

Control of Fine Chemicals and Pharmaceuticals

The ever-increasing output of complex, potent new drugs and pharmaceuticals has created problems of control undreamed of 50 years ago. To ensure the identity and purity of fine chemicals and pharmaceuticals, the analyst has had to develop new methods and instrumentation. Much progress has been made. Much work remains to be done. Some of the problems and their solutions are described in this month's Report for Analysts. The author presented this paper at the Symposium on Analysis of Fine Chemicals and Pharmaceuticals sponsored by the Division of Analytical Chemistry at the ACS meeting at Atlantic City last September.



W. B. Fortune, 43-year-old analytical chemist, has been director of control of Eli Lilly & Co., Indianapolis, since 1949. In this capacity he is responsible for the quality and purity of more than 1100 pharmaceuticals and biologicals. He received his B. S. degree in chemistry from Mount Union College, Alliance, Ohio, in 1934 and his Ph. D. in analytical chemistry from Purdue in 1938. With the exception of the period 1941-1946, when he was with the army's military intelligence service, he has been associated with Eli Lilly. He started as a research chemist, became head of antibiotics development and production, and then director of control. He has published many papers and holds several patents in the field of analytical chemistry. He is author of the chapter on visual comparators in "Analytical Spectroscopy." He is an active member of the ACS and was chairman of the Indiana Section, and is a member of the American Pharmaceutical Association.

WITH the continuing activities of research chemists leading to the discovery of more and more complex, highly potent drugs and chemicals, the control of these fine chemicals and pharmaceuticals made from them has assumed a stature undreamed of a half century ago. With the tremendous advances in medicine which have occurred during the past 25 years has come a need for new methods and new instrumentation to ensure the identity and purity of the drugs evolving from this research.

One cannot fully appreciate the extent of control of fine chemicals and pharmaceuticals today without looking backward briefly to the history of written control procedures. Written control procedures probably date back to the alchemist of the 16th century. Throughout the years there were minor booklets of specifications for chemicals, such as the crude European pharmacopeias, the small pharmacopoeia used by the Army hospital at Lititz, Pa., in 1778, and that drafted by the Massachusetts Medical Society in 1808. Such local tables of specifications met with resistance in other parts of the country.

The first concrete action in the United States to establish control methods through the publication of a national pharmacopeia which would be acceptable in all parts of the United States was initiated in 1817 by the Medical Society of the County of New York.

A pharmacopeial convention was held in Washington, D. C., attended by representatives from all four parts of the then existing United States, to discuss this proposal. The data proposed were assembled into a single volume published in 1820, in both Latin and Eng-

lish. This first "Pharmacopeia of the United States of America" (3) was chiefly a book of recipes for the medical profession. However, it provided specific directions for making various pharmaceutical formulations of the time and therefore might be considered the first national set of control specifications.

As new revisions appeared, control procedures became more specific. By 1880 (6th revision), chemical nomenclature had been introduced, descriptions of crude drugs and chemicals were more comprehensive and exact, and constituents of pharmaceuticals were stated in "parts by weight." The first general tests for heavy metals and arsenic and the first purity rubric, that relating to permissible innocuous materials, appeared in 1905 (8th revision). The 1916 edition (9th revision) first gave official methods for determination of ash, crude fiber, volatile and nonvolatile extractive, melting, boiling, and congealing points, and specifications for standard thermometers.

In 1906, Congress enacted "The Food and Drug Act." Standards adopted under this act were those of the United States Pharmacopeia and the National Formulary. Thus the written national standards of the time acquired official status.

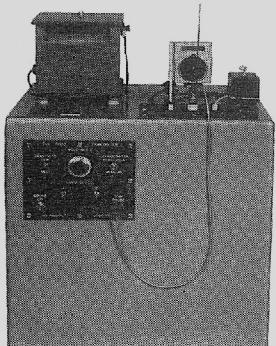
Control increased throughout the next 20 years, in that more and more pharmaceutical products were added to the pharmacopeia. In the eleventh revision period there appeared, for the first time, "reference standards" to be used for comparison and official assays. Such standards were provided for vitamin A, vitamin D, vitamin B₁,



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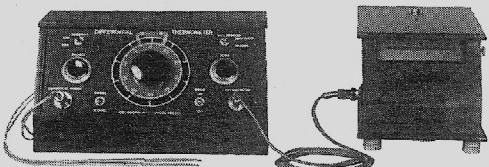
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REPORT FOR ANALYSTS



Adequate controls for new drugs and pharmaceuticals require continuous progress in developing new analytical methods and instrumentation

vitamin C, ergot, digitalis, epinephrine, ouabain, pepsin, posterior pituitary, estrone, aconite, and trypsin. Responsibility for distribution of these reference standards was delegated to the Director of Revision of the Pharmacopeia.

Continuing new requirements for fine chemicals and pharmaceutical products is aptly illustrated in the fact that USP XV, which became effective in December 1955, added 242 monographs which had not been present in USP XIV and deleted only 163, for a net gain of 79 monographs. Control standards and methods were required for each new monograph.

A history of the National Formulary, from its original publication to its present tenth revision, shows the same trend toward more specific and precise methods of control.

Industrial vs. Fine Chemicals and Pharmaceuticals

In any discussion of the control of fine chemicals and pharmaceuticals the question is raised as to the difference between these products and so-called industrial chemicals. Fine chemicals, usually considered as raw materials intended for use in pharmaceuticals or drug products, are required to meet rigid control standards, whereas the standards for most industrial chemicals are relatively lenient.

Technical grade zinc oxide, used in paints and tires, for example, must have at least 90% ZnO and may have a few tenths of 1% lead. The USP grade, used in lotions and ointments, must have at least 99% ZnO and must give a negative reaction to the test for lead. USP

glycerol has color standards which do not apply to the industrial grades.

Another striking example of the difference between industrial and fine chemicals is illustrated by precipitated calcium carbonate. That used for mineral feeds, according to standards of the Association of American Feed Control Officials (1), must contain at least 80% CaCO₃ compared to 98% for the USP grade. Unlike the feed grade, which has no additional standards for metals, USP precipitated calcium carbonate has a limit of 30 p.p.m. for heavy metals and 1% for magnesium and alkali salts.

The differences in production processes required for the two grades result in substantially higher costs for the USP grade.

The same degree of tolerance exists between fine chemicals and industrial grade chemicals with respect to tests for identity. General, nonspecific tests for identity, usually consisting of simply the analytical assay, are satisfactory for industrial chemicals whereas the identity tests for fine chemicals and pharmaceuticals are much more specific and stringent. Zinc oxide used in a paint may have present appreciably large quantities of zinc carbonate without seriously affecting the final product; in a pharmaceutical product even small amounts of a foreign material may produce extremely serious side effects. Strychnine as an impurity in saccharin is a good example. Because they are used for humans and animals, the identity of pharmaceuticals and the fine chemicals going into them must be beyond question and identity methods established accordingly.



Pharmaceutical elegance, with freedom from impurities, requires care in handling drugs and pharmaceuticals at every stage of processing

Classical Methods Limitations

Let us consider briefly the old classical methods which have been used and in many instances are still being used for the control of industrial chemicals and some of the older fine chemicals. In our rapidly changing chemical world, these classical methods have some limitations.

Melting Point. In determining melting point, it should be relatively simple to introduce a small amount of chemical material into a capillary melting point tube, to place this alongside a thermometer in a bath, and to read a temperature on the thermometer at the point when the observer first notices a change in the physical characteristics of the product in the capillary tube. In view of the very complex fine chemicals on the market today, however, such simplicity is unattainable.

The USP XV edition, describes no less than five procedures for determining melting ranges or temperatures of fine chemicals. Even if the observer can select some melting point temperature or range of temperatures, there are still several pitfalls in interpreting this as an absolute indication of identity.

For every degree of melting temperature there are several, often widely differing, organic compounds which may be present. Likewise the use of a melting point as a single criterion of identity is subject to the pitfall of absolute purity. It is conceivable that the presence of only a small amount of impurity might throw the melting point of the compound under test into those melting

ranges exhibited by entirely different compounds.

Another factor not ordinarily noted in the consideration of the melting point determination as an identity test, lies in the physical character of the material under test. The melting point of a substance in a very finely divided state may be significantly different from the melting point of a coarse crystalline form of the same product.

Thus, determination of melting point as an identity test of a fine chemical is subject to variations caused by impurities, physical character, method of determination, observed melting point, and interpretation. These same variables enter into the use of a melting point as a measure of purity of a product. We must conclude that the use of the melting point as a method for determining identity or purity of a compound should be considered only a very small link in a very long chain of circumstantial evidence.

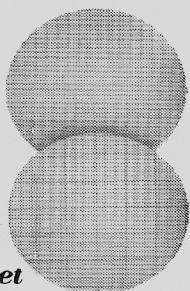
Specific Rotation. Some control chemists swear by specific rotation as a means of identification and determination of the purity of a compound, whereas other control chemists swear at this method. As long as the observed optical rotation of a substance is sufficiently large to permit reading the angular scale with a high degree of precision, the method has merit. We, however, frequently set it up as a control procedure and place considerable emphasis upon it as an identity test when the precision of the reading is so low as to make the determination almost valueless.

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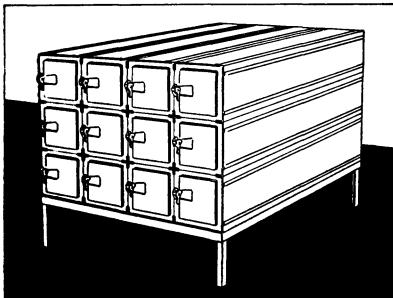
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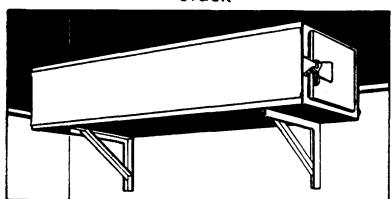
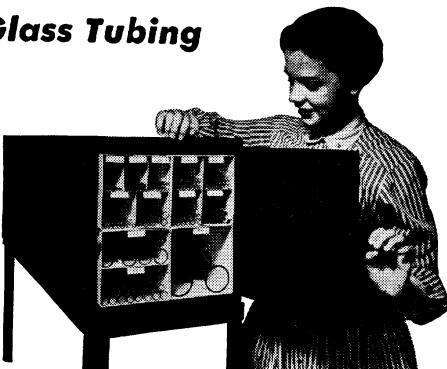
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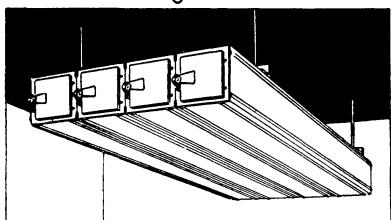
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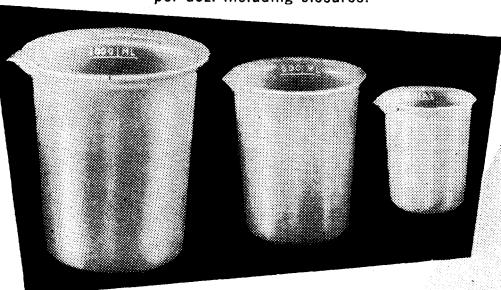
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of Revision, I well remember the comments concerning the proposal to add "specific rotation" as a required test under the monograph on folic acid. The standards of the test for specific rotation of folic acid state that when determined in a solution in 0.1N sodium hydroxide containing 50 mg. of folic acid in each 10 ml., the specific rotation is between +18 degrees and +23 degrees. Calculating back to the formula for specific rotation where $[\alpha]_D^{25} = 10a/lc$ it can readily be seen that a very slight error in reading the angular rotation on the polarimeter is magnified by 100 times in the formula itself. With the small angular rotation noted under these conditions for folic acid, the determination of specific rotation is of little value other than merely an indication, one more small link in a large chain.

Another factor which may enter into the measurement of specific rotation is the solubility of the compound under study. The concentration of the substance under study in the above formula is expressed in terms of grams of active substance in 100 ml. of solution. If the solubility is very low, a saturated solution will still give a very low value for c in the formula and consequently the observed angular rotation may be so small as to lack seriously in precision of reading.

Specific rotation has a very definite value in identifying pure, optically active compounds. Specific rotation, for example, identifies a pure calcium salt of pantothenic acid as the dextro compound or the racemic mixture. However, measurement of specific rotation is again only a small part of the circumstantial evidence which must be collected to prove the identity and purity of a compound and it cannot bear the full responsibility in itself for such proof.

Identity Tests. In any set of control standards "identity tests" are usually specified. The old classical identity test usually consists of dissolving a small amount of the compound under study in a solvent, adding a few drops of some test solution, and observing the formation of a color. Sometimes the only difference in identity between two compounds is that one forms a "light blue color" whereas the other forms a "blue color." Even more confusing is the situation where we have the statement, "a light green color is formed, rapidly changing to blue."

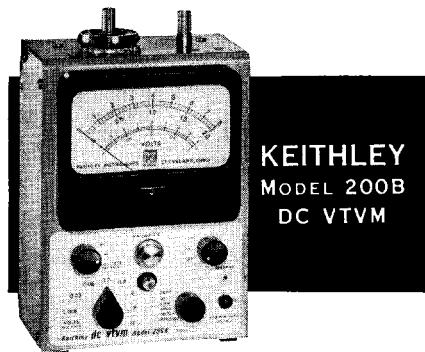
Other identity tests are frequently even less specific. If the chemist selects the first identity test given in a monograph for a product or makes only one of the various identity tests because of shortage of time or other contributing

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factors, he may find himself completely inaccurate in his final conclusion. For example, certain tests in the monographs on amobarbital, phenobarbital, amobarbital sodium, phenobarbital sodium, and secobarbital sodium read identically the same.

The chemist must also realize that, frequently, classical identity tests as specified in control specifications cover only a general field of products and are not specific for any one member within the field. For example, it may be noted that ascorbic acid reduces Fehling's solution. This does not mean, as might be inferred if the single identification test were taken as a criterion of identity, that the product being tested can be only ascorbic acid, since Fehling's solution will be reduced by any reducing substance, even a solution of glucose. A similar degree of nonspecificity was indicated recently in the proposed control specifications for reserpine. The identification tests as proposed would have given positive results for practically all of the known alkaloids extracted from rauwolfia species.

Thus the challenge is thrown to the control chemists to establish control tests of identity on the various new chemicals coming out of research today, tests of identity which are specific for the product and which are not affected adversely by small amounts of impurities which may give rise to false impressions.

Purity Tests. Purity tests are subject to many of the variables noted in identity tests. The old classical gravimetric or titrimetric determinations may be subject to error, giving a false sense of security to the chemist who is analyzing a fine chemical or a new pharmaceutical product. Coprecipitation of impurities with the desired constituent in gravimetric assays has troubled the chemist for many years. Fleeting end points in titrimetric procedures may cause variations from chemist to chemist and laboratory to laboratory. The determination of total alkalinity of racemic pantothenate may vary by as much as 0.2 ml. of 0.1N hydrochloric acid using phenolphthalein as the indicator, owing to the rate of titration as carried out by the chemist making the determination. In order to avoid this variation, the control procedure has been changed to direct the addition of the maximum permissible amount of acid, after which two drops of phenolphthalein are added and "no pink color is produced within 5 seconds." Classical purity tests may often provide insufficient information for proper control. In the paper by Strode, Stewart, Schott, and Caldwell (5) the statement was made "the USP limit test for free salicylic acid in acetylsalicylic acid and

aspirin tablets does not provide sufficient information for manufacturing process control."

Purity tests frequently are not specific for a single ingredient or a single member of a family of compounds which might be present. Schulz and Neuss (4) noted that current methods employed in determination of corticosteroids fail to distinguish between the hydrocortisones and cortisones. Likewise, in our experience, we have seen methods fail to distinguish between reserpine and deserpidine products.

About six months ago, during the manufacture of a pharmaceutical formulation, it was noted that occasional lots of USP diethylstilbestrol were not completely soluble in a vegetable oil. No apparent deviation from USP standards could be found. The analytical research chemists in our laboratory went to work on the problem and within a few months determined that the purity test for diethylstilbestrol as specified in USP XV is not specific for pure diethylstilbestrol and will include in the total weight of the precipitate formed at least three other products which are either beginning raw materials in the synthesis or by-products of the synthesis. Knowing the non-specificity of the purity assay, our chemists were soon able to work out a purity assay which determines only the pure diethylstilbestrol present. The methods will be mentioned later.

Effects of Impurities. Let us consider the effects of impurities not detected by our classical assay and the effects of nonspecificity of identity tests which are currently used for many products of pharmaceutical and fine chemical manufacturing today. Impurities in certain raw materials often materially reduce yields and stability of pharmaceutical formulations.

Many pharmaceutical formulations today are prepared through the skill of the pharmaceutical chemists in compounding together a large number of incompatible drugs and vitamins. I know of a case recently where many tens of thousands of dollars worth of a multi-vitamin pharmaceutical formulation had to be rejected because of the presence of an unexpected impurity in one of the raw materials which went into the formulation, an impurity which did not cause too much trouble while the raw material was in a dry condition but which resulted in almost complete deterioration of the vitamin in a matter of a few days when put into the specific pharmaceutical formulation.

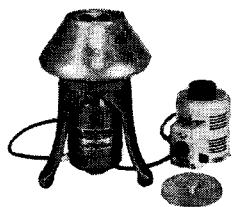
Unforeseen impurities can have a tremendous effect on the stability of even raw materials. Impurities in acetylsalicylic acid, for example, can

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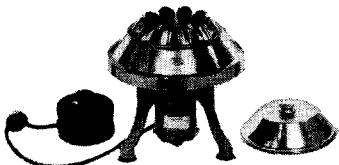
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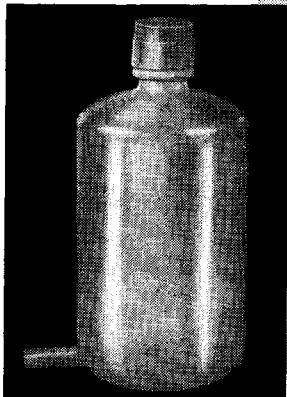
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cause hydrolysis and consequent instability in a very short time. Pharmaceutical elegance can be seriously impaired by the presence of minor impurities in starting raw materials. A lot of gelatin used in preparing soft gelatin capsules for a multiple vitamin product, for example, was contaminated with an unusual amount of iron. This unexpected contaminant was not picked up by the usual control testing of the gelatin. About 30 days after encapsulation, this lot of soft gelatin capsules appeared to have been thoroughly sprinkled with black pepper. The difficulty was traced to the reaction of vitamin C with the iron.

We in the pharmaceutical field are faced with a constantly hanging Sword of Damocles with respect to complete identity of the fine chemicals used in the pharmaceuticals produced. A nonspecific identity test which permitted the use of a relatively toxic raw material instead of a nontoxic one could produce side reactions and even death in patients using the pharmaceutical formulation. No pharmaceutical company can long exist if it makes such errors. Even mild side reactions from toxic impurities could rapidly lead to loss of prestige and confidence in that company by the physicians and pharmacists who prescribe and dispense such products.

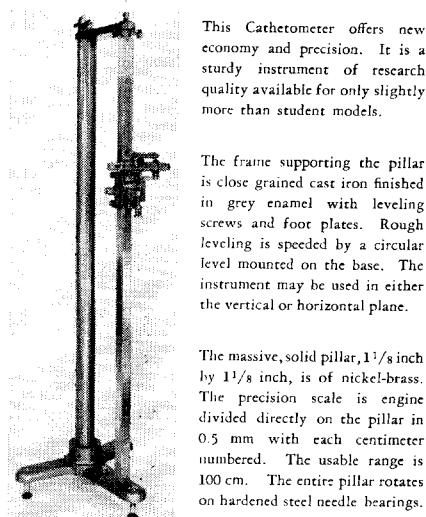
Analytical Research Needed

Industry must establish adequate analytical research facilities to find better control methods, if the new fine chemicals and complex pharmaceuticals are to be used. Most producers of fine chemicals and pharmaceuticals today have established research groups within their analytical departments whose specific responsibilities are to adapt new instrumentation and new and more precise methods of determination of purity and identity to this constantly increasing group of fine chemicals and pharmaceutical products.

Ten years ago our company had no designated chemists assigned to the specific job of developing new methods and adapting new instrumentation to the field of pharmaceutical products and to the assay of the fine chemicals from which they are made up. Today we have an analytical research group working full time and sometimes overtime on basic analytical research and developmental work necessary to transform a new method into a routine assay. This group consists of two Ph.D. analytical chemists, seven master degree analysts, and six bachelor degree chemists. They are not content with classical methods. In fact, they use classical methods only where these

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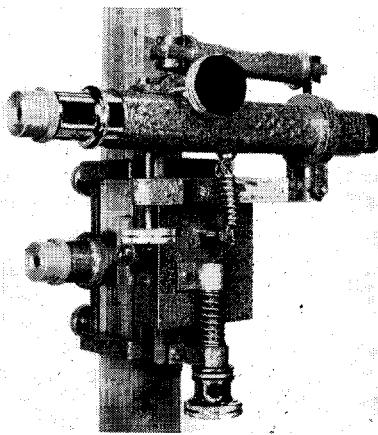


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have the necessary precision and specificity.

New Techniques

What are the new techniques and instrumentation with which this analytical research group is working?

Spectrophotometry. First on the list I would place spectrophotometry. Twenty years ago one of the early visual recording spectrophotometers with which I worked required 2 hours of maintenance for every hour of research use. Today's instrument of this type will run for many hours without any maintenance. Visual spectrophotometry was the first in a series of steps which permitted scientific evaluation of the many processes and methods then available.

Within the past 20 years we have seen the evolution of the ultraviolet spectrophotometer. This instrument and methods based on ultraviolet spectrophotometry are now commonplace in laboratories and in control specifications. Many new methods in USP XV are based on the use of ultraviolet spectrophotometry. One disadvantage with this technique is that absorptivity bands are relatively broad. Although broad bands are excellent for measurement purposes where no interferences are present at that particular wave length, they are relatively poor for identity purposes.

About 10 years ago the analytical chemist had his eyes opened to a new portion of the spectrum, the infrared, and infrared spectrophotometry as an analytical method was born. At the time when our analytical chemistry department acquired its first infrared spectrophotometer, we could foresee perhaps one hour's work per day on the instrument. Today we are using two instruments 8 hours per day.

Sharp bands in the infrared are excellent for establishing identity of many fine chemicals and can also be used for quantitative work. Comparison of infrared bands of unknown organic compounds with a series of spectra of known compounds permits identification of the unknown. In addition, this technique permits rapid identification of substituted groups and linkages in many organic compounds and thus aids the analytical research chemist in establishing an assay for a new organic fine chemical.

Infrared spectrophotometric procedures have permitted us to determine previously undetermined combinations. Acetylsalicylic acid, acetophenetidin, and caffeine capsules, as listed in the tenth edition of the National Formulary, provide for an assay for acetylsalicylic acid and an assay for the combination of acetophenetidin and caffeine. The method is time-consuming and is subject to inherent

errors due to the interference of the individual constituents upon each other. By means of an infrared spectrophotometric method, each constituent can be determined separately, and with a high degree of precision. In addition, the entire assay takes only about 30 minutes as compared with several hours for the old gravimetric and titrimetric type of assay.

A very new entry into the field of spectrophotometry is the fluorospectrophotometer. This instrument provides a narrow band light source in the ultraviolet or low visible range. The sample is excited in this very narrow range and the fluorescence resulting from such excitation is read in another narrow band range at some other point in the spectrum. It is expected that this instrument will provide another tool for increasing the specificity and precision of assays for purity and for identity of many organic products.

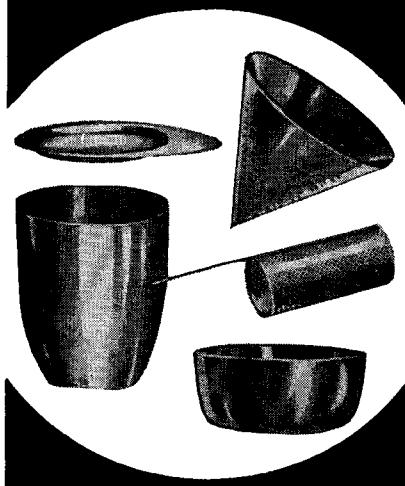
X-Ray Spectrometry. Another analytical tool is x-ray spectrometry. This relatively new tool fingerprints crystalline substances by x-rays in essentially the same manner as do ultraviolet and infrared. A number of fine chemicals purchased by our company are now being subjected to this means of identity determination. It is predicted that such identification will become general in the near future for those crystalline substances which show specific x-ray patterns.

Spectroscopy. Flame and arc spectroscopy are contributing greatly to the specificity of methods for identity and purity determinations. The heavy metals test specified by USP XV and N.F. X is very general in that it determines only semiquantitatively those metals whose sulfides are colored. All fine chemicals which are subject to contamination with heavy metals can have the heavy metal assay made on the spectrograph. In our own experience we routinely assay most of our incoming raw materials known to be subject to heavy metal contamination. The spectrographic plate is read quantitatively for the presence of copper, lead, tin, antimony, and mercury. It is interesting to note that the use of the spectrograph has permitted us to put on the market an antibiotic which had almost been abandoned because of instability. The spectrograph pointed out the specific metal contaminant present, thereby leading to its elimination and the solution of the instability problem.

Crystallography. Crystallography is yet another tool which has been grossly overlooked in control specifications. Measurement of the three refractive indices of a crystal under the microscope provides a method of

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identification fully comparable to the fingerprint system of the Federal Bureau of Investigation. The possibilities of crystals of two different compounds having all three indices of refraction identical are no greater than the possibility of two people in the United States having identically the same fingerprints. Of course, this method is available only for those compounds which can be formed into stable crystals.

Chromatography. Another rapidly advancing research tool is chromatography. Although known to the biochemical researcher for many years, it has been only during the past 10 years that chromatography has assumed a position of stature in the analytical field. Research work on synthetic penicillins and the characterization of the various penicillins would have been almost impossible without the analytical separation step carried out on chromatographic columns. Analytical separation of amino acids has also been greatly facilitated by the use of chromatographic columns.

More recently development of paper strip chromatography has brought about significant advances in analytical methods. This technique provides the analytical chemists with an invaluable method for purity determination. The first knowledge of the presence of deserpidine in a fine chemical thought to be pure reserpine came about when the chemical was chromatographed on a paper strip. A small difference in the R_f value led to the suspicion of a contaminant having the same chemical characteristics as reserpine. Chemists tried other solvent systems until one was established which definitely and finally separated deserpidine from reserpine.

As described earlier, the presence of three impurities in USP diethylstilbestrol was discovered by the use of paper strip chromatography. After detecting and isolating these impurities, the analytical research group then was able to develop precise identity and purity tests utilizing ultraviolet spectrophotometry, x-ray spectrometry, and paper strip chromatography. A proposal for a revised monograph on diethylstilbestrol which embodies the above tests has been prepared for the Committee of Revision of the U.S. Pharmacopeia.

Paper strip chromatography has also been adapted to quantitative work through development of a scanning device attachment for the ultraviolet spectrophotometer (2). With this device the paper can be scanned over the entire length of the strip, the desired constituent located, and identified from the spectrophotometric curve produced.

Frequently, measurements of the area occupied by the desired constituent on the paper strip chromatogram can be used for quantitative estimation of the amount present.

One of the most recent developments in the analytical field has been that of gas phase chromatography and instrumentation for this method. Basically, the method depends upon converting organic liquid mixtures to the vapor phase and chromatographing the vapor through a temperated gradient. One of the first assays carried out by this method in our own experience has been the assay on 2-bromopentane, a raw material used in the synthesis of a pharmaceutical product. Contaminants in the starting material were believed responsible for low yields. By gas phase chromatography we were able to show the presence of other isomers of bromopentane, along with a small percentage of pentenes. A knowledge of the contaminants present permitted a process change which increased yields significantly.

Radioactive Tracers. Another new analytical tool depends on radioactive tracer materials. Through the addition of small amounts of such tracers in an assay the quantitation of separation techniques has been achieved, thus establishing a means of increasing the precision of purity measurements. The recently issued first supplement to USP XV carries a modified assay for vitamin B_{12} utilizing tracer methods.

Other Tools. No report on tools of recent origin for use by the analytical chemist would be complete without at least mentioning nonaqueous titration, polarography, voltammetry, fluorometry, and many other instrumental methods. Space and time do not permit a complete discussion of the possibilities of the use of each of these tools.

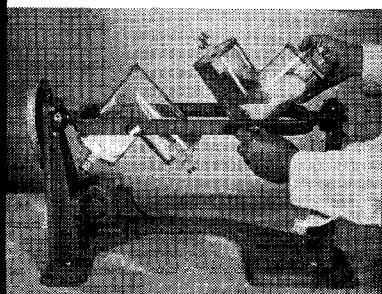
Physical Appearance Important

One final point must be made with relation to the specificity of an assay, and that is "pharmaceutical elegance." The physical appearance of a pharmaceutical which is to be used by human patients is of far greater importance than the appearance of many industrial chemical products.

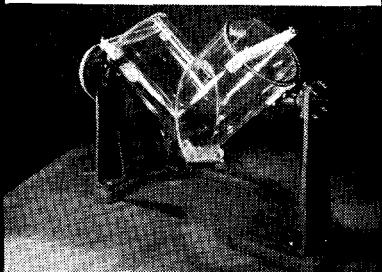
In years past probably every supplier has been faced with the situation wherein a customer has referred back to him a shipment with a statement that "it contains too much dirt and extraneous material." The only criterion for the evaluation of the degree of extraneous material present was the eye of the inspecting chemist. If the examination happened to be made in a brightly lighted place the chemical might be rejected because of the presence of small black

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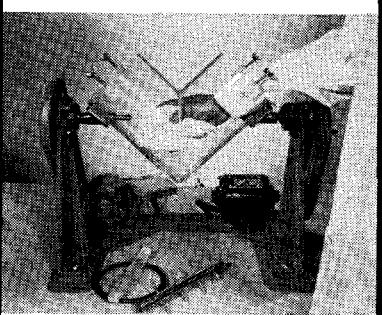
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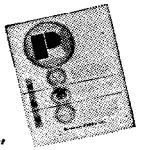
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specks seen on the surface of the contents of the container. The same container might be examined by another chemist in a less well illuminated area and might be passed.

Recently a test has been devised whereby a certain weight of fine chemical is put into solution and filtered through a standard 1-inch filter paper disk. Standards have been established which now permit the chemist to make an objective statement of the amount of extraneous material present in a specified weight of chemical.

Since 1938 the Federal Food, Drug and Cosmetic Act [Section 501 (a) (2)] has carried the statement that "a drug shall be deemed to be adulterated if it has been prepared, packed or held under unsanitary conditions whereby it may have been contaminated with filth," Until recently the question of degree of contamination with extraneous materials has been purely subjective. Now, with the aid of the analytical research chemists who have examined many hundreds of lots of chemicals and who have prepared reference standards from uniformly ground spectrographic carbon, we can assure ourselves that the chemicals going into our pharmaceutical products are of a quality which cannot be deemed to be adulterated under this section of the Drug Act.

Some Tests Superfluous

In discussing various tools which have become available to the analytical chemist during the past decade or two, we have purposely passed over lightly some tests found in various control specifications. These include determinations of moisture, ash, sulfate, chloride, and a number of others.

It is suggested that frequently some of these tests may be superfluous and could well be omitted, depending upon the final use to which the chemical is put. Unless the moisture content has a specific bearing on either the identity or the purity determination, or has some effect upon the stability of the chemical during a storage period, the presence of a few tenths per cent will usually offer nothing additional in the way of purity or identification. Likewise, one could consider the presence of chloride ion of no importance when the chemical is to be made up in physiological saline solution.

Analytical specifications prepared by the control unit should be practical and should reduce to a minimum any unimportant tests. It would be well if all producers and consumers would read the specifications which they have prepared for their various products and

give careful consideration to the value of the multitude of unimportant tests frequently placed in such specifications.

Suggested Purity Criteria

What are the criteria of purity for fine chemicals and pharmaceuticals which are needed today? In the author's opinion these criteria may be broken down into four specific requirements:

1. The product must be identified beyond question. Tools for this may lie in the realm of infrared spectrophotometry, x-ray spectrometry, chromatography, crystallography, or other physical chemical measurements.

2. The product must be free from products of similar composition. The tools available for this may be paper chromatography, gas phase chromatography, partition chromatography, or other partition techniques.

3. The product must be potent (pure). Assay methods listed as available for this determination are ultraviolet spectrophotometry, spectroscopy, nonaqueous titration, and a number of other instrumental methods mentioned above.

4. The product must be pharmaceutically elegant. This means that the product must be free from extraneous color or dirt. The standardized extraneous material test mentioned above, which has been worked out in recent years, is applicable here.

Let me paraphrase an advertisement which appeared in a recent edition of *Chemical and Engineering News*, "the spot on a paper strip—the peaks of an infrared curve—the refractive index of a crystal—these are a few of the little things that add to the final quality of a fine chemical."

When you have met the above criteria using precise instruments and equipment and truly analytical methods, then, and only then, do you have a product worthy of being labeled under your company name as a fine chemical or a pharmaceutical.

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