities or to any of their duly constituted committees.

The consequences of some of these regulations will need very careful study to determine what information is freely available, and as a consequence what could legally be anticipated at the time of registration of a drug.

The legal systems in other countries will need careful scrutiny to ascertain what limitations, if any, would be placed on disclosure of analytical methodology and specifications for newly registered drugs.

It is certain that there will be many complications and difficulties to surmount before standardized procedures can be worked out for early sharing of this valuable information. It is equally certain that undesirable duplication, complexity, waste of resources and proliferation will occur if we cannot soon work to this end.

Summary. — At a time when the production and distribution of drugs and drug products is no longer confined within the national boundaries of particular countries, many thoughtful people are concerning themselves with the idea of standardisation of quality control procedures and specifications. For medicines currently marketed in different countries, a multitude of standards and specifications for both the raw materials and finished products exists. Plans for the regionalisation of drug standards have been put into operation but realistic estimates of progress agree that it will be measured and dignified. In one area there is the possibility for earlier action in reaching agreement on adequate specifications. The process of registration of a new drug substance for the first time presents an opportunity to make known to drug regulation authorities, academic and industrial pharmaceutical specialists, and other interested parties, the qualities and characteristics of the newly proposed agent and its dosage forms.

A wide range of information will be needed on the chemical, physical, biological and physicochemical properties of the dosage forms as well as the raw materials of the active and inactive ingredients. Many of these requirements have already been described (3). There may be apprehension that the disclosure of some of this information could imperil the confidentiality of certain manufacturing processes or trade secrets, and adequate steps would be demanded to prevent this happening. The promulgation of a standard, at or shortly after the time of registration, should have been preceded by experimental tests, in the laboratories of the Authority, to verify the robustness of the analytical methodology. In some cases more extensive confirmation by collaborative study may be warranted.

The elaboration of these concepts will be presented and examples brought forward of problems that have occurred in the past, and means to prevent them in the future.

Résumé (*Rapport entre l'autorisation à vendre et la pharmacopée*). — Puisque la production et la distribution des médicaments et des produits pharmaceutiques s'étend à présent bien au delà des frontières nationales, nombre de personnes prévoyantes ont abordé l'idée de spécifier en détail et de standardiser les systèmes du contrôle de qualité des medicaments. Pour les médicaments vendus à l'heure actuelle dans les divers pays, il existe une quantité de règlements standardisés et de spécifications concernant les matières premières aussi bien que les produits finis. Des projets pour règlementer par régions les standards des médicaments ont été mis en œuvre, mais l'on prévoit que le progrès sera lent et limité. Il y a un champ ou l'on envisage la possibilité d'arriver bientôt à un accord pour établir des spécifications satisfaisantes. Le procédé concernant l'enregistrement de substances nouvelles offre une excellente opportunité pour faire connaître aux autorités sanitaires, aux spécialistes des universités et de l'industrie pharmaceutique, et à d'autres personnes intéressées, les caractéristiques, les qualités, et le type de la composition de la nouvelle substance.

Des informations détaillées devront être fournies pas seulement à l'égard des propriétés chimiques, physiques, biologiques et physico-chimiques des différents produits, mais aussi des matières premières et des ingrédients actifs et inactifs employés dans la préparation. Plusieurs de ces requêtes ont été déjà décrites. Néanmoins, il y a le danger que la divulgation de certaines informations puisse mettre en risque le caractère confidentiel de certains procédés de production et de distribution. Il faudra donc prendre des mesures afin de prévenir et éviter de tels inconvenients. La promulgation d'une mesure standard au moment de l'enregistrement, ou peu après, devrait être précedée d'expériences scrupuleuses exécutées dans les laboratoires des autorités sanitaires afin de contrôler la validité de la méthode analytique suivie. Dans certain cas, l'on pourrait exiger l'exécution en collaboration de recherches plus approfondies.

L'auteur a presenté ici l'élaboration des idées décrites plus haut et a fourni aussi des examples de problèmes qui se sont présentés par le passé et les moyens pour les prévenir à l'avenir.

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Information chapter sin pharmacopoeias

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The original objectives of the United States Pharmacopoeia (USP) are clearly delineated in the preface to the first edition, published in 1820. The opening paragraph of the preface states: « It is the object of a pharmacopoeia to select from among substances which possess medicinal power, those, the utility of which is most fully established and best understood; and to form from them preparations and compositions, in which their powers may be exerted to the greatest advantage. It should likewise distinguish those articles by convenient and definite names, such as may prevent trouble or uncertainty in the intercourse of physicians and apothecaries ».

Paraphrased in contemporary terms, the preface says that the major functions of a pharmacopœia are: to choose the best drug substances in the current *materia medica*; to standardize these substances and the most effective dosage forms containing them; and to name them simply and unambiguously. These doctrines have always remained the guiding principles for USP activities.

Immediately after the opening statement of purposes, the preface to the first USP continues prophetically: «The value of a pharmacopoeia depends upon the fidelity with which it conforms to the best state of medical knowledge of the day. Its usefulness depends upon the sanction it receives from the medical community and the public; and the extent to which it governs the language and practice of those for whose use it is intended ».

From 1820 onwards, USP has been recognized among the medical and pharmaceutical communities as an authoritative compendium of drug standards. Although it has been and is still issued under the auspices of a non-governmental institution, it has also continuously enjoyed the sanction of public ratification. In 1906, when the Pure Food and Drug Law was enacted as the first federal legislation in the United States to control the production and distribution of drugs in interestate commerce, the Congress officially confirmed certain requirements of the then current USP as legally enforceable standards. Thus, the standards and tests in USP monographs became official regulatory instruments for drug control. This status was

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reaffirmed in the Federal Food, Drug and Cosmetic Act of 1938, and it remains in effect to this day.

USP has relied upon a volunteer group of scientists, the Committee of Revision, to maintain conformity of its standards and tests to the best state of medical and pharmaceutical knowledge of the day. Under their guidance, complete revisions of the pharmacopoeia have been published periodically — every ten years during the nineteenth century and every five years more recently. Because of the rapid progress in contemporary medical and pharmaceutical sciences, USP has now adopted a program of continuous revision.

Over the course of the years, USP Committees of Revision have also undertaken to instruct the users of the pharmacopoeia about scientific advances bearing upon the preparation and preservation of drugs; about the theory and practice of analytical techniques for the examination of drugs; about drug usages; and about regimens and modes of administration. Similarly helpful information has appeared in all modern pharmacopoeias. Unfortunately, however, informational passages sometimes have been incorporated in the monographs and appendices in such a manner that they have been inextricably intertwined with the statements setting forth the standards and the directions for analytical testing. An entanglement of this kind inevitably blurs the mandatory requirements and vitiates their enforcement by the regulatory agencies. This consideration is of vital importance.

The relationship of pharmacopoeias to regulatory agencies has been profoundly influenced by two significant changes in medical and pharmaceutical practice during the past decades. First, large manufacturing establishments gradually replaced independent apothecaries compounding prescriptions in their individual pharmacies as the main source of dosage form production. Later, the proliferation of powerful but potentially hazardous drugs brought public demands for stringent centralized regulatory control. As a direct result of these developments, governmental agencies have been given increased responsibility not only to enforce mandatory pharmacopoeial standards more vigorously, but also to approve the processes and quality control programs proposed by manufacturers for the preparation of new drugs, to inspect the plants of drug producers periodically, and to ensure that drug fabricators comply with the current good manufacturing practices regulations promulgated by agencies of the government. In the United States, amendments to the Federal Food, Drug and Cosmetic Act and related legislation have also empowered the Food and Drug Administration to designate official names for drugs, superseding all other assigned names; to certify all batches of insulin and antibiotics for human use prior to distribution; and to issue licenses for the legal preparation and distribution of toxins, antitoxins, therapeutic sera, viruses and related biological products for human use.

These sweeping changes have radically affected the relationship of pharmacopoeias to regulatory agencies and they have altered the nature of the clientele to whom pharmacopoeias are addressed. Nineteenth century pharmacopoeias were intended for use primarily by physicians and pharmacists. Contemporary pharmacopoeias are intended for use by analytical scientists in regulatory agencies, in manufacturing plants, and in laboratories operated on behalf of purchasers. Because of the changes in drug manufacturing practices, in governmental responsibilities and initiatives, and in the needs of the clientele served by pharmacopoeias, it is now necessary to reorient and refine the contents of the official compendia.

In earlier times, drug monographs were simple descriptive essays. The quality, purity and strength of drugs were thought to be fully assured if preparative processes for ingredients and mixtures were adequately described. No analytical tests were provided to test the validity of this assumption. Today, the thrust of pharmacopoeial standardization is diametrically opposed to that simplistic approach. Pharmacopoeial standardization now depends almost exclusively upon physical, chemical, and biological tests that measure the properties and performance of the product proposed as an article of commerce. The official monograph for the article is comprised of a set of criteria or specifications, together with analytical test methods capable of determining whether an individual specimen of the product meets its specified criteria. Statements clarifying the purport of the standards and tests and requirements concerning packaging and labeling are provided in general notices and appendices. Textual material not directly related to standards, test methods, packaging and labeling is for the information of the reader, and is not considered legally enforceable.

It should not be inferred from the preoccupation of pharmacopoeias with final product testing that the quality and the purity of ingredients and intermediates, and the proper fabrication of drugs in accordance with the best manufacturing practices are no longer considered significant. On the contrary, they are of the utmost importance to the quality of the final product. But pharmacopœias are no longer recognized as authoritative vehicles for transmitting instructions and safeguards governing these considerations. Responsibility for these concerns are now vested in governmental regulatory agencies and in manufacturers' quality control systems. While pharmacopoeial bodies may offer suggestive proposals as to what could and might be done in that domain, they are not in a position to direct what should and must be done. If they now attempt to assume this function, the undertaking can only lead to conflict and confusion.

To avoid such confusion, the Committee of Revision has attempted to separate all informational passages in USP XIX from legally enforceable provisions, and to distinguish clearly between these two different kinds

of textual matter. In the monographs for drug substances, the structural formula, the molecular formula, the molecular weight, the scientific names, therapeutic category, description and solubility are presented before the definition rubric. The definition and all that follows are legally enforceable requirements. Similarly, for monographs on dosage form articles, information about the therapeutic category, usual dose, usual dose range, and available sizes precede the definition rubric and the mandatory requirements that follow it. The USP XIX monographs on diethylstilbestrol and diethylstilbestrol injection exemplify this principle of separation. In the appendix section of USP XIX, chapters pertaining to official requirements are first set forth, and information chapters are segregated in a group entitled « General Information ». The introduction to this group of chapters states: « The chapters in this section are primarily informational, and they contain no standards, tests, or assays, nor other mandatory specifications, with respect to any pharmacopoeial article. In some instances, particularly in the chapters on *Antibiotics* and *Biologics*, they outline briefly or refer to official requirements that are to be consulted elsewhere. The official requirements for pharmacopœial articles are set forth in the *General Notices* (p. 1–9), the individual monographs (p. 11–580), and the *General Tests and Assays* chapters (p. 582–672) of this pharmacopœia ».

Among the titles of information chapters in USP XIX are: « Automated Methods of Analysis »,« Pharmaceutical Dosage Forms », and« Sterilization ». The relationship of the last–named information chapter to the chapter on « Sterility Tests » illustrates the need for a line of demarcation between text that contains directions for the execution of an official test method and text merely intended to edify.

In USP XVIII, p. 854–856, the directions for performing the sterility test were dependent on the process whereby the test article had been sterilized. Note that the table, « Procedural Details for Sterility Tests » prescribes different sample sizes and different incubation times depending upon the mode of sterilization and the use or non–use of biological indicators. But a pharmacopoeial test must be applicable by all analysts as written, regardless of prior knowledge about the past history of the article. The chapter on Sterility Tests in USP XVIII might have been a useful guide for the manufacturers' quality control laboratory, but when utilized as a regulatory tool or as a purchaser's criterion of purity, its instructions resulted in ambiguities.

After much deliberation among its advisory panels, the Committee of Revision deciced to place explicit directions for performing a sterility test on pharmacopoeial articles in the chapter entitled « Sterility Tests » and to isolate educational text in the information chapter on « Sterilization ». Cross references are provided to relate the two chapters, and the function of each is explicitly stated. Note in particular the statement on p. 593 in

USP XIX: « Where a sterility test is applied to discrete units drawn from a group of similar units, the results obtained cannot be extrapolated with certainty to characterize the sterility status of the units that remain untested. For this reason, no sampling plan for applying sterility tests to a specified proportion of discrete units selected from a sterilization load is capable of demonstrating with perfect assurance that all of the untested units are in fact sterile. For the purpose of establishing and validating acceptable confidence levels regarding the sterility status of a sterilization load, it is necessary to take into consideration a number of operational factors relating to the design and execution of the sterilization process (see *Sterilization*, p. 709) ».

Note also that in the chapter on « Sterilization », USP XIX, p. 712, Table 2 on sampling and procedural conditions in performing the sterility tests is entitled « Suggested Procedural Guidelines in Utilizing Sterility Tests as an Adjunct for Assessing the Effectiveness of sterilization Processes ». The entire chapter on « Sterilization » is presented in the form of suggestions and not in an imperative style. In the United States, imperative directions on how producers shall sterilize drugs are the province of the manufacturers' operational quality control systems and the good manufacturing practices regulations promulgated by the regulatory agency; they are not in the province of USP.

The modern national pharmacopoeia is charged with important responsibilities. It must develop and issue appropriate standards and test methods suitable for use as instrumentalities in the regulatory control of drugs. It must also continue to indoctrinate pharmacists and allied health professionals in the proper handling and use of pharmacopoeial articles and in the preparation of drugs that are compounded in hospitals and pharmacies. National pharmacopoeias can best fulfill both of these functions by maintaining a strict line of demarcation between text that presents mandatory requirements and information chapters that are intended solely for indoctrination.

Summary. — Pharmacopoeias have been established by governmental authorities to serve three primary purposes: 1) to compile a select list of currently utilized drugs, including the most efficient forms for their application; 2) to distinguish these articles by convenient and definite names; and 3) to publish objective standards and analytical methods suitable for testing the integrity of commercially available preparations. In addition, some pharmacopoeias also offer informational text intended to instruct pharmacists on the compounding, use, storage and labeling of drugs; to advise physicians about dosage regimens and preferred modes of administration; to counsel producers about good manufacturing practices, and to edify drug analysts

by explaining the theories underlying methods employed in compendial tests and assays. Examples of informational chapters in USP XIX are those on Pharmaceutical Dosage Forms, Stability Considerations in Dispensing Practice, and Sterilization.

Because of the official status of national pharmacopoeias and their use as regulatory instruments in drug control, pharmacopoeial text intended merely for the information of the reader should be identified as such, and should be separated and distinguished from the mandatory, legally enforceable requirements.

Résumé (*Chapîtres informatifs des pharmacopées*). — Les pharmacopées ont été établies par les autorités gouvernementales pour atteindre surtout trois buts: 1) rédiger une liste selectionnée des médicaments d'usage commun et des formes les plus efficaces pour leur application; 2) identifier ces médicaments avec des noms convenables et précis; 3) publier des standards objectifs et des méthodes analytiques les plus convenables pour contrôler l'integrité des préparations existantes sur le marché. En outre, il y a des pharmacopées qui contiennent des chapîtres informatifs dédiés à: instruire les pharmaciens sur la composition, l'emploi, le magasinage, et les façons de marquer les médicaments; informer les médecins sur le dosage et sur les ordonnances les plus appropriées; fournir des avis aux producteurs sur les meilleures méthodes de production; expliquer en détail aux analystes de médicaments les théories sur lesquelles sont fondées les méthodes employées pour les analyses et les épreuves. Des examples de chapîtres informatifs de la Pharmacopée des Etats Unis sont ceux qui regardent les formules de composition pharmaceutique, les façons d'application et la sterilisation.

En vue de la nature officielle des pharmacopées nationales et de leur emploi comme instruments règlant le contrôle des médicaments, les parties de la pharmacopée dédiées uniquement à l'information des lecteurs devraient être identifiées comme telles; elles devraient être aussi bien séparées des sections qui regardent les dispositions légalment obligatoires.