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THE EDITORIAL POLICY of this JOURNAL is to record the progress of the law in the field of food, drugs and cosmetics, and to provide a constructive discussion of it, according to the highest professional standards. The FOOD DRUG COSMETIC LAW JOURNAL is the only forum for current discussion of such law and it renders an important public service, for it is an invaluable means (1) to create a better knowledge and understanding of food, drug and cosmetic law, (2) to promote its due operation and development and thus (3) to effectuate its great remedial purposes. In short: While this law receives normal legal, administrative and judicial consideration, there remains a basic need for its appropriate study as a fundamental law of the land; the JOURNAL is designed to satisfy that need. The editorial policy also is to allow frank discussion of food-drug-cosmetic issues. The views stated are those of the contributors and not necessarily those of the publishers. On this basis, contributions and comments are invited.

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The deputy commissioner of the FDA, *John L. Harvey,* reports on the growth, organization, operations and plans of the FDA in a paper on page 590. The developments in the FDA's major reorganization which was begun during the past year and the Administration's proposed legislation are two of the topics covered in this informative article.

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Food·Drug·Cosmetic Law
Journal

Food Legislation in Europe

By J. P. K. VAN DER STEUR

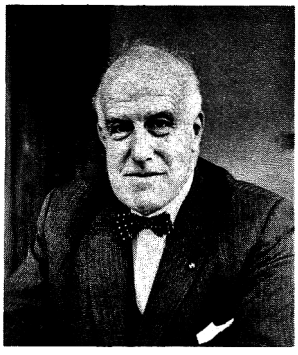
This Talk Was Presented at the New York Section of the Institute of Food Technologists on October 21, 1964, in New York City. Since 1942, Dr. van der Steur Has Been a Member of the Food Law Advisory Committee, Nominated by the Queen (Holland).

EUROPEAN LEGISLATION has been in a state of flux in recent years. Not only have food laws been altered principally in several countries, but at the same time harmonization is taking place as a result of the formation of greater economic and political entities.

Harmonization is being undertaken in Benelux, and in the European Economic Council. Attempts are also being made to draw up a foods code, Codex Alimentarius, for which the initiative was taken in Austria in 1955, and which has gradually grown into an organization attached to Food and Agriculture Organization/World Health Organization trying to draft food standards. If this organization could work quickly, the standards worked out could serve as harmonization examples for various groups of countries such as EEC and European Free Trade Association, thus avoiding duplication of work. Moreover, the advantage might be that industry would not meet with too many changes in the regulations, which always involve costs. For the time being, however, it does not look as though this possibility will have a great deal of success. I will revert to this subject later.

Objectives of European Food Legislation

Food legislation in nearly all European countries is aimed at two different objectives: (1) regulations to protect public health; (2) regulations to promote business integrity. These objectives are al-



Dr. van der Steur Is an Advisor to the Council of Dutch Employers Organizations for Food Law Problems.

ready very old and can be found on a stone plate from 2000 B. C. which can now be found in a museum in Ankara.

Besides this, food legislation should enable and follow the technological progress which has been so extensive for the past 20 years. Unfortunately, the food laws are often abused for political purposes or in order to help realize certain economic wishes.

The French legal system deviates from this dual objective, the sole aim being to protect the consumer against fradulent practices. A distinction is drawn between misrepresentation as regards the nature of the food, its composition, origin, the indication and the quantity. The protection of public health is based on the provisions relating to misrepresentation of the *composition* of the food.

The European system of law distinguishes between horizontal laws containing provisions that apply to all foods, and vertical laws or ordinances which lay down special regulations governing a specific food.

As a rule the horizontal laws are concerned with details of the protection of public health, and to a certain extent also promote business integrity, whereas the vertical ordinances serve primarily to control the quality standards and compositions of the individual foods.

Differences Between Horizontal and Vertical Laws in Various Countries

Fairly wide differences exist, however, between the various countries. Great Britain has a very comprehensive horizontal law, but very few vertical ordinances. The control of the special properties of the different foods is left to commercial usage. By contrast Holland has a restricted horizontal law, but very extensive regulations governing individual foods, which stipulate, for instance, which food additives

may be used and in what quantities. In Spain, on the other hand, a Codex contains side-by-side general chapters on horizontal questions, and chapters with regulations for certain foods.

In Germany and Austria there are special arrangements. Germany has only vertical ordinances relating to highly important products. For the remaining ones the commercial usage regarding the quality standards a product must satisfy is laid down in chapters of an official food standards book. These chapters have no force of law, but are accepted by the law courts as the proper definition of commercial usage, unless evidence to the contrary can be produced. The advantage of such a "food standards book" is that its chapters can be more rapidly adapted to new marketing or technical developments, than would be possible with an ordinance. When the latter is amended it has to pass through all the legislative bodies, which takes a very long time.

Of particular importance for legislation is a ruling on the problem of food additives. Only some of the European countries have legally defined the term, limiting it to food additives for which stringent control, for instance by means of positive lists, is necessary. German and Italian legislation, and in a somewhat different manner Belgian legislation, recognizes as food additives only those substances that possess no nutritive value. Moreover, vitamins are not covered by the definition. In Germany, the Netherlands and Italy, flavors occurring in natural foods and chemically identical flavors are *not* considered to be additives, either. Only the German law has laid down what is meant by nutritive value, namely: a substantial proportion of digestible fat, digestible protein or digestible carbohydrate—a definition which gives a considerable margin for difference of opinion and discussion.

Food Additives

As regards food additives, until about ten years ago almost every regulation was based on the principle that it was prohibited to use anything injurious to health, but all other additives were permitted, the manufacturer being responsible. As food additives are increasingly being used, legislation is now being directed toward permitting only those substances which occur on positive lists. In Europe the impetus was given by a meeting convened in Bad Godesberg, Germany, in 1954 by the Deutsche Forschungsgemeinschaft (German Research Association), whose results of annual meetings have been adopted and elaborated by FAO/WHO in cooperation with specialists from other

parts of the world. The first meeting resulted in the development of Eurotox, an organization which deals with any problems vitally affecting public health and seeks to direct this development. For instance, there have been after the meetings on food additives: meetings on air pollution problems, on standards for cosmetics, and on poisonous substances occur naturally and with which man might come into contact.

In recent years new laws have come into being, for example, in Germany, Italy and Belgium, in which the above principles are laid down to a greater or lesser extent. This shows that in Europe, too, the problem of food additives commands a widespread interest, and justly so. This period of growth is attended with numerous problems for which it is not always possible to find an immediate solution.

First, for including certain substances on positive lists the toxicological data must be provided in order to obtain a government's authorization. With the large number of countries in our continent this leads to repeated filing of applications in several countries, where the requirements regarding toxicological investigation may be different and changed time and again. This causes much loss of time and energy, and attempts to prevent this by establishing, at least inside the EEC, an organization like the Food and Drug Administration in America, have not been successful. An organization of this kind could lay down standards for the whole area and make the use of food additives subject to its authorization. In the opinion of many countries this would result in excessive centralization, interfering with the rights of the individual states.

Fortunately, however, there has of late been a greater tendency towards centralization. Toxicological examination and the available scope for this are greatly burdened by much duplication of work. There is little international cooperation and coordination of work. It is in most cases extremely difficult to obtain information on investigations already carried out elsewhere. Such exchange of information would be of great advantage especially in the case of substances that can be made in a chemically pure form.

Emulsifying Agents

Further discussions have been held regarding the obtaining of permission to use substances which are not chemically pure. There are many examples of this in the category of emulsifying agents, thickeners, etc. Substances are often involved which have been made from natural products by a simple process, such as gums,

alginates, etc., which often show very wide differences in composition. Besides, some emulsifying agents have been made from oils which are not always of the same composition: the iodine value of groundnut oil ranges between 80 and 105, and that of soyabean oil between 120 and 143.

Moreover, the treatment of these products may sometimes differ somewhat, which may lead to divergent constants. It has been suggested to investigate not only samples of such substances which have been made in accordance with the normal process, but also deviating samples of which, for instance, the temperature has been raised or which have been heated for a longer time. This, however, would make the toxicological examination more and more extensive and far too complicated. A partial solution could be to formulate the purity criteria for food additives as clearly as possible, permitting deviations within specified limits. These can be found for most substances, and guarantee that the food additives meet the requirements. Here I think we should also rely on the skill of the manufacturer, who will surely always make his product so as to achieve the best technical result and who will, therefore, continue to work along the same lines.

Coloring Material

Coloring agents are generally of a similar complex composition. Here, special attention must be given to the absence of intermediates, while here again the composition of the permitted coloring agents to be used should be constant. This is achieved by making standard samples to be used as material for comparison during the chromatographic analysis to which the coloring agents are subjected. The carcinogenic effect of some previously used coloring agents has given rise to revised views on food additives. This showed the need for toxicological investigation preceding the use of food additives. In Europe the carcinogenic effect of coloring material is still often investigated by means of injection tests.

It is still doubtful whether this method of administering, which deviates so much from the normal one, is decisive as to whether some coloring agent can be used or not. The same applies to other food additives, where injection also sometimes reveals tumors, whereas with oral administration no abnormality is found.

Flavoring Substances

Another problem which presents itself relates to aromatic substances. Generally, there are substances which are used in extremely

small amounts, and therefore their use has hardly ever been found to have a detrimental effect. If, however, some *system* is to be brought into aromatic substances and the way in which they may be permitted, two categories can be distinguished which can be considered from different angles:

(1) Aromatic substances occurring in natural foods or in vegetable matter used in preparing foods and identical chemically pure substances applied in similar quantities. These have been consumed by the population for many years without giving trouble; and

(2) Aromatic substances which can be made synthetically but which do not occur in natural foods.

Simply permitting the first group would not involve any greater danger to public health than has so far been the case. The second group may include substances which are injurious to health, although the small amounts applied greatly reduce the risk. Toxicological investigation would be necessary, whereby preference should be given to substances of which the largest amounts are applied.

Drawing up positive lists of flavorings the use of which is permitted, is an extremely difficult and complicated matter, in my opinion, for the following reasons:

(1) The quantities used are, generally, so small that maintaining a check on the correct application of the regulations becomes extremely difficult. For the majority of the flavoring components special analysis methods have to be established which are very complicated and can only be applied at great pains. It is for this reason that it is impracticable for an inspection laboratory to identify an unknown substance which does not occur on the list but nevertheless has been added.

(2) The use of flavorings identical with those occurring in natural foods may be required to restore the original flavor part of which has disappeared during the manufacturing process. They may be added to the product itself or to the product in a different form, such as to coffee powder. The food contains the same substance partly derived from the natural product, partly produced in a chemically pure form and then added. There is hardly any sense in mentioning these substances on a positive list; their addition is undetectable.

(3) If synthetic substances identical with those occurring in natural foods, are used in other foodstuffs, such as butter flavoring in margarine, it seems to me that hardly any objections can be made to this from a toxicological point of view, particularly if these sub-

stances have been examined toxicologically. For there is the double security of a consumption of many years' standing and of the toxicological examination, while, moreover, taste sets rigorous limits as to the quantities to be added. If nevertheless these substances have to be mentioned on a positive list, the following points must be considered.

Procuring these flavorings is a task involving many years' work and requiring a capital investment of many millions. The industry undertaking this task must therefore be sure that it is allowed to use the substances found, which enable it to give its products a singular quality, in its own products exclusively, for a number of years. This is only possible if these additions are patented or if they are kept secret. Patenting is difficult for these substances. In Europe where patent laws differ from country to country, a patent can be taken out in a few countries only. In other countries, for example, in Germany, it is very difficult and virtually impossible to patent flavoring materials. If certain flavorings are patented in one country they will become known as soon as the patents are published. In countries where they cannot be patented they can be used by competitors, who do not have to pay anything for it. Consequently, most of these substances are never patented, and are never published. German, Dutch and Italian laws contain an exceptive clause so that *there* these substances may be used without their having to be mentioned on a positive list. The authorities may, however, require manufacturers to prove that the flavorings occur in known foods and that they are applied in a pure form.

The development of chemistry in general and of physical apparatus such as spectrophotometers, mass-spectrometers, apparatus for gas-chromatography, etc., in particular, have promoted developments in the field of flavorings in a way one had never dreamt of. This led to considerable improvements regarding the taste of all sorts of products, which we must not suppress. Factory preparation of many products causes their taste to become flat which does not have a favorable effect on the quality of the goods. Boiling down of jam, drying of products or heating give loss of flavor or a change in flavor. But now, chemistry gets a chance to restore the original taste of the fresh product with the aid of substances which are completely identical with those originally present in the fresh product.

These endeavors are so important that they must be supported as much as possible and not be obstructed by unnecessary publication.

No manufacturer will invest large amounts of capital in research, if he knows that competitors can make use of his work without any costs. It is my opinion that all flavorings present in natural foods should be permitted, also if they are prepared purely synthetically, without their having to be mentioned on positive lists or published in one way or another.

There are some other additives which can be made in a pure form, and are used as such. I think of preservatives, anti-oxidants, acids and salts the constant composition of which is not subject to doubt in general. In most cases it is a chemical entity, in some cases a mixture (for example, polyphosphates). The additives in question are not usually substances which one wants to keep secret for some reason or other and the results of toxicological examinations may therefore be published so that they become available to everybody.

Toxicology

The toxicological examination of food additives is a very important field which is still in need of further development. First of all, the number of European laboratories applying themselves to toxicological examinations is much too small and, furthermore, it is extremely difficult to find enough competent toxicologists. This led to my motion in the second joint FAO/WHO conference in Rome on June 24-25, 1963, that the following recommendation be mentioned in the minutes:

> Governments are urged to create adequate facilities for the biological testing of food additives and for the training of toxicologists in this field.

Most laboratories that are used for this purpose belong to universities or to governments. Private laboratories for this purpose are practically unknown in Europe. Indeed, large industrial firms have their own biological laboratories but smaller firms have to apply to laboratories which have not been set up for this purpose. The high expenses involved are often a real burden to smaller firms, which can certainly make excellent discoveries, but the turnover which must carry these high expenses is much smaller in their case. Toxicological examination can provide a reasonable degree of reliability as to the harmlessness of a substance for human consumption. But recent experience has shown that much research is still necessary in this field. This means not only that experiments must be carried out on various types of animals but also that ultimately the substance must be tested on human beings. Until recently there was a large number of coun-

tries which strongly objected to this idea, but these objections have been gradually abolished.

We aim at reliable conclusions, to be drawn from investigations which are kept within reasonable limits. It is particularly this problem that has to be solved by more extensive research. Professor Lammers of Utrecht University in his inaugural address gave his views on "the predictive value of the pharmacological experiment." According to him the answer cannot simply be "good" or "bad."

> The answer must be less emphatic. It must express the idea that although a certain optimism is justified, there are always a large number of factors owing to which an investigation based on experiments on animals cannot provide a correct insight. But, above all, the conclusion must be drawn that every investigation must be as extensive as possible and adapted, as it were, to the special nature of the substance. There is no such thing as a pre-fabricated procedure.

Research only will carry us further.

Positive Lists

Up until now our ideas about the application of food additives and the specific problems connected with it, were based on the opinion that only those substances may be used that occur on positive lists, with the exception of flavorings identical with those present in natural foodstuffs, but which are added in a chemically pure form. However, there is a marked tendency in Europe to change the opinion regarding the strict principle of prohibition for all food additives with the exception of those mentioned on positive lists. By way of example, I should like to quote Dr. Steiger, who supervises the harmonization of foods legislation in the EEC. He expressed his opinion in a lecture which was delivered in Germany in June, 1964, during a meeting of the German "Bund für Lebensmittelrecht und Lebensmittelkunde" (Society for Food Legislation and Food Science).

Translation:

> Now it cannot be argued that we have used the "prohibition principle" in the case of our food *additive* directives, for they include permitted lists with the consequence that all the other additives are indeed *prohibited.*

However, *even* with food additives that does not mean any *absolute* committal to the prohibition principle. If I may refer again to the situation which will result when the six or eight directives on the *main* additives likely to affect public health have been issued, these directives will have to be summarized in a standard additives directive. In my opinion the question will then arise as to whether in this directive we should further lay down in the first section a relatively broad additive definition and make the permitted lists obligatory in a second

section—in other words we use so far the prohibition principle. *But then* in the third section we will lay down that all other additives (according to the broad definition) are subject *only* to the abuse principle. On account of the great significance of such a formula for the protection of consumers' health one should then of course provide for the Commission of the EEC, delegated by the Council of Ministers, to be able to put an end to abuse by some rapidly effective method, for example, to make lists of prohibited substances so called negative lists.

If such an arrangement were possible we would even arrive at a combination of the two principles in this problematical field of additives—without endangering the cause. Incidentally, these considerations prove anew that we must be as flexible as possible in the EEC, especially in respect of problems which may have become obdurate or have reached a deadlock on national level and, if necessary, by breaking new ground.

Following this train of thought we should be able to allow flavorings, particularly flavorings identical with those occurring naturally in foods, without a positive list and we could prohibit toxic flavoring substances natural or synthetic on a negative list.

Harmonization

As I have already said, attempts are being made to bring more uniformity into the diversity of legislation in the different European countries. The reason for this is to be found in various economic agreements, for example, such as that resulting from the 1958 Benelux Treaty which had already been planned in 1944, and in 1957 the Treaty of Rome on which the formation of the EEC is based. Both treaties consider it necessary to facilitate trade between the countries concerned by harmonizing legislation, of which the food and drugs acts form an important part. Harmonization has been achieved on several scores within the Benelux countries, among these pasta, honey, coloring matter, cocoa and chocolate, and micro-biological control of foods on the presence of pathogenic bacteria.

According to the original treaty, harmonization within Benelux should have been completed in 1963. Because not much had been achieved that year it was decided to introduce an accelerated harmonization procedure in 1964 through which a number of provisions hampering trade would become obsolete. This accelerated harmonization was to take place under the direction of the chairman of the Health Councils for Belgium, Holland and Luxembourg.

There has been much opposition to this because all three countries belong to the EEC. After Benelux harmonization it is the turn of EEC harmonization and both of these might bring about costly changes in industrial regulations. As points in favor of the Benelux harmonization it is often stated that a common standpoint would give Benelux a stronger position in the EEC negotiations, but this common standpoint can also be obtained by deliberations beforehand without its resulting in harmonized Benelux legislation.

European Economic Council

For this reason harmonization of the laws of EEC countries and the way in which it is brought about are more important. So far laws on coloring matter and preservatives have been harmonized. However, no definite directive for factory made products has been established as yet.

The draft directives for foods legislation in the EEC are being drawn up by a sub-department of the EEC General Agricultural Directorate. This sub-department is headed by Dr. Steiger. He has a working group in which the ministries of the member states are represented by at least one member. There are, apart from this working group, special working parties each dealing with a number of foods under the chairmanship of an EEC official, in which the ministries of the member states are again represented by an expert.

The special working party concerned draws up a preliminary draft directive. They also consult specialists of the member states. They also may, at this stage even, ask the opinion of the industrial organizations of the EEC.

As soon as the preliminary draft is finished it is submitted to the Union des Industres de la Communauté Européenne—representing the entire industry in the EEC-countries—and the EEC association of consumers for their opinion. Using their advice as far as he thinks useful Dr. Steiger's working group then draws up the final draft of the EEC directive and submits it to the EEC Commission for approval.

The EEC Commission sends the draft to the EEC Council of Ministers, who decide officially whether the Economic and Social Committee and the Assembly of the EEC should be consulted about the draft.

The EEC Council of Ministers submits the draft to the governments of the member states to obtain the official opinions of the

various countries, before adopting the directive officially. At this stage, the member states may again consult industry, scientists and consumers of their country. After the directive has been issued by the Council of Ministers, it is gazetted.

Officially published directives have no immediate effect on the trade and industry of the member states. It only means that the member states must amend their national legislative provisions within a year in so far their legislation should deviate from the EEC directive. The member states are not obliged to use the same wording as that of the directive but the effect of the harmonization must correspond with that envisaged by the directive. The national legislations must be amended in such a way that foods which do not meet the requirements set by the EEC directive must no longer be on the market in EEC countries after another year has expired. Trade and industry may bring their opinion to bear upon an EEC directive in various stages. The farther the legislation procedure has progressed the more difficult it becomes to have a directive changed. It would therefore be an advantage if industry could participate in the negotiations which take place between Dr. Steiger and the government experts of the various countries.

I have mentioned already that in EEC a directive for coloring matters and for preservatives had been established which has now to be taken up in the legislation of the member states. A directive for anti-oxidants is nearly finished. It is gratifying that in the chaos which exists in the field of dye stuffs which are allowed in various countries to be used in foods, they have succeeded in EEC to agree on a limited but satisfactory list. Further on, it has been questioned whether new developments which would make necessary additions to positive lists, could be realized rather quickly. It is a hopeful sign that now a modification of the directive for coloring material has already been established.

Codex Alimentarius

Apart from the harmonization taking place within the EEC endeavors are being made to set up food standards which will be contained in a *Codex Alimentarius* to be drawn up by a Codex Committee working under the auspices of FAO and WHO.

In May of this year Mr. Koenig of the United States delivered an excellent lecture on the subject during the International Food Standards Symposium held in Washington. It does not seem neces-

sary, therefore, to go into it in detail, but for the sake of completeness I should like to mention the main points of the policy.

The plan for a European *Codex Alimentarius* originated at the time with Dr. Hans Frenzel, an Austrian, who thought that a European and, possibly, a world-wide *Codex-Alimentarius* would be an instrument with the aid of which it would be a simple matter to set up food standards on which the legislations of the various countries could be based, since they had to be harmonized anyhow to facilitate the world trade in these products. After the committee had been operating for some years as an independent European committee, it was incorporated in WHO/FAO in 1963. The way in which the regional European Committee will carry out its task is being discussed, but the main points have already been settled at previous meetings.

The Codex Committee operates as follows: At the annual meetings of the Codex Committee which take place alternately at Rome (seat of the FAO) and at Geneva (seat of WHO), the terms of reference to be used as a basis in drafting the various chapters of the *Codex Alimentarius* are decided upon and distributed. Drafts may be drawn up by an international expert panel under the chairmanship of one of the member states, or by an international association of trade and industry or an international scientific association. If an expert panel under the chairmanship of a member state is charged with this task all member states are allowed to send representatives of government, trade, industry and science to the committee; international associations accredited to the Codex Committee have the same right. If an international association of trade and industry or an international scientific organization is charged with the task of drawing up a chapter, these associations themselves will appoint the members of the expert panel.

The expert panel mentioned above will submit the draft chapter to the General Secretariat of the Codex Committee as soon as it has finished its work. The Secretariat passes it on to the governments of the member states together with the documentation. The draft is read for the first time and discussed at the annual meeting and preliminary comments are given.

After the first reading at the annual meeting the draft is sent within a period of several months to the member states for their official opinion. According to a decision taken unanimously by the

Codex Committee at their annual meeting at Rome in July 1963, each member state is to set up a national Codex Committee comprising representatives of government, trade and industry. The task of this committee is to formulate the opinion of the country concerned about the various draft chapters.

The General Secretariat of the Codex Committee collects the opinions of the various countries and passes them on to the expert panel concerned, which draws up an amended draft taking into account the opinions of the countries. The second reading of the (amended) draft takes place at the next annual meeting of the Codex Committee, after which it is again submitted to the member states for their opinion. This procedure is continued until either a sufficient number of all member states, or the majority of the member states in a certain region (for example, the continent) agrees with the version of the draft, in which case the chapter concerned of the *Codex Alimentarius* is published with an indication of the member states which have accepted the chapter.

The officially published chapters of the *Codex Alimentarius Mundialis* have legal effect only in those member states which have accepted them. If a certain standard was accepted as a *minimum* standard, the accepting country must not set lower standards but may set higher ones.

If the chapter concerned was accepted as *trading* standard, the accepting country must not refuse imports for reasons of foods legislation, as long as they comply with the standards set, but it is free to set lower or higher standards, within its own territory, for its own products.

Labelling

The manifold regulations existing in the various European countries clearly show that there are vast differences as to the labelling of food. There is a general rule that the food label must clearly show the usual name of the product, so as to give an indication of the particular regulations applicable to it.

There is one great difficulty that emerged in connection with the harmonization of the legislation in the EEC countries, and that is likely to become even greater when other countries such as Great Britain, Switzerland, Austria, Greece and the Scandinavian countries are going to be included in a united Europe, namely the language. The EEC was set up to create a large economic unit within which

free trade would be possible. There is no trouble at all in the case of products that are sold in one country only, as the declaration denoting the type of product has to be printed only in the language of the country concerned.

But what language should be used for products that are going to be sold in various countries, when one does not know beforehand in which countries even? It was proposed in the EEC to make it obligatory for the name of the product as prescribed in the Food Law, to be mentioned in one Latin and one Germanic language. But this was rejected as it did not solve the problem. Some products such as margarine would not give rise to difficulties, chocolate would be somewhat more difficult, although this name would be understood anywhere, but the various types of jam, vegetables, etc., would cause great difficulties. Ample discussions could not solve the problem, not even for the relatively small number of EEC countries, so that the problem is bound to cause even greater difficulties in a fully integrated Europe.

It seems to me that the solution is to be found in allowing the manufacturer a high degree of freedom with the restriction that the name of the type of product should be clearly printed on the product in one language, so that it is easy for officials to recognize it. In any case the name should be given in the language of the country where it is sold, if this is one country only. Manufacturers will somehow choose the way leading to the highest turnover and they will have to inform the consumer accordingly, when the product is sold in various countries.

Apart from this it is usually required that the manufacturer's name and domicile is mentioned on the product, or the importer's name and domicile, in the case of imports. In come countries such as Holland it is not always required to declare these data on the pack, although the food inspectors must be able to trace the manufacturer in the case of deviations. This is easy with important standard brands, but in other cases the factory can always be traced via a code.

A declaration of the weight is generally thought to be very useful, but this also gives rise to certain complications. Products which are often sold in vending machines at a fixed price such as chocolate bars cannot always be of the same weight. The fixed price is attained by varying the weight of the product when the price of the raw materials rises or falls. One might start declaring the weight of

products when they are heavier than 100 g. For other products such as dried soups it is more important to know for how many plates of soup the contents will be sufficient than the exact weight of the contents.

Declaration of the weight of ready-made meals (deep-frozen or dried) also gives rise to difficulties because of their varying composition owing to the prices of raw materials, while moreover the dry weight of these products does not convey anything.

Declaration of the composition, in general lines at least, seems to be useful for the consumer. But this should not go too far, as many products, such as margarine are subject to certain modifications, a varying fat composition, for instance, in connection with the season and with the market price of the raw materials, while the packaging cannot be altered every time. In most European countries declaration of composition is not obligatory. In Italy only, the composition must be printed on the pack. But it seems to me perfectly superfluous for all food additives to be declared if they appear on positive lists and are permitted in standardized foods. They do not mean a thing to the great majority of consumers and those who know more or wish to know more about them can easily inform themselves on them. Considering the language difficulties mentioned above you will realize that in Europe a tendency is already noticeable not to print more information on the packaging than necessary. Otherwise there would not be enough space on the pack.

In German restaurants it is obligatory for food additives present in the food to be mentioned on the menu. Thus it happens that the various dishes on the menu are followed by a series of asterisks which refer to a list of additives at the back, which nobody ever bothers to read. In this case, too, there is a fluctuation of tendencies, first some years ago, towards more and more declarations, while at present the opposite is perceivable, at least in official circles. The consumers' organizations are still extremely keen on getting more and more information printed on the labels and on limiting the use of new processing methods and new additions.

In many countries the consumers also wish a declaration of the processing date and of the ultimate date of consumption. In the case of preserved food it is useless and undesirable to print the processing date on the packaging in a form intelligible to the public. *Unnecessary*, as in many cases the date does not provide a clue as to the quality

of the product. In the case of jam from SO_2—treated fruit for instance, it may happen that a jam bearing a later date has been processed from much older pulp than a jam processed at an earlier date. As to vegetables there are good and bad seasons. An older tin with vegetables of a good season may be of a better quality than a later one with vegetables of a bad season. *Undesirable,* as the conconsumer is likely to take the packaging with the latest date on it, so that the older tins accumulate, getting older and older. It may be desirable to mention the ultimate consumption date on products which may become detrimental to health if they are kept too long. But the value of the processing date and ultimate date of consumption is strongly reduced by the fact that keeping conditions—temperature, relative humidity of the air, etc.—may vary considerably. Only Italy in its new Food Law made it obligatory to mention the processing date.

Conclusion

I have tried to give you an idea of what is going on in the field of foods legislation in Europe. Much of it will be known to you, but there will also be many aspects which are new. The contrasts that exist between the foods legislation and the foods inspection in the various countries may remind you of the differences that exist between the various states of the United States. Your country has set up a federal legislation, which we are trying to attain through harmonization, within the Common Market for the moment, and later in the whole of Western Europe. When you consider the controversies which may exist between federal authorities and those of the various states, it will be clear to you that we are up against the same sort of difficulty in trying to harmonize the food legislation in Western Europe. But our difficulties are intensified by the fact that we do not have one federal government, but have to do with many governments —some of which do not like the idea of supra-national regulations very much—in trying to arrive at a harmonization. Furthermore, we have to deal with very different ideas of the experts representing their governments and we have to consider the widely varying interest of the industries in the various countries.

But as you, like all well-meaning people, try to span the contrasts that may exist between the federal government and those of the various states, so we are working confidently at the future of a united Europe, in which many problems we are facing today will have been solved for the benefit of the whole.

There is one problem, which you do not have and that will be with us forever—namely, the language problem. These languages which give each nation a character of its own which we would not like to part with, also make it more difficult to cooperate with other nations and often lead to misunderstandings. It is not possible to find, for every word and every concept, an equivalent in the other language. We, Dutchmen, consider ourselves fortunate that we, a small nation in a vast world where few people speak our language, are forced to learn several languages and are able to contribute toward a better mutual understanding of the nations. If this lecture should prove to be a help in attaining this end, then I shall feel amply awarded. **[The End]**

PESTICIDE RESIDUE TEST INVENTED BY FDA CHEMIST

A sensitive detection device for identifying and measuring organophosphorous pesticide residues in food products has been invented by a Food and Drug Administration chemist.

Mrs. Laura Giuffrida, a specialist in the application of instruments to chemistry in FDA's Bureau of Scientific Research, devised and perfected the new device during the past two and a half years. Mrs. Giuffrida calls the device a "sodium thermionic detector."

Several pesticides now widely used by farmers contain phosphorous. These compounds are becoming more popular because they remain on the plant or in the soil for shorter periods than pesticides containing chlorinated hydrocarbons.

The FDA has the responsibility for determining that the amount of pesticide residue remaining in food crops will be safe for consumers. FDA scientists set safety limits or "tolerances" on the amounts of pesticide residues permitted on crops. During the past two years, FDA sampled and analyzed more than 25,000 interstate shipments of raw agricultural products which had been exposed to pesticide chemicals.

Until the new device was developed, detection and measurement of organophosphorous pesticides were difficult. The new detector, which is now being developed for extensive use in FDA's 18 district laboratories, makes possible the specific determination of phosphorous compounds present. Mrs. Giuffrida said the dectector may also prove useful in the drug and petroleum fields for the analysis of phosphorous compounds.

Mrs. Giuffrida, in her initial studies on organophosphorous compounds, noted occasional increased responses to such compounds when using a gas chromatographic unit equipped with a hydrogen flame detector. Further investigations showed that when a sodium salt was present on the detector, the unit became highly sensitive to phosphorus. Realizing the importance of this phenomenon, Mrs. Giuffrida designed a detector for phosphorus that incorporated a sodium salt into its design.

A special advantage of this unit is that it can detect the presence of phosphorus—in minute quantities—even with other elements present that could interfere with results from conventional means of detection.

Report on the Growth, Organization, Operations and Plans of the FDA

By JOHN L. HARVEY

This Report Was Delivered Before the Food, Drug and Cosmetic Division of the American Bar Association in New York City on August 12, 1964. Mr. Harvey Is Deputy Commissioner of the Food and Drug Administration, United States Department of Health, Education and Welfare. This Article Is Reprinted, With Permission, from the November 1964 Issue of *The Business Lawyer*.

THIS MEETING gives us an opportunity to discuss some of the more important developments dealing with the Food and Drug Administration in the year since your last meeting, and I will touch on a very few of these.

Perhaps the most important development from the standpoint of FDA, the industries with which we deal, and the consumers whose interests we protect, was the major reorganization which took place during the past fiscal year. There has been widespread publicity about the specific units which were created in this reorganization, much of which followed the recommendations of the 1962 report of the Second Citizens Advisory Committee.

I see no point to repeating this listing, but instead would like to tell you how this has worked out in the approximately eight months that the reorganization has been in effect.

Already Mr. Larrick and I have been freed of some of the detailed and operational day-to-day workloads which formerly took so much of our time, and we do find that we are able to do a better job of coordination and leadership.

We have made significant progress in upgrading our scientific programs with the result of elevating the role of the scientist in the operations of FDA.

We have made some progress in establishing a more effective means of processing the various petitions, applications, and the like

which we receive from industry. I do not mean to say we have achieved our ultimate objectives in this area, and further plans to improve are being implemented.

Our planning office is making significant progress on two fronts: planning for immediate needs and developing long range, or what we call five-year plans which we hope can be updated every year. We have materially improved our supervision and coordination of regulatory and enforcement offices, in no small measure as a result of improved communications between field and headquarters operations including the Office of the Commissioner and the separate bureaus.

Our new Bureau of Education and Voluntary Compliance is off to what we believe to be a very good start and we have been pleased with the response of industry to the educational efforts already accomplished. However, we expect these are only the beginning.

The reorganization contemplated the appointment of a National Advisory Council comprised of representative citizens to advise the Commissioner on national needs and the effectiveness of FDA's program policy. It is anticipated that the council will serve as a contributing source in planning, developing and executing FDA programs, and will permit us to establish an even closer relationship with many outside groups having knowledge and experience which will be of value to us. Appointment of the members of the council will be made by the Secretary and we expect an announcement shortly.

We appointed our new Medical Director, Dr. Joseph F. Sadusk, Jr., and those of you who have had occasion to deal with him in the last few months will, of course, recognize that we are indeed fortunate that he accepted this post.

The reorganization contemplated the establishment of the new position of Associate Commissioner for Medicine and Science to give even greater consideration to the role of the scientist in matters where policy decisions are involved. So far the position has not been filled. Similarly, we have not as yet appointed a director of the Bureau of Education and Voluntary Compliance and a director of the Bureau of Scientific Research. We hope to have an announcement on these three within a matter of months.

Administration's Proposed Legislation

Legislation is a subject always of interest to those who follow FDA matters. Although there are a number of bills at various stages

of committee considerations in both Houses involving matters under our jurisdiction, the primary substantive legislation in which we have vital interest is the "Food, Drug and Cosmetic Act Amendments of 1963," introduced by the Administration in the House of Representatives on June 4, 1963 (H. R. 6788). An identical bill was introduced by Senator Hill in the upper House on March 2, 1964 (S. 2580). The Administration's proposed legislation does essentially four things:

(1) The amendments would extend and clarify the inspection authority under the Food, Drug and Cosmetic Act, so that it can be determined whether foods, nonprescription drugs, cosmetics and therapeutic devices are being manufactured and marketed in accordance with the law. You will recall that as part of the Kefauver-Harris Drug Amendments of 1962, increased inspectional authority was granted for establishments manufacturing prescription drugs. This amendment clarified our authority to request and obtain, when inspecting such establishments, all things, including records, files, papers, processes, controls, and facilities which have a bearing on violations of the law with respect to the commodities produced. Our experience has shown that in order to adequately carry out our responsibilities, and so that a food and drug inspector can do the things he is trained to do, such clarified authority must be extended beyond prescription drugs.

With science and industry producing more and more potent, and sometimes toxic food additives and pesticides used on food crops, there can be no substitute for the clear authority to obtain facts in carrying out the FDA's responsibility to protect the consumer.

(2) The amendments would approve cosmetics for safety before they may be marketed. The present untested or inadequately tested cosmetics may be freely marketed until such time as injuries to consumers or independent tests by the government show that the cosmetics are hazardous or harmful. Our records are replete with instances where women have been injured by such cosmetics.

(3) The amendments would require that devices on the market be manufactured in accordance with good manufacturing practice and that new devices be approved for safety and effectiveness before they are marketed. Devices under the Food, Drug and Cosmetic Act include not only legitimate surgical adjuncts, but worthless or near worthless gadgets sold directly to the layman or to pseudo-medical practitioners for treating cancer and various other serious diseases. These devices may now be marketed with impunity, sometimes for

years, until the FDA has gathered the necessary proof to establish the worthlessness of such a device in a court action. I need not remind this audience of the difficulties in sustaining such a position. The proposed bill would adopt in principal the preclearance procedure now in effect for new drugs and would require their manufacture under appropriately controlled conditions to assure reliability and pretesting before the marketing of such devices for safety and efficacy.

(4) The amendments would require suitable warning labels against the hazard of avoidable accidental injury from articles covered by the Food, Drug and Cosmetic Act, where such warnings are necessary for safe use. This amendment would close a gap in consumer protection which was allowed to remain in the law when the Federal Hazardous Substances Labeling Act was enacted in 1960. In the case of foods, warnings would be required only for pressurized dispensers because this is the only area in which the need for warnings have become apparent. In the case of drugs and devices, the proposed cautionary labeling amendment would be a clarification of present provisions as to label warnings.

We can only report at the moment that these proposed bills have been introduced into both Houses and that there is no present schedule for hearings. We are optimistic that substantive legislation along these lines will be enacted. We were pleased and gratified that President Johnson, in a consumer message to the Congress on February 5, 1964, recommended enactment of the various proposals just discussed. Commissioner Larrick testified on Senator Dodd's bill dealing with additional controls of certain dangerous drugs earlier this month.

Finally, I would like to report to you and possibly clarify to some extent, recent regulations dealing with two drug matters included in the Kefauver-Harris Drug Amendments.

Although the Kefauver-Harris Drug Amendments contained several far-reaching provisions, the amendments dealing with the addition of "effectiveness" and the record-keeping and reporting requirements, together form probably the most important.

"Effectiveness" Provisions of 1962 Drug Amendments

Under the law prior to the 1962 Drug Amendments, new drugs were cleared on the basis of safety alone. There was no requirement that they be shown to be effective, as well as safe for their intended use.

Testifying in support of the Drug Amendments of 1962, the then Secretary of Health, Education and Welfare, Abraham Ribicoff, put the case for effectiveness as follows:

> A final point concerning this proposal is that it enables us to require that all the claims be medically justified. Under the existing safety clearance, we can consider effectiveness but not whether the claims of benefit are exaggerated. When the decision is reached that the drug has therapeutic merit justifying the risk of any adverse effects, we have exhausted our jurisdiction. We have no basis for insisting that the manufacturer or distributor justify the full scope of each of the claims that he proposes to make.
>
> As a direct result of this, there is promotional material now going to the medical profession for approved new drugs which has claims that are not fully supported by any clinical data submitted in the new drug application or by any other data that we know of.

When the bill was finally enacted into law, it provided that a new drug should not be permitted on the market unless there was "substantial evidence" to support all the claims that were to be made for it. And "substantial evidence" was specifically defined by Congress as:

> . . . adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.

Records and Reporting Provisions of 1962 Amendments

The late Senator Kefauver, during the floor discussion of the drug bill in the Senate, stated that the section on records and reporting:

> . . . would require the keeping of records of experience on new drugs and antibiotics. A company would have to keep records as to the effectiveness and as to the side effects of drugs and FDA would have access to that information. This has been one of the great failures in the past. Records have not been available to the Food and Drug Administration. It could not learn, for example, how many cases of aplastic anemias have been reported to the company because the records were not available to it.

The law as enacted authorized regulations and special orders to require adverse effects and other clinical experience and relevant data, with respect to new drugs and antibiotics already on the market, to be reported to FDA.

With reference to "new-new" drugs, the amendments became effective on the date of enactment, October 10, 1962. NDA's (new drug applications) since that date have had to stand the test of effectiveness, and a drug had to be shown, by substantial evidence, to not

only be safe for the recommended conditions and under the labeled directions, but must also have been demonstrated that it will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling. On June 20, 1963, another milestone was reached in the publication of new drug regulations which included the reporting procedures both as to frequency and to content.

For those drugs which already had effective new-drug applications on the date of enactment, the law provided a two-year moratorium on the need to demonstrate substantial evidence of the drug's effectiveness. This, in our opinion, meant that generally speaking, and during this period, a drug which had previously been subject to the new drug procedure would not be removed from the market on the sole ground of lack of substantial evidence of effectiveness for uses claimed for them by previously cleared labeling. This grace period, expires October 10, 1964, after which time it was the clear intent of Congress that the vast majority of drugs would be both safe and efficacious and that the labeling thereof would have received the approval of the FDA.

On February 28, 1964, we published proposed regulations in the *Federal Register* which were designed to prepare for this approaching deadline by calling for a review of, and the bringing up to date, the effectiveness data on this important group of drugs. Many comments were received and I take this occasion to reiterate again that such comments are most seriously considered and it is very seldom that a final order does not reflect to a substantive degree, the considered opinions received. On May 28, the final order was published which provides the current rules under which drug companies should submit the information to us about the data they have been accumulating.

The rules provided that on or before July 27, firms manufacturing or sponsoring new drugs were required to report to us such drugs which are still on the market and those which have been discontinued or never marketed. If discontinued, we wanted to know why; such information may have an important bearing on the consideration of other similar drugs. By November 27, 1964, additional information will be required. Briefly, what we are asking for is a copy of the label on the package of each drug and of the package insert or brochure bearing directions of information for use of the article and that a responsible official of the manufacturing or sponsoring firm submit to us a statement, if such be the case, that the drug's label, package insert and

other promotional material currently in use offer the drug only for the conditions which were covered by the original NDA, antibiotic submission or approved supplement. This condition should prevail in most instances as it has been required that any substantive change in the labeling of a new drug requires the submission of data and a supplemental NDA. Where the firm's review discloses that supplemental NDA's have not been changed entirely in conformity with labeling or promotional claims, we will require submission of the scientific or other data relied upon by the firm to support the additional claims. We also will require information on any side effects, contraindications, or untoward reactions which may have been due to the drug, but which have not been reported to us previously. Obviously, if the claims go beyond those that can be fairly supported by clinical experience or sound scientific data, we will want to know what the firm plans to do about either discontinuing or obtaining acceptance of unapproved claims and revising the promotional material to fit the conditions. We sincerely hope and trust that this operation will not be beyond the resources of either industry or our medical and administrative staffs. I cannot improve on the comments Commissioner Larrick made when he said:

> We are glad that Congress has given us this unique opportunity to review past medical decisions permitting several thousand new drugs to go on the market. This review will include not only a new look at the safety of these drugs, but a first-time comparison of the actual promotional claims with the medical evidence on which they are based.

There has developed a not unusual divergence of views between ourselves and some in the drug industry regarding the status of certain drugs originally classed as new drugs, but later, because of accumulated experience, deemed on safety considerations alone, to be no longer "new drugs." In our view, Congress called for a review of all medical claims for new drugs cleared in the past upon consideration of safety alone, and that a drug with any claim unsupported by substantial medical evidence should be discontinued at the end of the two-year moratorium. We hold that the "grandfather clause" keeps us from proceeding under the 1962 Amendments against unsupported claims involving only two classes of drugs: (1) those on the market before 1938 and therefore exempted from new drug clearance entirely by the 1938 Act; and (2) those introduced after 1938 which were generally recognized as safe and therefore were never cleared as new drugs. Of course, we have at anytime the right to proceed against products which we believe can be shown in court to bear false or misleading labeling.

Two Current Legal Actions

A suit for declaratory judgment has been filed in the Wilmington, Delaware, district court by the Pharmaceutical Manufacturers Association on behalf of its members, seeking a ruling that would eliminate from the purview of our order "'new drugs" which were on October 10, 1962, generally recognized as safe and those drugs which are now considered both safe and effective. It would of course be most improper for me to try the issues in this forum and we will await the judgment of the court. In the meantime, without committing either side, we have published an interim order which allows drug firms who have drugs in these categories to request an extension of time for the detailed submission of effectiveness data. We have invited such firms to submit, in addition to the preliminary information already furnished under the May 28 regulations, a list of drugs on which they hold this opinion. If we can fairly conclude that the weight of present scientific knowledge is that the drugs listed are generally considered to be safe and to be effective for the labeling representations, we will hold the remaining requirements in abeyance pending the court's determination of the issue.

One other important legal action involved our interpretation of the provision in the prescription drug advertising section dealing with the appearance of the established name in connection with the grade name in the advertisement. As we interpret the law, it calls for the established name to appear everytime the trade name appears, and in a legal action brought in the Wilmington federal district court the industry challenged this view and our position was not upheld in the court's decision. We and our legal counsel are not convinced that the matter should rest at that point, and an appeal has been taken.

Conclusion

In closing, I would like to point out that we have tried to make it extremely plain that legal actions challenging our regulations are, to us, wholly impersonal. We have always believed that when someone feels strongly that a requirement in a regulation is not justified by the terms of the statute, a court challenge of the issues should be welcomed so that there can be a resolution of the points for all to see. Such actions in the past have, in our judgment, served to clarify important matters and have resulted in decisions which have enabled us to do a better job in carrying out the intent of Congress. **[The End]**

Federal Drug Legislation and the New *National Formulary*

By EDWARD G. FELDMANN

The Author Is Director of Revision of the *National Formulary* and Director of the Scientific Division, American Pharmaceutical Association.

ALMOST 20 YEARS AGO, Dr. Justin L. Powers wrote an article on the "history, significance and future" of the *National Formulary*.[1] Many significant changes have subsequently occurred in this legally recognized compendium [2] which now make it most appropriate to update the position of the *National Formulary*. However, more specifically it appears desirable here to discuss the effects on the *National Formulary* which have resulted from the ensuing amendments to the Federal Food Drug and Cosmetic Act, coupled with matters of administrative practice as formally promulgated in the *Federal Register* as well as less formally described in the public comments of government officials.

The review prepared by Dr. Powers was published only eight years after the present Act was adopted in 1938, and the full impact of the various provisions of that greatly expanded and strengthened law were only beginning to be realized. A somewhat comparable situation exists today with respect to the Drug Amendments of 1962.

Position of the *National Formulary* Further Clarified

The position of the *National Formulary* itself was materially enhanced by the 1938 Act. While the original Federal Food and Drugs Law of 1906 had recognized both the N. F. and the *United States Pharmacopeia* as "official compendia," the 1938 Act further clarified

[1] Powers, Justin L., "History, Significance and Future of the *National Formulary*," 1 FOOD DRUG COSMETIC LAW QUARTERLY 577-587, December 1946.

[2] Federal Food, Drug and Cosmetic Act, as amended, Section 201(j), FOOD DRUG COSMETIC LAW REPORTS ¶ 70,055.

the position of these volumes as books of legal standards for drugs. This statute requires that drugs purporting to be those listed in the N. F. must conform to the standards of strength, quality and purity described in that compendium. Furthermore, a clause was newly introduced stating specifically that all determinations of these standards must be made in accordance with the tests or methods of assay set forth in the text of the compendium.[3]

While a number of other provisions of the law—such as the definition of a "drug," the packaging of drugs, and the labeling of drugs—also recognize the authority of the N. F., the requirement that the methods used in determining compliance must be those specifically set forth in the book unquestionably did the most to enhance its position, and its value for enforcement purposes. In the absence of such a provision in the 1906 Act, both the government and the manufacturer were able to separately and independently select and use different methods of analysis to demonstrate compliance or the lack thereof. In view of the fact that the methods chosen could just as well have been based upon personal whim or malicious intent as upon careful scientific judgment, not unexpectedly the analytical results might have varied widely, thereby making them totally unsuitable for enforcement purposes.

This requirement, therefore, of the 1938 Act has proved to be highly beneficial and desirable in providing a mutually agreeable and arbitrary method for the testing of a given product recognized in the N. F. However, this does not mean that for routine, internal quality control procedures the firm must employ the compendium methods. Such methods are required or must be utilized, however, in the event of a court case or regulatory action. While this philosophy has always been understood by knowledgeable persons, it has been subject to some confusion or misunderstanding by inexperienced drug inspectors and new quality control personnel—particularly in light of related provisions regarding "good manufacturing practices" which have been introduced to the Act[4] by the Drug Amendments of 1962. In order to assure complete clarification regarding this matter, N. F. XII carries the following statement in the General Notices:[5]

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[3] Federal Food, Drug and Cosmetic Act, as amended, Section 501(b), FOOD DRUG COSMETIC LAW REPORTS ¶ 70,111.

[4] Federal Food, Drug and Cosmetic Act, as amended, Section 501(a), FOOD DRUG COSMETIC LAW REPORTS ¶ 71,025.

[5] *The National Formulary*, 12th ed., Mack Publishing Company, Easton, Pennsylvania, 1965, p. 4.

Assay and test procedures are provided for determining compliance with N. F. standards of purity and strength. Compliance also may be shown by use of alternative methods, chosen for convenience under special circumstances, provided the results thereby obtained are of equivalent accuracy. However, in the event of doubt or dispute, only the result obtained by the procedure given in this *National Formulary* is authoritative.

This therefore takes specific cognizance of the general suitability and routine usefulness of *"house standards"* [6] but not to the exclusion of the official compendium procedures in matters of possible litigation. It naturally follows that as a result of the 1938 Act, the N. F. test and assay procedures had to become far more general in application as to the products which might be tested and far more specific and definitive as to the individual ingredient in those products. The intensity of the efforts which the official compendia have directed at this challenge and obligation may be judged from a statement by the Director of the FDA Division of Pharmaceutical Chemistry: [7]

Prior to the enactment of the Food and Drugs Act, the United States Pharmacopeia and the *National Formulary* were primarily compilations of information on drugs which were useful to pharmacists, physicians and parmaceutical manufacturers. Their inclusion in the Act gave them an entirely new status as legal standards to be used in the enforcement of the law. Since that time, the committees charged with the revision of these compendia have made every effort to revise these compilations so that they would be adequate for this purpose.

Effect of the 1962 Drug Amendments

In a sense, the most dramatic change of recent years in the nature of the N. F. is reflected in the monographs of N. F. XII. Historically, the pattern of compendia revision has been a relatively slow, evolutionary process, with the result that although major changes took place, they did so gradually and generally were not markedly apparent unless two succeeding editions were directly compared.

In N. F. XII, however, we are struck by the absence of synonyms from all of the monographs, and the absence of identity, purity, and assay specifications from each of the antibiotic monographs. These

[6] *House standards* are procedures of quality control testing and assay which generally, if not always, are abbreviated or less intricate methods of analysis than the compendium methods. As such they may be either simpler types of assay, or they may exclude or greatly reduce the various separation or purification steps of the compendium assays, because of the specific product knowledge available to the manufacturer's control department and to his control analyst.

[7] Frank H. Wiley, "The Analysis of Drugs," 16 FOOD DRUG COSMETIC LAW JOURNAL 733-737, December 1961. In his presentation Dr. Wiley also discusses at some length the need for enforceable official compendia standards and the consequences of Section 501(b) of the Act.

changes are a direct result of the pertinent provisions of the Drug Amendments of 1962 (Kefauver-Harris amendments). In the opinion of this writer the enactment of these specific sections in the amendments was quite regrettable for reasons which already have been detailed.[8] Upon being enacted, however, the Committee on N. F. subsequently studied the provisions carefully in order that the intent of Congress might be served in the most orderly manner and with the least confusion to practitioners and the public.

The new section of the Act pertaining to the standardization of drug names,[9] in effect provides that one and only one "official name" [10] may be applied to any single drug described in the N. F. Furthermore, the same section provides that the name which is employed for that purpose must have the attributes of "usefulness and simplicity." Consequently, the study and review of N. F. monograph titles made by the revision committee involved: (a) a consideration in each case as to whether the former monograph title or one of the synonyms would be more appropriate as the single name to be used for the respective article in N. F. XII; (b) the deletion of all other secondary names; and (c) the condensation of certain lengthy monograph titles to shorter and simpler names.

In many cases the matter of selection became exceedingly difficult. For example, precisely what is meant by the phrase "usefulness and simplicity"? Furthermore, to whom should the names be useful and simple? The legislative history of the Amendments sheds little light on these questions, but suggests that it is desirable for the official names to be relatively euphonious and short. It has also been interpreted that the names should generally be chosen with a view toward the suitability of their use by health practitioners, as contrasted to scientists or the lay public.

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[8] Edward G. Feldmann, "Unwarranted Encroachment—Effect of Drug Amendments on Official Compendia," *Journal of American Pharmaceutical Associations,* NS 2, 640-641, November 1962.

[9] Federal Food, Drug and Cosmetic Act, as amended, Section 508, FOOD DRUG COSMETIC LAW REPORTS ¶ 70,201: "Authority to Designate Official Names."

[10] The term "official name" is rather peculiar in itself, and appears for the first time in the 1962 Amendments. Previously, all references in the Act to nonproprietary names were to the "common or usual name," or in the case of compendium articles to "a drug the name of which is recognized in an official compendium." In the compendia, the term used in referring to the nonproprietary names of recognized articles has been the "official title" or "monograph title."

Also introduced for the first time with the 1962 Amendments is the term "established name" which is employed in connection with drug labeling requirements and is defined in Section 502(e)(2), FOOD DRUG COSMETIC LAW REPORTS ¶ 70,143.

While objections have been voiced from many quarters regarding those provisions of the Amendments which are intended to standardize drug names, and while it is true that the Amendments themselves are rather vague on certain aspects of this problem, nevertheless, it does appear that the review of the individual drug names and the nomenclature practices in general which was necessitated by the Amendments has been a worthwhile undertaking and eventually will prove to be beneficial.

The second striking difference in N. F. XII monographs is the elimination of identity, purity and assay standards from the antibiotic monographs.

The original antibiotic certification requirements were limited to five antibiotics and their derivatives (penicillin, streptomycin, chlortetracycline, chloramphenicol and bacitracin). Because these first antibiotic drugs were available only in the form of extremely crude concentrates at the time they initially were marketed for medicinal use, it was quite natural that a batch-to-batch certification program was adopted as a temporary expedient to assure their proper biological potency. However, rapid scientific advances soon made it possible to produce these antibiotics as essentially pure, crystalline substances with a degree of purity comparable to other fine chemicals.

Their greatly improved purity, coupled with the detailed monograph specifications adopted for them by the official compendia, indicated that there was no need to extend the certification program to include the various additional antibiotics which were introduced during the next decade. In fact, many knowledgeable observers expressed the opinion that the antibiotic certification program for the five original antibiotics no longer served its intended purpose and should have been abolished. However, in spite of the fact that the advocates of antibiotic certification could not advance any substantial scientifically based arguments in its favor, the words "or any other antibiotic drug" were introduced along with a broad definition of the word "antibiotic." [11]

The Committee on N. F. considered the various ramifications of this action and specifically noted that the continuation of chemical and biological test procedures in the N. F. antibiotic monographs would result in dual—and perhaps conflicting—standards and specifi-

[11] Federal Food, Drug and Cosmetic Act, as amended, Section 507, FOOD DRUG COSMETIC LAW REPORTS ¶ 74,041.

cations for the antibiotics. Since both sets of standards have legal recognition, it is apparent that manufacturers, enforcement officials and others would be faced with a serious dilemma under these conditions. As a result, the N. F. Committee concluded that the public interest would be best served if only one set of standards were provided. Since Congress, through the Drug Amendments, made it obligatory for the appropriate government agency to promulgate and implement regulations for batch certification of all antibiotics, the N. F. Committee adopted a course of action which provided for the elimination of such specifications from the compendium monographs for antibiotics.

The fundamental objection of the N. F., as regards antibiotic certification, lies not so much in the fact that each batch of these drugs is now subject to test in an FDA laboratory, but rather that the federal government is now authorized to promulgate regulations for all antibiotics "prescribing standards of identity and of strength, quality, and purity; and tests and methods of assay to determine compliance with such standards." In the United States, this has been a time-honored function of the health professions through the revision and publication programs of the official compendia. Therefore, the antibiotic amendments represent a serious inroad into an efficient and competent system of providing drug standards by thoroughly democratic processes.

Effect of Scientific and Technical Advances

Three major developments have been gradually evolving during the past several revisions of the N. F., which are the direct result of scientific and technical advances in medical therapy, pharmaceutical manufacture, and drug analysis. While these are more directly technical in nature, nevertheless these matters have significant legal implications. As FDA Commissioner Larrick has noted:[12]

> Neither the Legislative nor the Executive Branches of the Government can successfully impose requirements upon drug research and use that are significantly in advance of the requirements the public, including the scientific community, considers proper. Nor may they fail to provide for the controls the public, including the scientific community, recognizes as desirable.

With regard to the N. F., one of the three major developments has pertained to the basis of selecting articles for admission to the compendium, the second relates to the character of the test and assay

[12] George P. Larrick, Statement Before United States House Subcommittee on Intergovernmental Relations, L. H. Fountain, Chairman, March 24, 1964.

procedures, and the third to a safeguard being employed to afford greater confidence in N. F. assays.

Admissions Policy.—In view of the legal status of the N. F. and particularly the references in the Act to ". . . a drug the name of which is recognized in the official National Formulary . . . ," the matter of selection of the drugs to be admitted to new editions of this compendium assumes very considerable significance. Historically, the extent of use of a particular drug or pharmaceutical preparation had served as the major criterion for admission of articles to the compendium, as evidenced by the great reliance previously placed upon prescription ingredient surveys. Beginning with the publication of N. F. X in 1955, there had been a trend toward somewhat increased attention to the therapeutic merit of the drugs considered for admission. Parenthetically it might be noted that at the same time patent status was also dropped as a bar to N. F. recognition.

As the first major action in the preparation of N. F. XII, the Committee on N. F., in 1961, struck down the philosophy of extent of use, and established therapeutic value as the sole basis for admission of drugs to the compendium. It is interesting to note that by adopting this new policy the N. F. anticipated the concern and subsequent action of Congress when it introduced "effectiveness" or efficacy as a new requirement under the Drug Amendments of 1962.[13]

Test and Assay Procedures.—At the time the first Federal Food and Drug Law was enacted, virtually all drug preparations were prepared extemporaneously by the local pharmacist. Even a single generation ago, the pharmacist personally compounded many, if not the majority, of the orders for prescription medication which he received. Historically, formularies and pharmacopeias had the fundamental purpose of providing formulas for the preparation of drug products and directions for testing the finished products. Since the laboratory equipment which might be expected in the average pharmacy would not be highly elaborate, the respective procedures given in the earlier editions of the N. F. were relatively simple in nature although generally adequate for the purpose intended.

In recent years precompounded drugs obtained from large, well-equipped pharmaceutical manufacturing firms are being used almost exclusively by the pharmacist in dispensing prescription medication.

[13] Federal Food, Drug and Cosmetic Act, as amended, Sections 201 and 505, FOOD DRUG COSMETIC LAW REPORTS ¶ 71,021, 71,053.

As a consequence, the N. F. no longer maintains the view that any test which it provides should be capable of being performed in a properly equipped community pharmacy. This has permitted the compendium to adopt many complex and elaborate test procedures over the past 15 years. Most fortunately this change in philosophy coincided with a remarkable surge in the growth and advancement of pharmaceutical analysis. The result has been that numerous highly sophisticated test procedures—which are both more selective and more accurate—have been introduced widely into the N. F. over this period. It can be expected that the nature of future monograph test procedures will continue to reflect and closely parallel the further development and advances of pharmaceutical analysis.

Closely allied to the adoption of better techniques of testing has been a concomitant improvement in pharmaceutical manufacturing methodology. This has become vitally essential because many presently available drugs are highly potent in extremely minute quantities which require very accurate control of the amount of active ingredient contained in each dosage unit, such as a tablet or capsule. The new N. F. provides the first real breakthrough in this field, through the revolutionary specifications it includes for content uniformity of tablets. Also provided is a complete revision of the weight variation requirements including the adoption of specifications for creams, ointments and powders.

Consequently, the N. F. continues to present standards and specifications devised and adopted by the pharmacy profession with assistance from physicians and other health practitioners; however, those standards are now generally quite complex and are primarily intended for use and application by highly trained government and industrial analysts using elaborate equipment and techniques.

Reference Standards.—The greatest proportion of the new analytical procedures involve various spectrometric tests and assays. In the view of many authorities in the field of chemical and pharmaceutical instrumentation and analysis, the absorption characteristics of a drug are analogous to other physical properties and may be measured and compared directly with published values which could be provided as part of the compendium monograph assay. These authorities readily admit that like any other physical measurement the accuracy of this approach is based entirely upon the premise that the equipment used has been suitably calibrated, and has been checked to assure its proper functioning.

However, federal FDA officials have adopted the position that such instruments are highly susceptible to some changes in adjustment which would have a substantial effect on the results or data obtained by such a measurement. It is further claimed that such errors may readily go undetected because there is no assurance that the reliability of the instrument will be verified routinely by the analyst on a regular basis. Consequently, in order to ensure beyond doubt the complete reliability—and therefore the enforceability—of the N. F. spectrometric procedures, the Committee on N. F. has adopted a general policy of comparing the sample under investigation against a suitable reference substance. In most cases this reference substance is a highly purified sample of the drug itself. These reference substances are designated as N. F. Reference Standards and over ninety such standards are now required for the various tests in N. F. XII, and are distributed from the N. F. office on a self-sustaining basis.

Present and Future Significance of the N. F.[14]

As the character of the admissions to the N. F. has changed, and even more particularly, as the complexity of the test methods has increased, there has been a simultaneous transition in the manner in which the standards described have been generally obtained. Formerly, the revision Committee members themselves did most of the original laboratory work to develop suitable test procedures for incorporation into the monographs. By this means the official compendia spoke for the health professions in establishing appropriate minimum standards of purity, identity and strength for the various articles admitted. The need and desirability of this function was readily apparent at that time because of the frequent unreliability of the control testing procedures developed by individual manufacturers along with the general weakness of drug laws, as well as the agencies charged with their enforcement.

Today, however, this picture has changed markedly. Practically every manufacturer now appreciates the necessity of extensive research, development and quality control. Even those few who do not are required to devote comparable effort to these aspects due to competi-

[14] In this connection the reader is also referred to the reference cited at footnote 1 in this paper, and to the *National Formulary*, 12th ed., Mack Publishing Company, Easton, Pa., 1965, pp. xix-xx.

tion and the "good manufacturing practice" provision of the 1962 Drug Amendments [15] and the pertinent detailed regulations. Furthermore, the greatly increased powers and appropriations conferred upon the pertinent government agencies—and specifically the federal FDA —have made these government agencies extremely formidable in carrying out their programs of drug law enforcement. Against this combined background of strong manufacturers' quality control and strong government enforcement, the position of the official compendia is not so dominant as it previously had been, and the present role of the compendia is therefore not as clear.

Much of the strength of our system of drug standardization—which is generally recognized as the highest in the world—may be directly attributed to the fact that American pharmacists and physicians, in establishing the N. F. and the *United States Pharmacopeia* long before the first drug law was enacted, voluntarily accepted responsibility for determining the quality standards for the drugs which those practitioners would dispense and prescribe in the practice of their respective professions. Congress wisely noted the existence of this system and subscribed to and endorsed the principle by according these compendia official recognition in both the 1906 and 1938 Acts. The desirability and need for the professions to continue serving in this capacity has not diminished. Indeed, it may be argued that in light of a powerful industry and a powerful government, it becomes imperative that the compendia themselves grow in strength and influence in order to maintain a proper and judicious balance between those responsible for the various phases of drug manufacture, drug standardization and drug enforcement.

In this sense we might compare our system to the delicate set of checks and balances which was wisely provided by the United States Constitution through the creation of the three separate branches of our federal government. By the same token, the official compendia—as the recognized and appointed spokesmen of the health professions—may have a more demanding role than ever before. It is now the responsibility of the respective revision committees to consider and judge the individual scientific merits of differing viewpoints pertaining to drug standardization which may be advanced separately by industry and government scientists relative to specific drugs. These differences may range from relatively minor matters of procedural details to very fundamental philosophies affecting broad areas of drug standardization.

[15] Cited at footnote 4.

Conclusion

In recent years there has been an increasing awareness that the views of independent bodies are frequently necessary in order to resolve as properly as possible the difficult problems which develop in those areas of science where the benefits and the risks, the ideal and the practical, have to be delicately weighed and balanced. The recent appointment of special committees of experts by the National Academy of Sciences and by the FDA in the area of drug efficacy and safety attests to the recognized need for such counsel. In the N. F., Congress itself, in effect, appointed such a body for the arbitration of industry-government differences of opinion and for the establishment of the most scientifically appropriate drug standards. Clearly such activities are first and foremost in the public interest, and it is this function which is and will remain the primary significance of the N. F. **[The End]**

NATIONAL ADVISORY FOOD AND DRUG COUNCIL APPOINTED

Appointment of a National Food and Drug Council to consult with the Food and Drug Administration, has been announced by Secretary of Health, Education and Welfare Anthony J. Celebrezze.

The Council consists of 18 members appointed for terms of one to three years, allowing for a rotation of membership. The initial meeting of the Council will be held in Washington, D. C. on December 1.

Commenting on the action, Secretary Celebrezze said:

"This Council fulfills a major recommendation of the Second Citizens Advisory Committee on FDA organization and policies. It will make available to the Department and the Food and Drug Administration the knowledge and experience of an outstanding group of citizens. Their advice and counsel should contribute substantially to FDA's effectiveness in discharging its many and growing responsibilities for consumer protection."

FDA Commissioner George P. Larrick pointed out that the Council broadly represents the public, including such elements as consumer groups, science, industry, law, medicine, pharmacy, veterinary medicine, education, agriculture, communications, labor, government, voluntary health organizations and women's organizations.

"This Council will be especially helpful in our planning for the future. We look forward with interest and pleasure to receiving their views and suggestions on how the FDA can best utilize its resources," Mr. Larrick said.

The FDA Commissioner will serve as chairman of the Council, *ex officio*. Kenneth L. Milstead, special assistant to the Commissioner for the Advisory Council, will serve as liaison officer between the Council and the FDA. Regular meetings will be held twice each year with ad hoc meetings to deal with special problems to be called at the discretion of the Commissioner.

Remarks on the Latin-American Food Code

By FRANKLIN M. DEPEW

Mr. Depew, President of the Food Law Institute, Inc., Presented This Paper as Part of a Round Table Discussion at a Meeting of the Institute of Food Technologists on May 25, 1964, in Washington, D. C.

THE ADVANTAGES of, and need for, the establishment of uniform guiding principles and model standards for manufactured foods were first officially recognized by a resolution proposed by Dr. Antonio Ceriotti, and adopted by the first South American Chemical Congress meeting in Buenos Aires, in 1924. That resolution called for the drafting of a *Codex Alimentarius Sudamericanus.* However, it was not until 1955 at the Sixth Latin-American Chemical Congress that the matter received serious consideration. At that meeting a drafting committee was established under the chairmanship of Dr. Carlos A. Grau of Argentina.

Dr. Grau has an international reputation as a chemist, pharmacologist and pioneer in modern food legislation. He is the author of the Food Code of the Province of Buenos Aires which served as the model for the First National Food Code of Argentina which was adopted in 1953, and which in turn greatly influenced the preliminary draft of the Latin-American Food Code.

The preliminary draft of the Code was completed at the end of 1958. The Food Law Institute arranged to translate this draft into English and to distribute it to American industry for comments. Dr. Grau has advised that this distribution brought forth some 400 comments through the Food Law Institute and the United States

Department of Commerce and that some 300 changes were made in the draft to conform to these comments. The official revised Spanish edition of the Code was approved in principle by the Seventh Latin-American Chemical Congress which met in Mexico City in 1959. It was published in Spanish in August 1960. This volume constitutes the first model for international food standards ever completed.

Portions of this official revised Spanish edition have been translated into English by Ann M. Wolf in behalf of the Food Law Institute and published in the FOOD DRUG COSMETIC LAW JOURNAL.[1] Comments by representatives of industry were invited and received. These were passed to Dr. Grau. Those received prior to the Eighth Latin-American Chemical Congress held in Buenos Aires in September 1962 were incorporated in the revised copy of the Code which was reviewed and approved. At this Congress the name of the body working on this draft was changed to the Latin-American Food Council. It was further resolved to recommend to government agencies and special organizations the unification of existing food standards on the basis of the Code, and to publicize this suggestion as widely as possible.

Untranslated Chapters of the Code

Not yet translated are Chapter VI (Meat Products), Chapter VII (Fats), Chapter VIII (Dairy Products), Chapter IX (Flour and Flour Products), Chapter XI (Vegetable Products), Chapter XIII (Fermented Beverages), Chapter XVII (Dietetic Products), Chapter XVIII (Miscellaneous Products), and Chapter XVIII (Appendix—Household Articles).

At the Joint FAO-WHO Conference on Food Standards held in Geneva, October 1-5, 1962, the assembled delegates lauded the work done under the leadership of Dr. Grau in preparing this Latin-American Food Code. The Food Law Institute supplied the delegates with a copy of the code in Spanish, together with English translations of

[1] These translations appear in the following issues of the FOOD DRUG COSMETIC LAW JOURNAL: Introduction and Index—October 1960; Chapter I (General Provisions), Chapter II (General Requirements for Food Factories and Food Outlets), Chapter III (The Storage, Preservation and Processing of Foods) and Chapter V (Labelling)—April 1963; Chapter IV (Utensils, Receptacles, Containers, Wrappers, Machinery and Accessories) — February 1961; Chapter X (Sugar and Sugar Products)—May 1961; Chapter XII (Nonalcoholic Beverages and Refreshing Foods and Drinks)—June 1962; Chapter XIV (Spiritous Beverages)—September 1963; and Chapter XVI (Correctives and Improving Agents—Additives)—November 1961.

those parts of the code translated into English at that time. The *Codex Alimentarius* Commission meeting in Rome, June 25-July 3, 1963, considered Chapter I on the general provisions and part of Chapter XVI covering edible fungi (mushrooms) of the Latin-American Food Code in first reading and referred them to governments for detailed comments. Thus, it appears possible that some portions of the Latin-American Food Code may be adopted by governments outside of Latin-America.

Dr. Grau informs me that it is planned to publish a revised, up-to-date revision of the code in Spanish some time in the near future. This hopefully will include appropriate industry revisions suggested to date.

Dr. Aristo Buller Souto of Sao Paulo, Brazil, a member of the Latin-American Food Council, has recently undertaken a study for WHO to determine the feasibility of drafting uniform food standards for five Central American republics; namely Costa Rica, El Salvador, Guatemala, Honduras and Panama. His report to WHO will, I believe, suggest that the provisions of the Latin-American Food Code serve as the basic model for the food standards of these countries.

Three Countries Use the Code as a Model

The practical significance of the Latin-American Food Code as a "model" is best illustrated by the following examples:

(1) The Republic of Panama issued Presidential Decree No. 256, dated June 13, 1962 (Gaceta Oficial of July 20, 1962) promulgating a regulation for the registration and control of foods and beverages. This new regulation contains many provisions which have been taken over verbatim from the Latin-American Food Code or have been obviously influenced by it.

(2) The government of Peru promulgated on June 19, 1963 a new food code with many provisions which are identical with or similar to the respective provisions of the Latin-American Food Code.

(3) The Government of Ecuador promulgated on September 16, 1963 Decree No. 462 (Registro Oficial of November 4, 1963) introducing, on a temporary basis, the entire Latin-American Food Code "at present in force" as the controlling food law of Ecuador, pending the preparation and approval of a national food code, the drafting of which has been entrusted to a special commission. **[The End]**

Report of the FEMA Food Additives Committee

By R. L. HALL

The Following Is a Report, Dated April 14, 1964, of the Food Additives Committee of the Flavoring Extract Manufacturers' Association. Mr. Hall Is Chairman of the Committee.

AS IN OUR PAST REPORTS, we shall review here the major activities of the Food Additives Committee during the past year and offer some comment about present and future prospects. To avoid needless repetition of material that could become both extensive and complex, we will not cover in any detail subjects presented in previous annual reports.

Since our last report, we have filed with the Food and Drug Administration two progress reports on June 26 and December 27, 1963. These reports covered 131 and 50 substances, respectively. On December 27, we filed an extensive request, covering 24 substances of interest to the Flavoring Extract Manufacturers' Association, on which no conclusions had yet been reached. The progressive decrease in the number of substances covered by these reports is an indication of the extent to which the backlog of food additive problems has disappeared.

General Recognition of Safety

In late June last year, we issued a draft publication which lists all substances which were at that time on an FDA White List or an FEMA GRAS (Generally Accepted As Safe) list. The publication reports the average maximum use levels for each substance in each food category on which information was available. This information is important, not only because it entered into the judgment that these substances were generally recognized as safe, but also because no future use can automatically be assumed to be generally recognized as safe unless that use conforms, in a general way, to the pattern on which the original judgment was based. General recognition of safety is a concept legally and practically inseparable from the conditions of intended use. It is the function of this tabulation and of the later, final version which will shortly be available, to provide

general guidance to industry in interpreting these historical use data as guide lines to good manufacturing practice. It is important to emphasize that we are not, by this publication, attempting to restrain the future by the dead hand of the past. The concept of general recognition of safety, however, is not a blank check. While considerable and reasonable flexibility is necessary, general guide lines, based on experience, are necessary both to establish and to continue general recognition of safety.

The comments and suggestions of users of this draft, as well as some further developments, have made revision necessary. A redraft of the introduction has been in the hands of the Committee and the expert panel for some time, and a revision of the listing itself waits only the final disposition of a few remaining substances. We also expect to publish this listing and introduction in an appropriate national publication, such as *Food Technology*.

Present Status of Flavoring Substances

Since our last annual meeting, the expert panel has met three times—November 1 and 2, December 19, and January 10. These meetings were concerned with evaluating the information available on remaining substances, and with a discussion of procedures relating to further publication and to the future of new flavoring substances. This latter point, in particular, will be discussed later in this report. These meetings of the expert panel resulted in further additions to our list of GRAS flavoring ingredients and in the dropping of still others on which sufficient information was not available, or about which there was some basis for concern. At this time, the status of flavoring substances under the Food Additives Amendment is as follows:

Natural products (botanicals, extractives, etc.) appearing on FDA White Lists	265
Synthetic flavoring substances and flavoring adjuncts appearing both on an FDA White List and on an FEMA GRAS list	27
Synthetic flavoring substances and adjuncts appearing on FEMA GRAS lists	715
Natural products (botanicals, extractives, etc.) now appearing or will shortly appear on an FEMA GRAS list	91
Synthetic flavoring substances and adjuncts being held, awaiting more information or further consideration	20
Natural products (botanicals, extractives, etc.) being held, awaiting more information or further consideration	1
Substances already dropped from use and given no further consideration because of inadequate data, lack of industrial interest, or question of safety	276
Substances judged to be foods per se rather than flavoring ingredients or adjuncts	22
Total	1,417

Expansion of Available Data

Ever since the formal completion of survey, approximately five years ago, additional data have continued to trickle in, usually as a result of the correction of errors or the discovery of omissions. Our original survey included all members of the FEMA and related flavor trade associations, and a selection of large food manufacturers representing the major categories of processed foods. With one exception, all large flavor manufacturers participated and, in general, the larger food manufacturers cooperated well. Many small companies participated fully; others felt unequal to meeting the unusual demands for information made by our survey. Thus, the survey was intended to be representative, rather than comprehensive.

Last year, two categories of flavor users became aware that a more full participation by them in the original survey would have been desirable. Chewing gum manufacturers and producers of hard candy and lozenges have special problems, particularly with respect to the high levels of flavor used in their products which were, in many cases, not fully represented in our survey and which, though important to them, represent but a small fraction of the total flavors consumed. Peter Barton Hutt of the firm of Covington & Burling, counsel for the National Association of Chewing Gum Manufacturers, accordingly conducted a resurvey of the chewing gum industry in cooperation with their major flavor suppliers. Although not complete, it represented a large expansion of data available to us in more dependable form. At the same time, additional data on hard candy and lozenges were given to us by a number of manufacturers of these products. All of this information was incorporated into our survey, and was again reviewed by the expert panel to see if it rendered advisable a revision of its previous judgments. No revisions were needed. This information did, however, necessitate some further development of the guide lines for interpreting average maximum use levels which will be published in the introduction to our final tabulation.

The Wine Institute and related trade associations were faced with still another problem, involving some of the natural flavoring products they use, a few of which are used only in flavored wines and liqueurs. Unfortunately, the information available, even after considerable research, did not meet the criteria established by the expert panel for general recognition of safety. The Wine Institute then took the only course open to it, and filed a petition for a regulation covering the use of these substances in alcoholic beverages.

Current Committee Activities

Current activities of the Committee are concerned with disposition of the remaining substances still under extension, the possibility of a comprehensive regulation covering flavors which may be issued by the FDA, and the problem of handling new flavor substances under the provisions of the Food Additives Amendment. At present, there are 24 substances on extension as a result of an FEMA request. Three of these have been judged to be GRAS, leaving 21. The results of toxicity studies and some further information will be available on a few others within the next few weeks. It is possible that some additional substances will be judged to be GRAS as a result of this. It is likely, however, that we cannot accumulate enough information on a number of the items to satisfy the expert panel, and a note to that effect is now being sent out to our membership and other interested firms. Perhaps the FDA may be able to include in a comprehensive regulation, if one issues, or in a later amendment to such a regulation, one or more of these items on the basis of information available to them, even though they do not meet the GRAS criteria of the expert panel, but we should not count on this possibility.

Possible Regulation by the FDA

As most of you are aware from the trade press and from publications such as *Food Chemical News,* the FDA is considering a general regulation which would embody almost all of the substances on the FEMA GRAS list. It would be neither possible nor appropriate to comment at length on a regulation, the details of which we do not know. In any event, the regulation will first be published as a proposed order, with an opportunity for comment. It does seem reasonable, however, to make the following observations:

In our discussions on this subject with officials of the FDA, we have emphasized in the strongest possible terms that rigid use limits are not a feasible means of regulating a subject as broad and complex as food flavor usage. In particular, our FEMA average maximum use levels, while they provide guide lines to common use, are themselves in no way a basis for maximum use limits. We hope and believe that any regulation which may issue will be realistic in this respect, even though it obviously is desirable to spell out with clarity what constitutes or is implied by good manufacturing practice. The Administration has already published such definitions for several other industries.

It is inevitable that some items which have appeared on the FEMA GRAS list will be omitted from a general regulation for a variety of valid reasons. It seems likely that in no case are these reasons concerned with the safety of the substance itself, but rather with prior, present or future determinations of status. For example, the Administration may choose to omit substances which it has already decided are GRAS. If a substance is covered by a previous regulation or published prior sanction, this also may be omitted. We know that some of the substances we regard as flavor adjuncts have been regarded legally as color additives and may require, under the Color Additives Amendment, separate treatment. It is our hope that these can be listed on the authority of the Commissioner, since many of these are vegetable compounds long in limited use, about which no question of safety exists, but which could not support the $3,000 filing fee required of new color additives.

There may well be other cases of omissions. We expect to be able to provide you promptly with an explanation of all omissions in order that you may not be concerned by any apparent conflict between the proposed regulation and our present FEMA GRAS list.

The Committee believes that such a regulation would have several advantages in clearing up any uncertainty or confusion that may exist among those who do not understand that the Food Additives Amendment permits a number of different ways of arriving at a conclusion concerning the safe use of a food ingredient. Certainly this advantage, if the regulation itself is drawn in workable form, would be a considerable one. At the same time, we remain completely convinced of both the scientific soundness and the legal validity of the course of action we have so far pursued. The substances on our list are generally recognized as safe whether covered by a regulation or not. There is ample precedent in FDA regulations for inclusion of a substance that is, in fact, GRAS. It goes without stating, however, that if unfavorable evidence concerning the safety of a flavoring substance is developed from any source—government or private—there can be no divergence in policy between the FDA and ourselves on this point. We have repeatedly made it clear that our GRAS lists are subject to revision in the light of new information, and this must continue to be the case.

New Flavor Ingredients

There remains for the future Committee the problem of coping with new flavor ingredients, having no previous history of use as such

under the terms of the Food Additives Amendment. It is the thought of the Committee that there are two possible approaches to handling this subject, and it would be well to treat them quite candidly at this time. The first of these is the obvious one of filing a petition for a regulation under the Food Additives Amendment. The practicability of this approach depends upon several factors which cannot now be known. Among these are the particular nature of the new flavoring substance in question, its proposed levels of use, and the resultant dietary levels. If, for example, it is a proven constituent of existing natural foods and if it is proposed for use at levels and in a manner generally related to its natural occurrence, we might reasonably expect the FDA to require very little in the way of additional information on safety. If a pattern, by now fairly well established, is followed and if the substance requires no maximum use limits in the regulation in order to assure its safe use, then presumably no analytical method for determining its level in food would be required. If the substance does not occur naturally, but is chemically closely related to other substances whose safety is well established, it is also possible that the FDA might adopt a fairly lenient view of the type and quantity of information required to establish safe use. On the other hand, if the Administration were to feel that on any new substance, not enjoying past use as an intentional additive, extensive chronic toxicity work would be needed, this would, for all practical purposes, shut the door on research and development of additional flavoring ingredients. Only a handful of *existing* flavors enjoy commercial volume sufficient to have justified two-year toxicity studies. It is almost inconceivable that a new flavor not yet tried on the market or accepted by industrial users would have such indications of potential commercial value as to encourage its sponsor to invest in a program of chronic toxicity tests.

An Alternative Route

This uncertainty as to the policy of the FDA makes it desirable that we see if an alternative route exists. In the judgment of the Committee and expert panel, and supported by competent legal advice, one does. The wording of the Food Additives Amendment makes it clear that a food additive is anything which is "not generally recognized as safe," and that such general recognition of safety must be decided by experts qualified by training and experience to evaluate its safety, and that such evaluation must be, in the case of substances used after January 1, 1958, on the basis of "scientific procedures." This makes

it possible for a substance to become generally recognized as safe by qualified experts on the basis of scientific procedures. The fact that the substance is new means only that "common use in food" cannot be a basis for judgment. In the Committee's view, therefore, a possible alternative to the petition route would consist of the following:

(1) Obtaining expert advice on what data would be necessary on the compound in question which, if published and generally read, would be sufficient to establish general recognition of safety for the proposed use.

(2) Obtaining, by toxicity studies, metabolic tests, or other appropriate means, the information required.

(3) Publication, in a recognized scientific journal with wide circulation, of the results of the investigations together with information on the proposed use of the substance in food, the levels of use, the chemical identity of the material, etc.

(4) Special distribution of reprints of this article to a reasonable number of unquestionably competent pharmacologists and toxicologists.

(5) Passage of a period of time, estimated at at least six months, to provide for comment and criticism.

(6) Solicitation of comment. If no adverse comment appears either through private communication or publication after a reasonable period of time, it would clearly mean that the substance would be generally recognized as safe within the terms of the Food Additives Amendment.

Whether or not this alternative route is feasible depends, in large part, upon the criteria for new substances which may be applied by the FDA. This "GRAS route" might well have no advantage and indeed be even longer and more expensive than the petition route if the FDA is able to apply to new substances criteria in proportion to the significance of the use of these substances in the nation's food. In any case, the petition route would require Items 1 and 2 listed above. This is a serious disadvantage of both alternatives, for the firm which does the work and publishes the results will simply give every competitor a "free ride." If the Administration's standards are set too rigidly high, however, it may well be easier to establish the general recognition of safety on the basis of scientific procedures, as permitted by the law, than to follow the petition route. This subject deserves careful thought and study during the immediate future.

It would be unthinkable to close this report without acknowledging the continued help and support given the Committee by the Board of Governors, the President and the Executive Secretary. Dr. Bernard L. Oser has, as always, been an inexhaustible source of sound advice and ingenious counsel. The expert panel has given generously of their time, their thoughts and their talents. It has been a real privilege to work with a group of men as stimulating, capable, and independent as these.

If I may be permitted a personal note, this concludes seven years as the Chairman of the Food Additives Committee. I have enjoyed the work—perhaps too much—or I would have more quickly and effectively rotated out of the job. However, the task has been not only enjoyable, but possible only because of the interest, activity, and participation of the other members of the Committee, the Board, and of those of you who are members and other interested companies. I do not know of any committee or trade association activity which has enjoyed so nearly unanimous and effective support from its member companies and their personnel. It has been a real privilege to be a part of this effort, and I am grateful for that privilege. Finally, I want to acknowledge with deep thanks the indulgence of my own company for the time they have permitted me to spend. Last but not least, I want to thank my secretary, Miss Janis Klima, who has borne the brunt of putting into usable form the actual work of the Committee and the expert panel. I would also like to acknowledge the many others, too numerous to mention here, who have each contributed generously at various times to this activity. **[The End]**

ROBERT A. HARDT HONORED

The Remington Medal Presentation Dinner in honor of Robert A. Hardt, the 1964 Remington Medalist, will be held in New York City on December 9, 1964. The announcement was made by Professor Frank J. Pokorny, secretary of the New York Chapter of the American Pharmaceutical Association and chairman of the dinner committee. The Remington Medal is sponsored by the New York Chapter and is awarded to that person, who in the opinion of the committee has distinguished himself and brought honor to the profession of Pharmacy, either during the past year or cumulatively over a period of years. The Remington Medal Committee consists of the past presidents of the American Pharmaceutical Association.

Mr. Hardt, recently retired president of Armour Pharmaceutical Company, and presently consultant in professional relations to G. D. Searle & Company, is the fortieth recipient of the medal since its inception in the year 1918. He joins a most distinguished list of Remington Medalists, all of whom labored in the interests of their chosen profession, the field of pharmacy.

Uniform Microbiological Standards and Methods of Analysis in Frozen Foods

By EUGENE H. HOLEMAN

The Author, Director and State Chemist of the Tennessee Department of Agriculture, Presented This Paper at the Meeting of the Association of Official Agricultural Chemists, Microbiological Session, in Washington, D. C., on October 22, 1964.

FOR THREE QUARTERS OF A CENTURY or more the Association of Food and Drug Officials of the United States (AFDOUS) has been engaged in adopting resolutions, developing codes and issuing policy statements affecting the purity of foods. The AOAC (Association of Official Agricultural Chemists) and AFDOUS are both indebted to Dr. Harvey W. Wiley for his pioneering work on the wholesomeness of foods and methods used for food analysis. Because of our common background and interchange of membership through the years we have been continually engaged in the exchange of information on chemical methods. In several areas the AOAC has moved rapidly to develop uniform methods of analysis in conjunction with the issuance of state and federal standards, particularly in feed and fertilizer areas.

The Present Situation

Recent reviews and journal reports have summarized rather adequately the current situation in the microbiology of frozen foods. They tend to emphasize microbial standards and handling codes for chilled, precooked or frozen foods, thus indicating that the natural flavor, the induced flavor and the factors that lead to spoilage and/or healthful considerations are continually our concern. Experiences in the laboratory, the field, the plant and the control agency need reassessment frequently.[1]

[1] Dr. S. E. Hartsell, *The Microbiology of Frozen Foods,* Purdue University, 1961.

Microbiological Standards in Frozen Foods

M. F. Gunderson and others reporting on a study made for the National Association of Frozen Food Packers have concluded that the frozen food industry appears to be policing itself rather well, if bacteriological analyses of products on some markets are interpreted critically. Others will hold that the data are not really representative of the situation because there are well-known sources of error in the techniques. Some of these troubles are inherent in hand-me-down procedures used in clinical laboratories which are not adaptable definitively when used in the analysis of frozen foods.[2]

Views of Control Officials on Standardization of Methods of Analysis

With this introduction, which underscores the need for uniform, accurate methods of microbacteriological analysis, I will depart from this specific area for a few minutes in order to bring in some views of control officials who have had many years experience in developing standards and uniform methods of analysis.

(1) John W. Kuzmeski, Official Chemist, University of Massachusetts, Amherst, Massachusetts, writing about the wide variation in the determination of drugs, particularly arsenilic acid in feed, says:

> I am more interested in the development of uniform and satisfactory methods of analysis than I am in the setting of standards. However if the standards are to mean anything they must be followed by adequate methods to determine whether or not a particular product conforms to the standards.

(2) Dr. F. W. Quackenbush, State Chemist, Department of Biochemistry, Agricultural Experiment Station, Lafayette, Indiana, has the following to say relative to the standardization of methods:

> In that particular case we have an excellent example of standardization outrunning methods of analysis. About six years ago we were in the position of having AOAC methods for less than 25% of the drugs which were being added to feeds at guaranteed levels. Some of us in feed control work became quite concerned with this and on voicing our concern were asked to serve on a committee to do something about it. We organized the Committee on Analytical Methods for Drugs in Feeds, of which I was chairman for a number of years. The Committee proceeded to set up a task force to develop acceptable methods of analysis for each of the drugs which were being used in feeds. This was quite an active program for a while; however, within about five years time we were able to provide suitable methodology under AOAC status to analyze for

[2] Gunderson, M. F., "Frozen Food Industry Gives Initial Results of Bacterial Survey," 23 *Quick Frozen Foods* 31-33 (1961).

most all of the drugs which were being used in feeds. The Committee was disbanded and the referee on drugs in feeds was then given the responsibility of keeping current with methodology.

(3) C. Colton Carr, Chief Laboratory Division, Michigan Department of Agriculture has this thought provoking remark to make:

There is no question in my mind that standards must be predicated on good analytical methods. Too often legislators or lay administrators go "out on the limb," in setting up nice, clean-cut statutory or regulatory standards which defy enforcement due to lack of appropriate methods of analyses.

Mr. Carr goes on to say that:

We must get agreement between scientific experts before we can develop usable standards in enforcement work.

(4) Stacy B. Randle, State Chemist, Rutgers, State University, New Brunswick, New Jersey in commenting on the need for uniform methods of analysis in the enforcement of standards and for court proceedings makes a statement which needs to be given serious attention by AOAC.

I would further urge that you encourage *each laboratory director* to set aside a portion of time for each chemist to devote to research on new methods. It is unfortunate that a few laboratories in this country must bear the burden of the A. O. A. C. method making procedure.

(If we are to go out from this session and make a contribution on uniform methods of bacteriological analysis it will certainly take more than a few laboratories to do the job ahead of us.)

(5) Commissioner George P. Larrick, Food and Drug Administration, United States Department of Health, Education and Welfare made this remark before the National Association of Frozen Food Packers in Chicago on March 20, 1964:

Bacterial contamination of foods, including frozen foods, from such organisms as staphylococci and salmonellae, needs particular attention. Total bacteria counts and coliform determinations are not enough. The 1959-1960 joint Association of Food and Drug Officials of the United States—industry survey of bacterial contamination of frozen precooked foods, in which F. D. A. cooperated, was a start in pointing up the problem of insanitary conditions, temperature abuses, and other factors contributing to high bacterial counts. As a result of this survey, your Association began a program of sanitation seminars. You prepared an information booklet for these seminars entitled, 'Five Steps to Sanitary Quality of Frozen Foods.' This was a fine program, but the stress placed on the improvement in operating practices is one that needs constant reiteration and special vigilance. In this area you have the tools—in many cases, simple ones such as adequate handwashing facilities. Yet it is desirable that these be supplemented by *a bacteriological test program* if the efficiency of your procedures is to be checked out.

(6) Dr. Glenn G. Slocum's article "Advance in Food Bacteriology" presented at the meeting of the National Confectioners Association

and American Association of Candy Technologists in Washington, D. C., on May 20, 1963 said:

Bacteriologists and laboratory facilities have been established in 10 of the 18 FDA District offices, and others will be added as quarters become available. These field bacteriologists participate with inspectors in the sanitary inspection of food plants, collect factory samples of raw materials, in-process samples, and finished products for laboratory examination. Their findings are reported back to the plant management and may be of assistance in locating and eliminating sources of contamination. Our efforts are but part of the growing trend of interest by food microbiologists at all levels to develop more detailed and specific knowledge of the microbiology of foods and how to control such microorganisms.

(7) D. J. Mitchell, State Chemist, State Chemical Laboratory, Vermillion, South Dakota has the following to say relative to the same subject:

Two areas in which AFDOUS has been quite active, I think as far as standards are concerned make it desirable to have better methods. These areas are, of course, the frozen foods and bacteriological standards, and the diluted fruit juice drinks, which your Committee has done so much work on.

With these opinions of leaders in the regulatory field showing the need for uniform methodology and the thoughtful opinions of leading bacteriologists for reappraisal of microbiological procedures we can now take a look at the work of AFDOUS in establishing food control standards and microbiological methods.

Recent AFDOUS Activities

Food control official A. E. Abrahamson of New York City; Dr. Glenn Slocum, Food and Drug Administration; Carroll Brinsfield, Maryland; and many others, have been working on microbiological procedures and standards for a number of years. In 1956 when I was president of AFDOUS, the association accelerated its interest in the safe handling of frozen foods. Under the leadership of C. S. Brinsfield, Chief, Division of Food Control, Maryland Department of Health and H. P. Schmitt, Research Director, National Association of Frozen Food Packers, a group of consultants were brought together for the express purpose of studying methodology.[3] We have available a few copies of the outstanding report made by this committee. Their work can serve as a starting point for uniform microbiological methods of analysis for foods.

[3] Methodology Adopted December 6, 1957, for Microbiological Survey of Prepared Frozen Foods at the Plant Level. C. S. Brinsfield, Maryland Department of Health and H. P. Schmitt, National Association of Frozen Food Packers.

The work of the committee intensified the activities of the overall frozen food work being done by AFDOUS at that time, under the leadership of Milton P. Duffy of California, which resulted in the adoption of the AFDOUS Frozen Food Code on June 22, 1961.[4] This Code is now serving as the model to go by for producing and handling frozen foods for maintenance of quality and wholesomeness. Several states have adopted the Code as their official regulation for controlling frozen foods and many other states use the Code to interpret the adulteration and misbranding sections of their statute.

The final conclusion on adulteration from bacteriological sources however will not be decided upon the basis of handling methods. It will be decided upon the basis of bacteria counts. This is where the great need exists today, for uniform, reproduceable microbiological methods. Here is the responsibility, the challenge and opportunity of this group here today.[5]

Current Investigations

AFDOUS has spent seven years in developing information for the establishment of standards for diluted fruit juice beverages.[6] The FDA and some citrus industries have published standard proposals in the *Federal Register*. AFDOUS has under study food handling processes in the baking industry and will come up with some recommendations next year.

Most of us are familiar with the work done in New York City on establishing microbiological standards for shell fish products and the interest of the Department of Interior in microbiological methods. President Charles V. Marshall attended the 1964 AFDOUS Conference in Denver, Colorado and participated in the deliberations of the AFDOUS Committee on microbiological procedures. It is the thinking of many of us that the AOAC should coordinate all available and interested persons and associations to study and adopt uniform microbiological procedures.

As Dr. Charles V. Durkin of the FDA has said:

Uniform standards perform a multiplicity of functions for the consumer, for the regulatory agency and industry. They may be definitive for the product, pro-

[4] AFDOUS Frozen Food Code, June 22, 1961. Office of the Secretary, Topeka, Kansas.

[5] "Summary of Microbial Limits in Frozen Food Samples," *Quarterly Bulletin*, AFDOUS, October 1959, Office of the Secretary.

[6] AFDOUS Diluted Fruit Juice Standards, 1963. Office of the Secretary.

mote honesty and fair dealing for the consumer, and establish guidelines for industry and the regulatory agency concerned. Of special interest are those standards that establish criteria significant to safety and public health.

And, I will add in closing, the most important tool in enforcing food standards is dependable microbiological methods. The Association of Public Health Officials and the Association of Official Agricultural Chemists can combine their talents and come up with the desired results. **[The End]**

FDA REGISTRATION RULES REVISED

Several changes in regulations governing registration of drug and medicated feed establishment are now effective. These changes are designed to streamline the procedure and expedite the processing of annual registrations.

The next annual registration of drug manufacturers, medicated feed producers and other firms subject to this requirement is between November 15 and December 31. Prior to November 15 each registered firm will receive an FDA form containing its name and address and permanent registration number. To register for the next year the firm fills in the required information and returns the form to FDA. A validated copy will be returned to the firm as evidence of registration. Firms starting in business must register within five days after commencing operations. Copies of the registration form may be obtained at the nearest FDA district office or from Washington.

These changes in regulations, published in the *Federal Register* of November 5, provide a single form for both initial and subsequent annual registration.

The new form will omit the "additional information" section which initial registrants previously have been requested, but not required, to submit. An item of "required" information—all trade names under which business is conducted at the location registering—has been added to the form.

Other changes in the regulations include:

(1) Establishments submitting New Drug Applications or Antibiotic Forms 5, 6, or 10 will be required to register, if they have not already done so, before the application is made effective.

(2) Changes in individual ownership, corporate or partnership structure, or of address, during the year, will be submitted by letter in triplicate. The registration form need not be used for this purpose and such changes must be reported within five days after they occur.

(3) A validated copy of the registration will be sent only to the location shown for the registering establishment.

Registration of a firm does not in any way indicate federal government approval of the company or its products. Advertising or representing that a firm is registered, so as to signify government approval, is not permitted and may cause the firm's products to be misbranded. The fact that a firm is registered does not necessarily qualify it to receive prescription drugs, for example.

Copies of the revised regulations can be obtained from the Division of Industry Advice, Bureau of Education and Voluntary Compliance, Food and Drug Administration, Washington, D. C. 20204.

The Definition of the Efficacy of a Drug Under the Law

By JOSEPH F. SADUSK, JR., M.D.

Dr. Sadusk, Medical Director of the Food and Drug Administration, United States Department of Health, Education and Welfare, Presented This Paper in a Symposium on Drug Investigation and Therapy, at the Second Fall Meeting of the American College of Physicians, in Los Angeles, California on October 8, 1964.

IN 1912, an amendment to the Food and Drug Act of 1906 established the first federal authority to act against drugs that were labeled with false and fraudulent claims for therapeutic effectiveness. However, such false claims made "out of ignorance" could not be attacked under this amendment. In other words, the burden of proof was on the government to prove fraud on the part of the manufacturer.

The Elixir of Sulfanilamide disaster led to the new drug provisions of the Federal Food, Drug and Cosmetic Act of 1938. While basic provisions in this Act required a manufacturer to establish safety of a drug before it could be marketed, the Food and Drug Administration had to permit the marketing of such a new drug when an application showed it to be safe, even though evidence of effectiveness was lacking. Nevertheless, the Food and Drug Administration did have limited authority under these 1938 provisions to deal with effectiveness through its power to rule on safety, since many drugs are capable of causing serious adverse effects; and it was a common sense conclusion that a safety decision could be reached only on the basis that the potential benefits of a drug outweighed the risk involved in its use.

The Kefauver-Harris Amendments of 1962 revised the definition of a new drug to say that a new drug is one which by reason of its composition "is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof." As a result of these amendments, a new drug application can now be re-

jected not only when there is insufficient evidence to establish its safety, but also if there is a lack of substantial evidence to show that the drug will have the effect it purports or is represented to have under conditions of use recommended in the proposed labeling.

Definitions

Let us define several terms. The word "labeling" includes the contents of the package circular which the manufacturer is required to enclose with the bottle of medication. This circular may vary from several hundred to a thousand or more words, and briefly, but very specifically, presents the trade name, generic name, chemistry, pharmacology, clinical indications, precautions, side effects, contraindications, routes, methods and dosage. Much effort is expended by the manufacturer and the FDA on this labeling which represents a full summary of knowledge of chemists, pharmacologists, investigators and clinicians. Under the present conditions of distribution of this package circular, it does not get to the physician as effectively as we should like; though it is generally true that with a very modest effort the physician may obtain it from his pharmacist or examine it from a physician's sample package that comes to his desk. In addition, not only does the 1962 Amendment require the drug manufacturer to furnish a copy of the FDA-approved package circular for a new drug to the physician upon request, but all other promotional material for drugs, including advertisements, are required to contain summaries drawn from the package brochure. Nevertheless, the FDA is giving serious consideration to better methods of distribution of present package insert information to physicians and other practitioners, hospitals and pharmacists.

As used in the law, the term "substantial evidence" is defined to mean "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use" as recommended in the proposed labeling.

Let us inquire into this definition of efficacy as expressed in the law. We need to discuss further and in such detail as time permits the following phrases:

(1) Adequate and well-controlled investigations;

(2) Experts qualified by scientific training and experience; and

(3) On the basis of which it can fairly and responsibly be concluded that the drug will have its claimed effect.

The three parts of this definition arose out of the Congress' belief, based on the Kefauver investigations, that too many drugs were being promoted on the strength of random observations by physicians of no special competence in drug investigation, thus producing a type of evidence of essentially testimonial or other poorly controlled character. No really responsible group of medical experts could accept this sort of evidence as a basis for approval of medical claims.

In final analysis, what was intended here was to require the development of the kind of scientific evidence that would enable an expert group, such as consultants selected by the Council on Drugs of the American Medical Association to review a particular drug, to come to a conclusion that the drug could reasonably be expected to perform in the clinical practice for which it was intended in the way that the labeling said it would.

Let us take the three parts one by one.

Adequate and Well-Controlled Investigations

Obviously, many experimental factors must be controlled and, in general, the effect on the disease process in patients receiving the drug needs to be compared with patients with similar disease conditions who do not receive the drug. This is preferably done by placebo comparisons in well-designed double-blind clinical studies.

But this is not the only type of study that can be called well-controlled. Sometimes such studies are not ethically permissible or, for practical reasons, are not feasible. Here the design of the study, the competence and experience of the investigator, and the adequacy of the observations and laboratory and other test procedures that are employed to record and weigh the clinical effects of the drug take on paramount importance. With some drugs intended for use in disease states, the natural histories of which are reasonably well understood and in which the pharmacological behavior of the drug can be observed by objective measurements, the blind and double-blind studies take on less significance. And even in states where there are little or no objective measures of patient response, careful planning coupled with systematic observation and accurate recording of the patient's course may qualify as a well-controlled study. The use of

other disciplines such as statistics may provide the extra support to make the study an acceptable and convincing one.

Experts Qualified by Scientific Training and Experience

Now let us address ourselves to a discussion of the part of the law which defines an expert investigator—"experts qualified by scientific training and experience." Here we are faced with the need of determining the quality of the investigator who furnishes the evidence upon which the efficacy and safety of a drug is determined. Since the scientific community has not specifically defined or described those criteria which establish the competency of an investigator, it does not seem likely that a governmental agency will ever be able to establish such standards. It is clear that the FDA will have to approach this task as any scientific administrator does—to consider each investigator on the merits of his *curriculum vitae,* his past record of accomplishment, the scientific environment in which he is doing the investigation, and the nature and quality of the recorded observations. Certainly, it does not seem likely that the FDA will ever publish a list of so-called "qualified" investigators.

We have heard stated that only physicians in the course of their practice can determine the effectiveness of drugs, and what drug to employ in a particular patient. The law does not interfere with these ideas insofar as the use of a drug is concerned for that doctor's patient, but it does prevent the marketing of a new drug with labeling and advertising making unsupported therapeutic claims.

It is common knowledge that the pharmaceutical industry is faced with a significant issue in the shortage of qualified investigators. Drugs are becoming more and more complex and the use of the general doctor, without specific experience in clinical investigation, in testing drugs in his office in the midst of a busy practice is probably coming to an end. The need for training of physicians in the drug research field has reached a critical stage. This problem must be met by the joint efforts of government, industry and the scientific community.

On the Basis of Which It Can Fairly and Responsibly Be Concluded That the Drug Will Have Its Claimed Effect

The third and most important part of the definition of "substantial evidence" requires that it provide a basis on which a properly qualified expert can fairly and responsibly conclude that the drug will have the effectiveness claimed for it.

Neither legally nor medically is there any requirement that all investigators show effectiveness of the drug being studied. Nor is there a requirement that any fixed number of investigations be made, or a fixed number of investigators used, or indeed that the drug under study be found more effective than other drugs for the same purpose.

Since medical investigation cannot always be an exact science, the law does not require that the evidence demonstrate effectiveness beyond peradventure.

What is required is a body of scientific data drawn from the investigations that will be convincing to those responsible for the decision to approve or not to approve the marketing of the drug. It must be assumed that these responsible officials have the qualifications to make an evaluation of the data. If they do not, they must draw upon the scientific community for the resource people who do. Here we expect to obtain assistance from our advisory committees and panels which presently are in the planning state in the Bureau of Medicine. Here we expect to bring in a substantial number of consultants from the scientific community to advise us on decisions and to prepare guidelines for review.

But no panel and no consultant can help us unless provided with the kind of data that they are entitled to expect as a foundation for *responsible* decision. We cannot ask these experts to act on testimonials or random observations. We will not act on them ourselves.

What we want, and what the law requires, is data that would enable the appropriately qualified experts to say responsibly whether or not the drug may be expected to perform as it is represented. This kind of evidence is not hard for the qualified person to recognize when he sees it.

Difference in Opinion Between Industry and FDA

You are undoubtedly aware of the difference of opinion which exists between the FDA and industry as to the requirements for efficacy testing of drugs manufactured and approved prior to 1962. The FDA holds that the effectiveness provisions of the Kefauver-Harris Amendments apply not only to the approval of new drug applications received after enactment of the 1962 Amendments, but that after October 9, 1964 these provisions will also apply to all drugs for which new drug applications were cleared since 1938. However, the Pharmaceutical Manufacturers Association and a number of its member firms have filed suit in the federal court at Wilmington, Delaware,

in an effort to establish that the FDA does not have authority to require reports for drugs cleared through the new drug procedures in previous years, but which the industry now regards as "no longer new drugs."

The results of that litigation may have a very important bearing on whether the FDA may apply these new effectiveness provisions to many drugs now on the market. At issue is the question of whether the drug manufacturer must offer substantial evidence that the drug he is marketing is effective for the purposes claimed in its labeling; or whether he is entitled to continue to market it unless the FDA develops adequate evidence to assume the burden of proof in court that the drug is ineffective for the purposes claimed. This issue is of major concern to the medical profession, as well as to the public generally and drug manufacturers. The outcome will be of critical importance in determining whether the FDA can assure the effectiveness of the nation's drug supply.

Whether or not the issue to be resolved in favor of the FDA, the task of reevaluating the effectiveness of drugs now on the market must be accomplished. On the one hand, it would be on the basis of these new provisions of the law; on the other hand, it would be under the old law requiring case-by-case litigation in the courts. In either event, years of effort may be required even with the fullest cooperation of the medical community and the pharmaceutical industry.

Realizing the long and difficult task ahead for the Bureau of Medicine, the Commissioner presented a list of certain categories of drugs to the Subcommittee on Reorganization and Internal Organization of the Senate Committee on Government Operations on May 28, 1964, for priority review. He has very recently accepted from the Bureau of Medicine a list of these 13 categories of drugs in order of priority for the Bureau to apply its initial review efforts:

(1) Proteolytic enzymes (oral and injectable);

(2) Progestational agents;

(3) Drugs offered for anxiety and apprehensive states, most tranquilizers, monoamine oxidase inhibitors;

(4) Nonprescription iron preparations;

(5) Pediatric dosages;

(6) Topical ophthalmic antibiotic combinations;

(7) A number of sustained-release drugs;

(8) Other topical antibiotic combination products;

(9) Bioflavonoids;

(10) Hormone creams;

(11) Drugs used in pregnancy;

(12) Topical antihistamines; and

(13) Topical 'caines (local anesthetics).

It must be realized that this order of priority may change with time and indeed certain specific drugs, or even categories of drugs, may be deemed in the future to be of higher priority than those listed.

In closing, we trust you realize that the law now provides an instrumentality for the scientific community, the pharmaceutical industry, and the FDA to join and coordinate their efforts to reasonably assure our nation that everything possible has been done in the light of scientific knowledge to promote the safety, effectiveness, and reliability of the country's drug supply. **[The End]**

STATEMENT OF OWNERSHIP, MANAGEMENT AND CIRCULATION (Act of October 23, 1962; Section 4369, Title 39, United States Code)

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I certify that the statements made by me above are correct and complete:

(Signed) Henry L. Stewart

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