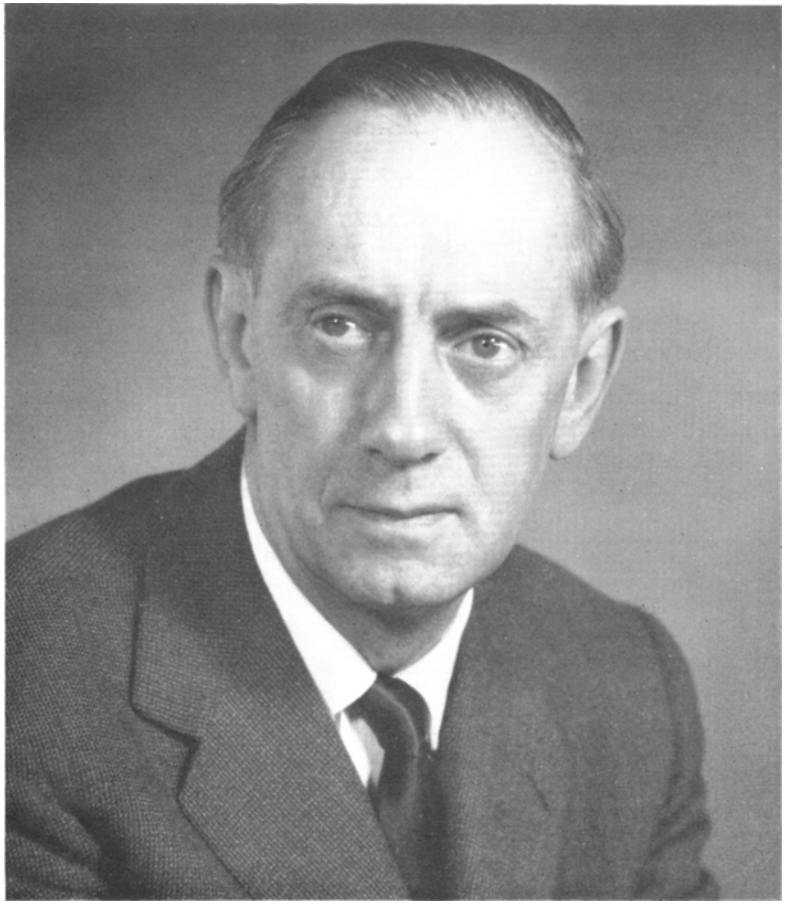

D. C. GARRATT

Chairman, 1961

BRITISH PHARMACEUTICAL CONFERENCE
Portsmouth, 1961

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CHAIRMAN'S ADDRESS

ANALYSIS ANALYSED

A More Rational Approach to Pharmaceutical Control

Few would dispute that in the last decade analytical chemistry has developed its potential value more rapidly than in the previous fifty years.

Analysis has now broken out from its earlier restricted sphere and become a completely new concept with the right to be considered a discipline in itself. Its phenomenal expansion, mainly due to new instrumental methods and a widening of their application, has been as much of value in the field of pharmaceutical production as in any other branch of industry.

This increase in the availability of analytical tools and techniques coincides with the necessity for more rigorous control of the potent drugs now available. Stricter control is also necessitated by modern methods of manufacture and filling, among which might be mentioned the use of new materials as containers, plastic closures, aerosol packs, and more exacting requirements in packaging and storage for overseas markets, and this further increases the responsibilities of the pharmaceutical analyst. With this change in the scope of analysis it is inevitable that more elaborate testing is applied.

The trend in the stringency of drug control can be seen by comparison of successive editions of the B.P. or B.P.C. Unfortunately this results in greatly increased costs of analysis; the instruments are costly and the skilled analyst has become more specialised and thus more expensive. This increase in costs, although small compared with other factors—particularly the price of the drug itself—must nevertheless be reflected in the price of the finished preparation. Further to complicate this situation legislation is contemplated for the stricter control of the price of medicinal products.

The rising cost of the National Health Service and, of course, the normal commercial hope of more economical production of drugs should justify a search for all causes of the present costs. The cost of analytical control must be considered amongst these and not accepted without question—which it often is—as a necessary overhead. As a contributory factor in the general cost of drugs, it would be as well to find its value and make some attempt to reduce it. It is my intention now to consider in more detail some of the reasons for this increasing "overhead", to outline some ideas on methods for reducing it and to question whether we are making the best use of our analytical resources. I shall digress from the main theme from time to time to consider various dependent

issues where it seems relevant to do so, but not losing sight of the main topic of cost. I shall conclude with some suggestions on the overall problem of the general aspects of pharmaceutical control.

A large analytical laboratory dealing with a multiplicity of products has the advantage that it can obtain information on costs which is of general application; very distorted figures can be obtained from assessment of more specialised work. The figure often calculated, particularly in the United States, is the percentage of the total production costs that is due to control. This may be unrealistic when the production costs include basic materials of substantial value and a better comparison is to relate control to the total overheads of production. To quote actual figures would be misleading since each firm has a different costing system but for my own laboratory, cost of analytical control as a percentage of total production overheads has risen significantly over a recent five year period from 7·07 to 8·02.

Further, a breakdown of these costs shows that staff salaries and pensions accounted for 74·1 per cent in the first year of this period and 79·1 per cent in the fifth year and it is fair to conclude that the major reason for increased costs is the increase in the market value of analysts, particularly if they are qualified. Therefore the most effective way to reduce costs is to reduce staff. Moreover, at the present time, analysts are at a premium and to reduce the need for them will help relieve the scarcity. It might be thought that a saving of costs could be effected by replacing qualified staff by skilled technicians of National or Higher National Certificate standard for much of the laboratory work where less responsibility is required, but at the present time technicians are even scarcer than graduates.

A Need for Analysts

One might pause here to enquire why there is a shortage of analysts. This is a national problem and not confined to one section of industry although, with the necessity for rigorous control in the rapidly expanding field of pharmaceutical products, the shortage is probably more acute there than elsewhere. The fault lies at the door of both industry and the academic institutions. In the past, the analyst has been the "poor relation" of the chemical profession and little encouragement had been given to any chemist to adopt analysis as a career. It must be admitted that much of the control work possible with the limited tools and methods available up to post-war times could have been done by a lower calibre of chemist than is needed today. Only if an analyst had a wide experience was he in demand and much of pharmaceutical analysis was unpublished work. However, since then the wide variety in methods available and the manipulative skill required in their application has increased so rapidly that it has become impossible for them to be assimilated by any but chemists devoted to analytical work as a profession; indeed specialists are already emerging from within the analytical field.

The rapidly increasing importance of the subject has been recognised in appointments to Chairs of Analytical Chemistry at Birmingham and

Belfast. Colleges of Advanced Technology in their contacts with Industry have realised the need for education in this specialised "profession within a profession" and are establishing Readerships in Analysis. Postgraduate courses are also being prepared. Nevertheless we must be deeply concerned not only at the scarcity of properly trained analysts but also at the apparent disinclination of chemists from the Universities to choose analytical chemistry as a career—mainly because they have little idea what modern analytical chemistry offers; serious active consideration should be given to means of inducing graduates to enter this kind of work.

No one would doubt that it is as necessary as in any other chemical career to give potential analytical chemists a good basic knowledge of chemistry in their degree course. However, I venture to suggest that analytical chemistry is becoming so important nationally that the time has come when more consideration should be given to the creation of an applied chemistry course in analytical chemistry, where the curriculum, at least in the final year, could be devoted to training in the specialised needs of the subject, with graduation in analytical chemistry. Analytical chemistry could also be accepted as a subject for diplomas in technology. Thus industry would be saved much valuable time in such training after graduation.

Pharmaceutical analysis is one specialised part of the analytical field with its own particular skills and it has undoubted justification for consideration as a branch of pharmaceutical study in its own right. The subject is of sufficient extent to be considered suitable for Diploma of Technology courses or, better, for a specialised course in pharmaceutical analysis after a Diploma of Technology. Pharmacy should not let pharmaceutical analysis remain largely in the hands of non-pharmacists; it is surely a strange situation that a large proportion of the leading pharmaceutical manufacturing houses in this country now employ a non-pharmacist as chief analyst.

Pitfalls of Assay Changes

The main cause for the increase in the amount of analytical control is the increased testing required on potent drugs and their formulated products, especially those used parenterally where it is necessary to do tests for sterility, toxicity, pyrogens and so forth. The most valuable contribution to the saving of man-power in pharmaceutical laboratories is the replacement of chemical methods by physical techniques and the adaptation of these to routine analysis. Papers have been given to this Conference from time to time on the application of such techniques as emission spectrography, flame photometry, ultra-violet, infra-red and fluorescence spectroscopy and gas-chromatography, all of which offer considerable advantages of speed in routine analysis.

It is certainly necessary to take all reasonable precautions against impurities in drugs but are all our tests necessary, each telling us something of value? If we are to spend money on analytical control let it be on testing that is worthwhile! Are all our expensive biological tests necessary? Need Protamine Zinc Insulin be tested for delayed activity if it contains

the right amount of insulin and protamine and the pH is correct? In replacing a "classical" determination by a modern technique are we gaining anything or just persuading ourselves that because it is new it must be better? Is it less expensive in apparatus, reagents, and time? Every time we change a specification or method of analysis we should be sure that it is an improvement.

A carefully controlled comparison was made of the cost of five different methods of assay available for determining the purity of one pharmaceutical chemical.

	Actual manipulative time (min.)	Total time	Cost of analyst's time s. d.	Reagent cost s. d.	Total cost s. d.
Non-aqueous titration	17	17 min.	8 6	4	8 10
Kjeldahl nitrogen	22	3¼ hr.	11 0	7	11 7
Extraction of base	30	1½ hr.	15 0	3 6	18 6
Bromination	17	50 min.	8 6	6	9 0
Ultra-violet absorption assay (solvent, water)	20	20 min.	10 0	0	10 0

Since only costs are being considered, let it be assumed that all methods are of equal accuracy. Comparison of these figures indicate that from consideration of both cost and time extraction is least economical. The others are little different in cost but the Kjeldahl method takes a long total time and bromination rather long. Non-aqueous titration and ultra-violet absorption are equivalent and take least time; since ultra-violet absorption assay is the more specific it is the method of choice. Nevertheless, had the chemical needed a solvent other than water for solution the cost of this would have significantly affected the assessment. For example, had the solvent been cyclohexane, the reagent cost would have been 1s. 8d., with chloroform, 3s. 4d., and with alcohol, 6s. 0d.

The compilers of our official publications should bear these considerations in mind.

Assay Precision

In my opinion there is little justification for many of the assays at present applied to the large range of pure synthetic drugs, yet it would seem that the aim is to include an assay wherever possible. Much time must be spent in laboratories all over the country indulging in this extravagance. Before deciding on a minimum acceptable purity for production material, the assay must be fixed. In most cases no figures are available of the variation to be expected in replicate analyses and I an confident that, with few exceptions, this assessment is not done; without this knowledge the purity figure fixed as minimum is meaningless. Strange though it may seem a bioassayist has an advantage over his chemical counterpart since, although his errors are large he does at least know their extent. How can the tightening of a standard for a drug from 98·5 to 99·0 per cent be justified when assay differences of 0·5 per cent are accepted in duplicate tests? It is very comforting to get an assay

result within the minimum standard demanded; if it is not the assay is repeated; with a good result on this second test, of course the first one was an error and the material is "up to standard". Or the more careful analyst might do a third assay to decide which of the earlier two results was correct; it is an even chance that the third result will agree within a reasonable difference with one or the other. Again, if it is close to the upper figure the quality of the material is accepted as satisfactory although the conclusion can be far from the truth.

There are a number of assays based upon measurement of ultra-violet extinction. This is basically a bad technique to use unless reference standard materials of high purity are available for analysis by comparison. Up to now the E(1 per cent, 1 cm.) values chosen for calculation have been obtained from data supplied by manufacturers and users and are either an average from a recorded range, which may be quite wide, or the highest known value; therefore if the E(1 per cent, 1 cm.) value for the pure material is not known the standard adopted is based on a commercial product as optimum and the final minimum purity figure is correspondingly low. Coupled with this anomaly the existence of instrumental variation must be recognised. Hence the present use of ultra-violet spectrophotometric assay as a measure of the purity of a fine chemical is unrealistic.

An even more reprehensible setting of an assay standard is associated with an added tolerance allowed because of the known non-reproducibility of results by the assay method adopted. This may be acceptable when determining the amount of an ingredient incorporated in a formulation, but as a basis for assessing the purity limit for a chemical it can have no value since it is allowing an added impurity tolerance up to the spread of the assay precision.

Although I would prefer to see most assays of pure substances deleted since they are only an added identity test of little specificity and the criteria of purity are concerned with the other substances present, assays are likely to stay in the present form of monograph or specification. If so, they can only be made worthwhile, when the precision of the assay is unknown, if the sample under test is assayed against a standard material of known purity under identical conditions. In this way, for example, extinction measurements by differential spectrometry can be applied to a limiting precision (due to variables in the instrument, light source, light scatter, cell imperfections) of 0·1 per cent.

Hence there is an urgent need for a bureau for maintainance of a collection of highly purified medicinal chemicals in which the amounts of any impurities are accurately known. An international collection is so cumbersome a means of establishing standards that a national collection is the best workable method. It would take some time to collect the necessary materials but if, in the future, manufacturers introducing a new drug on the market were required to provide an adequate supply of pure material as primary standard the task would be lightened considerably. The bureau should be under the control of, or in collaboration with, an organisation where full facilities are available for accurate physical measurements and must be prepared to study the materials

collected for standards with the full armoury of modern techniques (X-ray crystallography, mass-spectrometry, zone refining, and so on) in assessing purity.

There is also a need for analytical research for more specific tests of identity and assay. The analyst can hardly be blamed for shortcomings in this matter since the multiplicity of drugs being introduced in such a short period has given him far too little time. However, it is a vital need, particularly with the marketing of chemicals of closely similar chemical composition but different pharmacological activity or action. At present these often have little in the way of tests by which they may be distinguished, particularly when in admixture or in formulated products; one might mention, for example, stilboestrol and dienoestrol, prednisone and hydrocortisone, adrenaline acid tartrate and noradrenaline acid tartrate. Such problems are undoubtedly exercising the minds of various standardising committees.

The following example will illustrate the need for vigilance in the standards set for drugs. The application of the triphenyltetrazolium chloride assay (which is specific among steroids for 17,21-dihydroxy-20-oxosteroid) to different corticosteroids obtained from various sources, has shown that specimens can comply with all the official requirements but be deficient in content of 17,21-dihydroxy-20-oxosteroid to a considerable extent. This is illustrated in the comparison of analytical figures specified by the B.P. and U.S.P. monographs with those found on a sample of hydrocortisone acetate.

	B.P. standard	U.S.P. standard	Sample figures
Specific rotation	+157° to +167°	+158° to +165°	+159·1°
Loss on drying (maximum)	1 per cent	1 per cent	0·02 per cent
Sulphated ash (maximum)	0·1 per cent	negligible	0·02 per cent
Melting point	about 220°	216° to 222°	218·4°
Assay (ultra-violet)	96 to 104 per cent on dried material		101·3 per cent
"Tetrazolium" assay			90·5 per cent
Related foreign steroids		complies	

The sample would have satisfied a routine identity test by infra-red examination. This example does emphasise the need for devising tests of greater specificity. Paper chromatography will certainly have to play a part in characterising substances and detecting admixture.

Hence, there is a rapidly growing need for reconsideration of our conventional monographs and development of other methods of differentiation of organic substances, together with better appreciation of the true value of the purity tests used to establish the nature and quantity of impurities present to any significant extent. To implement this concept it must be presupposed that the latest instrumental techniques are now within the scope of the normally equipped laboratory; the plea that equipment is too expensive is no longer tenable since, as already indicated, the analyst is by far the greatest cost. Mention might be made of the greater significance of possible trace residues of highly toxic catalysts than of the so-commonly sought impurities, lead and arsenic. I suggest that

a monograph of the not-too-far-distant Pharmacopoeia might include such requirements as:

> Concentrate the impurities by the zone refining procedure (see Appendix), with a downward movement of the zones, at a rate of 2 cm. per hour, and 15 zone passes (carrying out the operation under nitrogen and maintaining the apparatus at a temperature of 0° C.). Remove sections 5 cm. long from the bottom, from the top, and from the centre of the column and prepare a mass spectrogram from each section (see Appendix).
>
> The section taken from the top of the column should show no more impurity than that taken from the centre of the column. Compare the mass spectrogram of the material from the bottom of the column with that from the centre of the column and estimate the amount of impurity in the bottom section. The amount of impurity indicated in the original material by this procedure should not be greater than 0·5 per cent.

A discussion on assay precision cannot be confined to the drugs themselves. Some latitude in the results can be tolerated when methods are applied to the determination of the quantity of drugs in formulated products since the present official limits are based on an allowance for manufacturing variation plus the minimum allowable purity of the drug used. Although it has already been shown that the standard for the drug used may be fallacious, the allowance for manufacturing error is generally more generous than a good commercial manufacturing firm would need (being given to cover extemporaneous preparation in pharmacies) so no difficulty is encountered in meeting the requirements. However, the more complex a formula becomes, the greater the errors of assay introduced and, therefore, even the present tolerances, generous though they may seem, may not be sufficient. Let me illustrate this with an example:

Compound Codeine Tablets were manufactured without the codeine phosphate; these tablets were powdered and intimately mixed with previously assayed codeine phosphate to give a known content of this ingredient within the B.P. limits. Portions of the powder were sent to analysts whose reputation for accurate work is beyond question with a request for a B.P. assay of codeine to be done; no indication was given that this was a collaborative trial. All results were within the B.P. limits but the spread was 9·2 per cent.

The result is not surprising; the assay is difficult, involving the determination of a small quantity of codeine in the presence of a large amount of other drugs, and many attempts have been made to improve its accuracy. The above example was only one of a number of collaborative trials with similar findings.

There have been, from time to time, allegations that certain less reputable manufacturing firms are deliberately using a quantity of drug to the minimum tolerance. This may be true but with such a spread of results possible are we sure we are justified in our contention, remembering that many firms may be showing higher results only because they add a small overage for safety and the particular assay may give low results generally?

Strict control of pharmaceutical manufacture is a necessity but more common sense must be shown in the judgment of borderline cases until more work has been done in assessing the precision of the assays (for which a considerable amount of investigation would be demanded) and

until national reference standard drugs are available for differential analysis. This thought is disturbing but analysts must be shaken out of their present apparent complacency regarding the accuracy of their results, since accuracy is essential to their professional reputation.

Hidden Costs

In assessing analytical costs the amount of testing of materials bought and manufactured and the cost of staff are obvious concerns, but there are smaller and hidden expenses which are worth mentioning; these added together are not to be ignored in the increasing costs of pharmaceutical control.

The need for analytical research into the precision of assays and for devising methods of greater specificity has been stressed. In this matter a re-assessment of older methods is worthy of consideration. There is also constant adaptation of new techniques to the special problems associated with pharmaceutical analysis. The comment is often made that such methods, usually involving expensive apparatus, are suitable for large laboratories but not applicable in smaller units. Admittedly larger laboratories have the facilities for the initial investigation and adaptation but many smaller laboratories either make no effort to apply these time-saving techniques or do not use their instruments fully, only applying instrumental techniques in official or recognised methods.

Industrial pharmaceutical laboratories do extensive voluntary work into analytical methods on behalf of official standardising committees and I know the committees are grateful for the help. Nevertheless the cost must be noted.

Control of packaging materials and packed goods and shelf-life assessment for all the new closures and presentations take up time not always directly assessed as analytical charge.

Another charge to the analytical services is sometimes overlooked. Pharmaceutical firms have to prepare a considerable number of documents to register their products overseas. Usually the importing country demands full specifications and methods of determination of all active ingredients—in some instances all ingredients, active or not.

A hidden cost of analysis may result from the time samples are held before reporting. For expensive drugs the value of the stock investment may be considerable.

The employment of trained method-study personnel—necessarily with a technical, and preferably analytical, background—is a subject worthy of attention in the attempt to reduce costs. The ancilliary services to a laboratory certainly justify investigation. Thus sampling may be too thorough; time and motion study methods may cut unnecessary travel between works and laboratory; a tidier and more efficient docket system may be possible. These and many other operations all bear investigation but before they are examined it is as well to give senior laboratory personnel a short course in method-study appreciation so that the incoming investigator meets with a tolerant reception and not an attitude of resistance to what might look to be criticism of the laboratory organisation.

The assessment of the analytical work itself by normal time and motion study techniques is more difficult and a critical evaluation of the activities of a large group of analysts dealing with an extensive and varied range of materials would be very time-consuming. The technique of "activity sampling" has much to recommend it. A method-study worker, using this technique, can obtain information on selected personnel in a comparatively short time and with a good assessment of the accuracy of his results, with the decided advantage of not upsetting the normal routine of those being studied. In this way one worker has been able to show in a matter of days that the paper work activities of a group of nine section heads occupy 26 per cent $\pm$ 4 per cent of their time and that about 73 per cent of this activity is devoted to one particular type of paper work. Such information enables one to assess how much method-study time might profitably be devoted to reducing paper work and which particular aspect of the problem to tackle first.

How is the value of method-study to be judged? Not necessarily—and certainly not only—by the reduction in the number of laboratory personnel or in other laboratory costs. It may be much more of a gain to be able to give a more efficient service at the same cost and with the same personnel, particularly if this were to be reflected in a reduction in the time taken for a sample to pass through the laboratory. However, sometimes a direct saving can be shown as, for example, in reducing by various means the usage of expensive solvents.

The very fact that method-study has been introduced and is being used will often stimulate laboratory personnel to examine closely the procedures in which they are involved and to make useful modifications without the direct intervention of method-study personnel. Some of the most valuable and, certainly, most acceptable schemes arise in this way.

It should be every analyst's concern to consider what can be done to reduce costs or at least to discourage their increasing. It has already been stressed that drug-standardising committees need to consider the comparative expense, particularly regarding the time required, for tests otherwise of equal merit and to re-assess the necessity for the present tests. Industrial pharmaceutical laboratories should also do this for reasons of internal economy, remembering that the B.P. and B.P.C. permit alternatives to the methods of determination described provided these are of equivalent accuracy. Working time can be considerably reduced by the use of such techniques as titration with EDTA to replace gravimetric methods, the use of paper chromatography in the re-investigation of questioned batches of insulin solutions to avoid costly bioassays, assessment of weight variation of tablets by sequential analysis, instrumental methods using quantitative infra-red measurements, gas-liquid chromatography and emission spectrography; many other examples can be quoted.

Duplication of Analyses

We have, no doubt, realised from time to time that a considerable amount of work is done by laboratories, confirming the quality of supplies received by their firm, which is repetition of work already done by the

supplier before dispatch. This practice is usual and it follows that, during the course of buying and selling, it is possible for several analyses to be done on each batch of a product.

Recent examination of the analytical records of my department for several thousands of batches of materials bought to the B.P., B.P.C., or B.Vet.C. specifications during the previous three years showed that only a few batches had been rejected. Moreover all rejections had been because of non-compliance with physical criteria only, e.g. colour, quality of solution, or presence of dirt, where the fault could be readily observed. The cost of analysis was about £15,000. Hence, avoidance of analysis would have resulted in a very impressive saving in analytical costs without concomitant disadvantage.

It will be accepted that any material offered by a reputable manufacturer has been adequately tested in their laboratories, hence it is reasonable that reputable companies should accept each other's analyses. If two firms involved in a commercial transaction were members of a group which had agreed to do this, the analytical figures relevant to the material bought could be supplied to the purchaser whose analyst need only carry out a check of a superficial kind, such as inspection, identity and simple solution to guard against dirt and adventitious contamination during packing; if these were satisfactory the consignment could be accepted on the vendor's certificate of analysis.

At an informal meeting between the chief analysts of fourteen leading pharmaceutical manufacturers, the principle of the reciprocal acceptance of analytical certificates for official products was unanimously approved, the working of the scheme to be negotiated between individual firms and to be considered as an agreement or understanding between the analysts concerned. A manufacturer would sell material with a certificate giving the batch analysis. The receiving analyst would use his discretion whether he would want to confirm any of the figures for his particular requirements. In order to provide the analyst of the purchasing firm with the means whereby the batch can be assessed for any special requirements it is desirable that the actual analytical figures should be given where such are normally determined (e.g. loss on drying, melting point, assay, etc.); the results of limit tests would not be quantitatively stated except where an actual figure is normally recorded. In all cases it is the responsibility of the receiving analyst to make what checks he thinks necessary, bearing in mind such things as the question of re-sale. Otherwise he accepts the goods on the analyses given and thus saves considerable analytical time.

Provided the scheme is operated between analysts each with respect for the other's professional integrity it is, in effect, little different from the receiving of analytical information from the analyst's own staff, which information he assesses and either accepts or requires to be supplemented with further work according to the figures presented.

Agreements of this type are now successfully operating betw everal of the previously mentioned firms and in all cases have been exte to cover other than official materials. It has been found that since cates of analysis are commonly provided for overseas buyers and ot tomers,

the adoption of such a scheme need not impose much extra burden on clerical staff if a sensible attitude towards documentation is adopted. Of course, some firms have to provide more certificates of analysis than they receive and to meet this an added charge to recover overheads involved in clerical work might be appropriate, but this would be considerably less than a comparable analytical cost. Further problems, such as those arising from flow-line production or blended batches, have not presented particular difficulties and the scheme is well worthy of expansion.

Possible Framework for Future Legislative Control

With the contemplated revision of legislation concerning medicines, a golden opportunity is presented for re-organisation of the overall control of drugs. Concisely, the provision of standards for all drugs should be dealt with by one organisation and the control of drugs to those standards should be the responsibility of another. Drug control should follow a logical course (*a*) notification (showing therapeutic indications, toxicity, clinical trials and methods of test), (*b*) fixing of standards, (*c*) control to those standards; (*a*) and (*b*) should be regulated by the General Medical Council or a similar body and (*c*) by the Ministry of Health.

The Medical Act (1956) requires the General Medical Council to publish from time to time new editions of the B.P. which should contain "descriptions of and standards for, and notes and other matter relating to medicines, preparations, materials, and other articles used in the practice of medicine, surgery or midwifery". Although it may not have been intended as such, the present B.P. is virtually a book of standards and includes those drugs considered either most effective or of widest clinical use. With the rapid increase in chemotherapy, selection is squeezing out the drugs of natural origin, and their galenicals, and the book has become mainly a collection of specifications (i.e. a list of requirements with which the material must comply) for pure synthetic chemicals and their simple formulations such as tablets and injections, with appropriate methods of analysis. The B.P.C. includes many more drugs in common use and it controls by formulation the manufacture of a large number of more complex preparations. The Codex, also, has to be selective and a glance at the deletions with successive editions gives a clear insight into the trend in pharmaceutical usage.

Standards for many drugs are therefore already available in these publications and some control is possible by insistence on these standards, although legally they are only presumptive. Because of the time involved in compiling these books, however, new drugs intended for official recognition must wait perhaps some three years for their standardisation.

As well as the officially recognised drugs, there are other drugs on the market, too recent, too ephemeral, or of too doubtful efficacy to be included, which should be controlled for purity. This may be of particular importance for some biological materials which, when first available, are relatively impure. Such drugs are not amenable to chemical or physical control methods; a few selected drugs requiring biological

methods of test are already controlled legally by Regulations under the Therapeutic Substances Act. Hence some form of procedure should be devised to enable standards to be provided speedily for all drugs.

The obvious and ideal way would be to fix standards before a drug is placed on the market. The General Medical Council have already indicated, in their President's disclosure of the substance of evidence submitted to the Interdepartmental Working Party on Legislation Concerning Medicines, that the Pharmacopoeia Commission had made a number of recommendations which would enable the Council to publish, as approved specifications, standards for all newly introduced drugs as soon as, or soon after, they were placed on sale in the United Kingdom. No information, however, is available on how the General Medical Council mean to implement their intentions. This should not prove difficult. The standards would be available since when a new drug is marketed its analytical specification would certainly have been already worked out by the manufacturer; even now the information required to compile official monographs must rely on data provided by manufacturers or some firm using the substance. The scheme could be implemented by some central authority in a similar manner to the method already used by the Ministry of Agriculture, Fisheries, and Food in their Agricultural Chemicals notification scheme which, although primarily intended to control pesticides on their toxicity, does require methods of analysis to be provided.

In the Notification of Pesticides Scheme, firms voluntarily notify the Ministry of Agriculture, Fisheries, and Food of new toxic chemicals and formulations which they propose to introduce into agricultural practice. The procedure is intended to provide only for the safe use of chemicals and is not concerned with the approval of claims for biological uses. Information requested on notification includes the active ingredient and its proposed concentration, type of formulation, methods of analysis, proposed uses, and adequate toxicological information. The Scheme covers any product utilising a completely new active principle, i.e. a chemical not previously commercially available in the United Kingdom, and any product containing an active principle that is not new but is in a new formulation which could produce a new or increased risk. Notification is not expected while the product or proposed new use is at the stage of laboratory or small-scale trials carried out under the direction and control of the notifying firm. Care is taken to avoid the procedure being slowed down. Should consultation outside Government Service be needed no information provided by the notifying firms is disclosed to any person having a connection with any commercial interest that might make it undesirable for him to be consulted; the notifying firm is consulted before any confidential information is disclosed. Likewise reputable pharmaceutical firms would certainly be prepared to supply methods of analysis for any of their products to the Ministry of Health.

Although I am not intending here to consider responsibilities on the therapeutic value of new drugs, such a scheme could also embody this aspect of drug control in a manner analogous to the Agricultural Chemicals Approval Scheme. This scheme is intended to provide only for the

approval of claims for biological uses and products cannot be approved unless they have been through the Notification Scheme. This procedure is voluntary and a scheme for drugs could also begin on a voluntary basis; if necessary it could be made obligatory later.

Notification of new drugs should also include those imported from foreign countries. This presents no problem provided the central authority has been set up. The converse is well known, with the extensive registration requirements already in existence for our drugs overseas, where description of the drug, dosage forms, pack, therapeutic indications, and methods of analysis all have to be provided *in extenso*.

The large increase in the number of drugs used and the developments in chemical, physical, and biological methods for their examination has placed those whose duties include the control of drugs on behalf of the consumer in a difficult position. The inclusion of drugs in the Food and Drugs Act appears to have been quite fortuitous and could be ascribed to the chance that Hassall in the middle of the last century based much of his disclosure of adulteration at that time on microscopical examination, for which crude drugs and spices was an excellent field. Samples of drugs taken under the Food and Drugs Act have been confined almost entirely to a selection of popular galenicals and comparison of many recent reports on this subject with those of forty years ago shows little change. This is no criticism of the body of public analysts who do an admirable job within their sphere of activity; it is simply that, as has already been implied, pharmaceutical analysis has outgrown the general field covered by the training and practice of most of these officials. The preparations selected for testing under the National Health Service scheme have generally been limited to the more commonly prescribed standard drugs and prescriptions. But the vogue in prescribing has altered considerably in the last few years, particularly in the proportion of proprietary preparations—few of which are tested. Thus we obviously do not have full control of drugs and a change of legislation or procedure is desirable if protection of the Ministry and the public is to be obtained, both in the dispensing of prescriptions and in open sale of medicines (and these should include any cosmetic where therapeutic value is claimed).

Hence I suggest that the control of drugs should be taken out of the Food and Drugs Act and incorporated in a new Medical Substances and Preparations Act built round Sections 11, 12, and 13 of the Pharmacy and Medicines Act. For effective enforcement, legislation should provide legal status for the standards of the B.P., B.P.C., and B.Vet.C. and also for standards for any other drugs officially recognised in the procedure for provision of standards I have just outlined. It may be desirable to incorporate authority for provision of standards with that for legal enforcement of those standards in one Act. An advisory body or bodies will be required to make recommendations under the new Act.

The Pharmaceutical Society, in evidence submitted to the Interdepartmental Working Party on Legislation Concerning Medicines, has likewise recommended that the control of medicines be separated from that of

other substances and vested in the Ministry of Health. It is undoubtedly the concern of the Ministry as the chief buyer of drugs.

If the sale of drugs both for human and veterinary use is to be controlled adequately and fully, such testing must be in the hands of experts in this field. This of necessity leads to the setting up of specialist laboratories and it follows that they must be of a regional type since local authorities could not maintain them. The regional laboratories should be directly responsible to the Ministry, who through them could also maintain the National Health Service testing scheme. Even these laboratories could not adequately cope with the complete control of drugs but the load of testing could be lightened, for instance, by the method used by the Ministry of Supply where, for approved firms, the contractor's own inspection organisation is given the initial responsibility, under the Inspection Directorate, for compliance of goods with specification. The Chief Inspector so approved under the Directorate of Chemical Inspection is generally the Chief Analyst of the company and certain conditions are laid down concerning his appointment and duties.

Control should also provide against the importation of inferior drugs to wholesale users in this country for use in formulations where tests would not disclose the quality of drug used. To guard against such a contingency it should be laid down that an imported consignment of a drug must not be sold or used unless it carries a certificate of purity from a recognised laboratory in this country. The Directory of Independent Consultants issued by the Royal Institute of Chemistry could be used as a basis for recognition or, better—by parallel with the present statutory requirements for competence as a public analyst under the Food and Drugs Act—a special diploma in drug analysis from the Pharmaceutical Society or the Royal Institute of Chemistry could be demanded. This could be incorporated as a requirement of competence in the proposed Medical Substances and Preparations Act. Such a requirement would be in keeping with the suggestion already made of the need for courses in pharmaceutical analysis.

In the time at my disposal I have endeavoured to show that with the exceptionally rapid increase in the need for new analytical techniques, due to more stringent control, the added cost to the production of drugs must be considered. Other forms of expenditure in an analytical laboratory that might be reduced by investigation have been mentioned.

In my opinion, because of this rapid increase, the pharmaceutical analyst has been given insufficient time to adjust his research to the needs and if the stringency of control described is necessary a closer assessment of his precision must be made. The use of reference standards for differential analysis is almost essential if consistent results are to be obtained and such a collection is an imperative need.

Full notification of all drugs and their control is a necessity and should be incorporated in a new drug Act if the service by Pharmacy to the public is to be maintained at its present high level.