The Establishment of Official Analytical Methodology†

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The FDA utilizes a wide variety of techniques, which are reviewed, for establishing its official methodology, ranging from a legislative mandate to delegation (with oversight perogatives) to professional societies. In all cases, the characteristics of the methods are functions of the purpose for which they are intended rather than the mechanism by which they were established.

The Food and Drug Administration (FDA) is a very substantial customer for methods of analysis. The key sections of the basic Federal Food and Drug Act of 1906 and its replacement, the Federal Food, Drug, and Cosmetic Act of 1938, required the use of analytical measurements for the enforcement of the classical adulteration and misbranding sections. All of our analyses are directed toward answering the question as to whether or not a product meets the requirements of the Federal Food, Drug, and Cosmetic Act and related statutes. But being a regulatory agency imposes on us certain restrictions, attitudes, and emphases which are not necessarily found in other laboratories performing analytical measurements.

The first of these duties is that we must adhere to what the law requires. The law states that we must follow the requirements of the *United States Pharmacopeia* to demonstrate noncompliance. Therefore, we must follow the methods of the Pharmacopeia, even if better methods may be available for other purposes. The second duty requires a yes or no answer to the question of whether or not the law has been violated. It does not permit a "maybe" or a probability. Finally, the emphasis in a regulatory laboratory is on reproducible methodology. We must be able to replicate our own results and other laboratories must be able to reproduce our values.

All laboratories profess that they require accurate, precise, specific, sensitive, and practical methods of analysis, specifically applicable to the commodities of interest. The operational and philosophical environment determines which of these often mutually incompatible requirements must be assigned the higher priorities. In this paper, I propose to examine the various ways in which the FDA establishes its official methodology, with particular emphasis on the relative importance of the various attributes.

I. METHODOLOGICAL REQUIREMENTS OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT

The Federal Food, Drug, and Cosmetic Act as originally enacted in 1938 contains references to methodology only in the drug provisions. The law specifically directs that for any drug recognized in an official compendium "determination as to strength, quality or purity shall be made in accordance with the tests or methods of assay set forth in such compendium". If methods do not exist or if, in the judgment of the Secretary of Health, Education, and Welfare, they are insufficient for the purpose, the Secretary shall promulgate regulations establishing methods, after a reasonable opportunity has been given for the official compendium to remedy the deficiency [Section 501(b)]. The official compendia, of course, are the *United States Pharmacopeia*, *Homeopathic Pharmacopeia*, and the *National Formulary* and their supplements [Section 201(j)]. Although deficiencies have been discovered from time to time in compendial methods, it has never been necessary to invoke the Secretary's authority to supersede the compendia.[1]

Methods are mentioned elsewhere in the law, but not with such specificity. In the case of new drugs [Section 505], tests or methods of assay are considered as part of the controls required for the manufacture, processing, and packing of the drug. If these methods are considered inadequate to preserve the identity, strength, quality, and purity of the drug, the New Drug Application will not be approved.

The Secretary of Health, Education, and Welfare is authorized to establish by regulation the tests or methods of assay necessary to determine compliance with standards of identity and of strength, quality, and purity for drugs containing insulin [Section 506] and antibiotics [Section 507]. Antibiotic methods must have the very special attribute of *rapidity*, stated as follows: "Such regulations shall prescribe only such tests and methods of assay as will provide for certification or rejection with the shortest time consistent with the purposes of this section" [Section 507(b)(5)]. The purposes are to ensure safety and efficacy of use. The practically identical statement appears in the New Animal Drug Amendment pertaining to certification of antibiotics in new animal drugs [Section 512(n)(2)].

New considerations with regard to requirements for methods of analysis were introduced with the first major amendment to the 1938 Act, the Pesticide Chemicals Amendment of 1954 [Section 408]. The petitioner, usually the manufacturer, for a tolerance for a pesticide chemical on an agricultural commodity (or, in some cases, an exemption from a tolerance), had to supply the results of tests on the amount of residue remaining and a description of the analytical methods used. Furthermore, a notice that a petition had been filed had to be published and include "the analytical methods available for the determination of the residue of the pesticide chemical. . ." [Section 408(d)(1)]. This is the section which permits the establishment of a tolerance "at zero level if the scientific data does not justify the establishment of a greater tolerance" [Section 408(b)]. This statement, which implied a *high level of sensitivity* at the *limit of detection*, seemed to be a perfectly reasonable requirement in the pre-gas chromatography state-of-the-art era. This statement also implied that because a method was available, it was applicable to the problem at hand.

The next major amendment, the Food Additive Amendment of 1958, requires the submission of a petition proposing the issuance of a regulation prescribing the conditions under which an additive may be safely used. The petition shall contain ". . . a description of practicable methods for determining the quantity of such additive in or on food, and any substance formed in or on food, because of its use; . . ." [Section 409(b)(2)(D)]. This is the amendment which contains the famous Delaney clause, "That no additive shall be deemed to be safe if it is found to induce cancer when ingested by man

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or animal . . ." except that an animal raised for food production is exempt from the proviso if the additive does not adversely affect the animal and that "no residue of the additive will be found (by methods of examination prescribed or approved by the Secretary by regulations . . .) in any edible portion of such animal after slaughter or in any food yielded by or derived from the living animal" [Section 409(c)(3)(A)]. Practically identical statements again appear in the New Animal Drugs Amendment of 1968.

This section introduced the concept of *practicable* analytical methods, a term not further defined by Congress. The FDA defined the term in its regulations regarding submission of food additive petitions (21CFR 121.51(c)(D)) and almost identically for color additives (21 CFR 8.4(c)C-2) as follows: "The test proposed shall be one that can be used for food-control purposes and that can be applied with consistent results by any properly equipped and trained laboratory personnel". This definition sufficed for ordinary food additives but the terms "food-control purposes" and "consistent results" required amplification when applied to residue levels. The preamble to the *Federal Register* document on furazolidone[2] defines practicable as: "A 'practicable' method is defined by FDA as one which reliably measures the compound through all residue levels of interest, and also is sufficiently rapid and reasonable in terms of the expertise and equipment required to be applicable for use in the surveillance and control of residues. 'Reliability' is a combination of accuracy, precision, and specificity. Accuracy and precision are quantitative terms. Accuracy is the measure of deviation from the true value, and 'precision' refers to the variability of measurements in replications either by one analyst or within a laboratory or between laboratories. . .. Specificity is a qualitative term. The measurements obtained by the method must reflect only the compound of interest."

The term "practicable" is also used in the New Animal Drugs Amendment of 1968 which requires "a description of practicable methods for determining the quantity, if any, of such drug in or on food, and any substance formed in or on food, because of its use" [Section 512(b)(7)]. The regulations introduce several additional terms without further elucidation. Applications for new animal drugs must contain "A description of practicable methods of analysis of *adequate sensitivity* to determine the amount of the new animal drug in its final dosage form including finished feeds and in drinking water should also be included. Methods should be included for any premix or other intermediate mix for such drugs. Where two or more active ingredients are included, methods should be quantitative and *specific* for each active ingredient" [Section 21CFR 514.1(b)(5)(vii)(a)] (emphasis added). In the case of new animal drugs which induce cancer, if the Secretary is requested to find, under the conditions of use reasonably certain to be followed in practice, that no residue of the drug will be found in the edible portion of the animal, "methods of analysis shall be submitted in such form as to be suitable for publication in the *Federal Register*" [Section 21 CFR 514.1(b)(7)(ii)]. The latter requirement for form of publication is hardly helpful in view of the diversity of forms for methods which have been published in this periodical. What is probably meant is that the method should be fully described so that it may be directly utilized by a laboratory.

The Color Additive Amendment of 1960 requires as a safety consideration "the availability of any needed practicable methods of analysis for determining the identity and quantity of (I) the pure dye and all intermediates and other impurities contained in such color additive, (II) such additive in or on any article of food, drug, or cosmetic, and (III) any substance formed in or on such article because of the use of such additive" [Section 706(b)(5)(A)(iv)]. This amendment also contains a so-called Delaney clause with the same exemption for no residue found in the animal tissue by approved methods, as provided for with regard to food additives and new animal drugs [Section 706(b)(5)(B)].

Finally, the basic authority for our working with organizations devoted to developing methods of analysis is contained in Section 707 which authorizes the Secretary "to cooperate with associations and scientific societies in the revision of the United States Pharmacopeia and in the development of methods of analysis and mechanical and physical tests necessary to carry out the work of the Food and Drug Administration".

To summarize this portion, the most basic mechanism available to the Food and Drug Administration for establishing methods of analysis is a directive written into the statute itself, as passed by Congress. Although there are statements with regard to the need for methods in various amendments to the basic law, the only direct reference is the requirement for the use of the drug compendia. A summary of references to methods in the current statute is given in Table I.

II. METHODOLOGICAL REQUIREMENTS INCORPORATED INTO THE REGULATIONS ISSUED UNDER THE FEDERAL FOOD, DRUG, AND COSMETIC ACT

Regulations are an amplification of the law, promulgated by the regulatory agency. They have the full force and effect of law and must be obeyed. Official methodology is often established by incorporating the method, or a reference to its appearance in a readily available publication, into the regulations. The Food and Drug Administration's regulations are published in what is known as "Title 21" of the *Code of Federal Regulations*, which is available as an annual update from the Government Printing Office. The abbreviated reference is "21CFR" followed by the section number. The Environmental Protection Agency's (EPA) regulations are consolidated in 40CFR. Between annual editions, announcements of new regulations, changes, and deletions are available through the government's newspaper, the *Federal Register*, which appears every workday. It too is available on subscription through the Government Printing Office. Items of interest to chemists published in the *Federal Register* are abstracted and appear in *Chemical Abstracts*.

The most important and all-inclusive pronouncement regarding methods is of relatively recent origin. It was not until 1972 that FDA officials realized that they had not stated formally the great importance they ascribe to the validated methods of the Association of Official Analytical Chemists (AOAC). This regulation states, "Where the method of analysis is not prescribed in a regulation, it is the policy of the Food and Drug Administration in its enforcement programs to utilize the methods of analysis of the Association of Official Analytical Chemists (AOAC) . . .". This regulation also contains a very significant statement which emphasizes the responsibility of an analyst to demonstrate that he can perform the method properly through the use of positive and negative controls and recovery and reproducibility studies.

Many regulations, particularly those establishing food standards, contain specific references to AOAC methods which FDA uses to determine compliance with the specifications. A list of methods specifically referenced or cited in full in the food standards is appended as Table II. Similarly, a number of the regulations for food additives contain references to AOAC methods. Occasionally, however, the description of a method is given in full in the regulations. Sometimes this is due to inertia, as with the phosphatase method for determining the use of underpasteurized milk in the manufacture of cheese. In this case the method was placed in the standard

Table I. Requirements of Methods of Analysis as Stated in the Federal Food, Drug, and Cosmetic Act

Attribute	Section and title	Definition or statement
Compendial	501(b), Drugs/adulteration	*U.S. Pharmacopeia, Homeopathic Pharmacopeia, National Formulary*
Adequacy	505(d)(3)	Inadequate to preserve identity, strength, quality, and purity
Rapidity	507(b)(5); 512(n)(2)	Shortest time consistent with insuring safety and efficacy
Determine zero level	408(b), Pesticide Chemicals	"establish the tolerance. . . at zero level"
Practicable	409(b)(2)(D), Food Additives	21CFR[a]
	512(b)(7), New Animal Drugs	21CFR[a]
	706(b)(5)(A)(iv) Color Additives	21CFR 8.4[a]
No residue	409(c)(3)(A) Food Additives	No residue by methods prescribed by regulation (Delaney clause)
	512(d)(1)(H) New Animal Drugs	
	706(b)(5)(B) Color Additives	

[a] Defined by regulation in the *Code of Federal Regulations*, Title 21 (21CFR).

before it was validated and approved by the AOAC, and no one has taken the trouble to replace the four pages in the regulations with a single sentence reference to the identical AOAC method. The analytical specifications for petroleum wax [21CFR 121.1156(b)], for example, are given in full due at least in part to the fact that there has never been sufficient interest in mounting a full-scale collaborative study by the AOAC. The method must therefore be accepted on the authority of the sponsoring laboratory, in this case, FDA.

The Food Additive regulations discussing eligibility for classification as generally recognized as safe (GRAS) is the authority for utilization of the *Food Chemical Codex*, a publication of the National Academy of Sciences/National Research Council, for establishing the quality of chemicals used in food [21CFR 121.3(d)]. This compendium of specifications and tests is similar in scope and format to the drug compendia.

One of the most extensive compilations of methods of analysis used by the Food and Drug Administration is contained in the regulations for the certification of antibiotic drugs. More than 400 pages of Parts 430 to 460 of 21CFR are devoted to tests and methods of assay—sterility, biological, and microbiological assays, general and specific chemical tests, and tests on specific dosage forms. This section also includes the specifications, interpretations, and special tests for each certifiable antibiotic preparation. An additional 100 pages (21CFR 536-555) are devoted to similar information and methods for certifiable animal drugs. Insulin [21CFR 429] and biological preparations [21CFR 610-680] have their tests and methods of assay laid down in the regulations.

Detailing methods of analysis in the regulations are of greatest value in highly concentrated industries, where the methods are performed only by the government and by a few manufacturers, as in the case with certifiable drugs, biologicals, and colors. The methods must be highly stable since a change involves a considerable legal effort on the part of the government and publication by proposal and final order in the *Federal Register*, and ultimate consolidation in the *Code of Federal Regulations*.

One other important example of establishing methodology by regulation is the *Pesticide Analytical Manual*. This is an interesting case because the production of the manual is performed by FDA but the authority for its use resides in an EPA regulation [40CFR 180.101]. The explanation for this apparent anomaly lies in the fact that the authority for promulgation of pesticide residue tolerances was transferred to EPA with the establishment of that agency, but the requirement for enforcement remained with FDA. This manual contains methods which have been found useful by FDA for determining pesticide residues, but which have not yet been subjected to the rigors of a full interlaboratory collaborative study as conducted by the AOAC. As soon as a method receives AOAC approval, it is deleted from the manual and replaced by an appropriate AOAC reference. This manual is the result of several hundred man-years of effort by FDA to develop reliable and practical methodology for identifying and quantifying any one of over 100 pesticides in any type of food sample.

The nutrient-labeling effort on the part of the FDA has developed by regulation a new set of analytical instructions. Because of the large variability in composition inherent in natural products, the instructions require analysis by AOAC methods on a composite of 12 consumer units from randomly chosen shipping cases. The value for added (fortified) nutrients must not fall below the label declaration, but for naturally present constituents, it may be 80% of the declared. In addition, allowance is made for variability generally recognized for the analytical method. There is no official explanation of this phrase since it really constitutes a tolerance on a tolerance. Practically all other FDA regulations include analytical variations within the limits set by the standards and specifications. The difficulty lies in what constitutes "generally recognized" variability—is it 1, 2, or 3 standard deviations of the within-laboratory (operator) or between-laboratory variabilities?

The special dietary regulations for infant food specifically require use of the AOAC methods for biological evaluation of protein quality (PER) and Kjeldahl nitrogen for the development of label statements of these dietary components [21CFR 125.5(c)(4)].

One of the difficulties with establishing methods by regulation is illustrated by the section designating the Canadian Food and Drug Directorate (now called Health and Welfare Canada) method for the determination of *cis,cis*-methylene-interrupted polyunsaturated fatty acids [21CFR 1.18(e)]. This method performed so poorly in a collaborative study that it could not be recommended for AOAC approval.

To summarize, methods may be designated as official by FDA by the use of regulations in two ways: (1) spelling them out in full for those cases where they are not expected to be used frequently or where changes are made very infrequently; and (2) by delegation to expert bodies either within (e.g.,

Table II. Methods of Analysis Utilized in the Definitions and Standards for Foods (1975)

Definition or standard	21CFR Section	Reference[a]
Water capacity and fill of container	10.6	Text in full
Cream-type pies Gelatin	11.5 11.6	41.015 (1970), aerobic plate count 41.016 (1970), coliform count
Bottled water	11.7	Part 400,[b] coliform organisms Part 100,[b] physical quality, chemical quality[b] Part 300,[b] radiological quality[b]
Cacao products	14	Shell in cacao nibs (1940) Fat Method I (1940)
Cereal flours	15	Granulation, text in full Ash (1940) Protein-Kjeldahl-Gunning-Arnold (1940) Moisture, vacuum oven method (1940)
Self-rising	15.50	Carbon dioxide, gasometric method (1940)
Crushed wheat	15.110	Moisture I. Drying with heat (1940)
White corn meal	15.500	20.70-20.71 (1945), moisture 20.70, 20.73 (1945), fat 20.70, 20.74 (1945), crude fiber
Rice products	15.525	38.32 (1955), thiamin 38.35 (1955), riboflavin 38.47 (1955), niacin (1955), iron, calcium
Macaroni products	16	Total solids, vacuum oven method (1940)
Enriched with fortified protein	16.15	14.134 (1970), protein 39.166-39.170 (1970), PER 14.125 (1970), total solids
Bakery products	17	13.70 (1950), total solids
Milk and cream	18	16.052 (1970),[c] fat, Roese-Gottlieb 16.032 (1970),[c] total solids 39.149-39.162 (1970), vitamin D
Sour cream	18.550	16.022 (1970), titratable acidity
Cheeses	19	15.124 (1950), moisture 15.131 (1950), fat Pasteurization, text in full
Mellorine	20.8	16.228 (1970), fat, Roese-Gottlieb 16.226 (1970), protein-Kjeldahl, or 16.227 (1970), dye binding 39.166-39.170 (1970), PER
Food flavorings	22.1	22.004-22.005 (1960), moisture of vanilla beans
Dextrose monohydrate	26.1	31.005 (1970), total solids 31.212(a) (1970), reducing sugars 31.208 (1970), sulfated ash 20.090-20.095 (1970), sulfur dioxide
Canned fruits and fruit juices	27	31.011 (1970), Brix Drained weight, text in full
Canned pineapple	27.50	29.009 (1965), solids-spindle
Canned pineapple juice	27.55	29.009 (1965), solids-spindle
Canned applesauce	27.80	22.019 (1970), soluble solids
Frozen concentrate for lemonade	27.101	*Ind. Eng. Chem. Anal. Ed.* **11**, 447 (1939), soluble solids
Canned pineapple-grapefruit juice; nectars	27.114 27.126	*JAOAC*,[d] **42**, 411 (1959), consistency 29.011 (1965), soluble solids
Fruit products Preserves	29 29.3	Soluble solids (1950) 22.019 (1970), soluble solids
Breaded shrimp	36.30	Shrimp content, text in full
Fish	37	Color of canned tuna, text in full Fill of container of canned tuna, text in full
Egg yolks	42.50	16.002-16.003 (1965), total solids
Margarine	45.1	16.163 (1970), fat
Peanut butter	46.1	25.004 (1965), fat
Frozen peas	50.3	Alcohol-insoluble solids, text in full Flotation test, text in full
Canned peas	51.2	Alcohol-insoluble solids, text in full
Canned green beans	51.11	Tough strings, text in full Fibrous material, text in full

Table II (*continued*)

Definition or standard	21CFR Section	Reference[a]
Canned corn	51.21	Alcohol-insoluble solids, text in full
Tomato juice	53.1	39.051-39.055 (1970), vitamin C
Tomato puree	53.20	*JAOAC*,[d] **52**, 1050(1969), tomato soluble solids
Tomato paste	53.30	

[a] All references, unless otherwise indicated, are to *Official Methods of Analysis of the Association of Official Analytical Chemists* with the specific edition indicated by the year of publication in parentheses. Multiple references within the same major section are given only once. [b] "Standard Methods for the Examination of Water and Wastewater", 13th ed, American Public Health Association, 1971. [c] And equivalent specific methods for other manufactured products. [d] *JAOAC = Journal of the Association of Official Analytical Chemists.*

Pesticide Analytical Manual) or without (e.g., AOAC) the FDA.

III. INFORMAL FOOD AND DRUG ADMINISTRATION METHODS

The FDA frequently issues compilations of methods which it has found useful in its day-to-day operations. One of the earliest provided instructions for the determination of antibiotics in milk, initially issued in 1958, when determining antibiotics by microbiological assay was considered rather exotic regulatory methodology. In 1965, FDA developed and compiled a number of laboratory procedures for detecting and measuring penicillin cross-contamination in various drug products.

The first FDA sponsored book-length manual was prepared by Grove and Randall[3] to explain the technical rationale supporting the various analytical methods for antibiotics, both official and nonofficial. This was followed by the unique *Manual of Cosmetic Analysis* personally prepared by Dr. Sylvan Newberger, who almost single-handedly developed the analytical chemistry of cosmetics. The first edition was published by the AOAC in 1962 and it proved so popular that it was reprinted twice and is now out of print. A completely revised and updated version, prepared by Dr. Newberger's colleagues and successors, is expected to appear in May 1977.

A *Food Additives Manual* was published by FDA in 1965 and a revised version in 1973. This manual consists of methods usually supplied by petitioners in support of their requests for a food additive regulation. In many cases the published methods received only a desk review, but not an FDA laboratory trial. Some of the methods have been subjected to a successful interlaboratory collaborative study and are now AOAC-approved. Other methods have performed so poorly that new methods have had to be developed for the same purpose and reported in the literature. Because of the lack of a laboratory program in support of this manual, it badly needs a thorough review and revision.

A very successful FDA manual is the *Bacteriological Analytical Manual* originally published in 1965. The fourth edition has just appeared and is being distributed by the AOAC. It contains in great detail those microbiological procedures which are used by the FDA laboratories for the examination of official samples. The most important of these methods have been subjected to interlaboratory collaborative studies and have received AOAC approval.

In the category of informal FDA methodology are those methods which appear in FDA scientific house organs. The first of these is *FDA By-Lines*, a bimonthly publication whose origin can be traced to the *Food Control Statement* which began in the 1920s. It is devoted primarily to historical, philosophical, survey, review, and symposia papers.

A more recent addition to the dissemination of methodology, techniques, and evaluations is the *Laboratory Information Bulletin*. This publication, which is now in its second decade, appears frequently but irregularly. Over 1900 bulletins have appeared plus a number of revisions and supplements bearing the same number as the original. This publication is intended to disseminate useful information and new methods very quickly. Since it dispenses with peer reviews, it carries a caution to the effect that the user must validate the methods for his intended use. Nevertheless, a respectable number of official FDA methods originated as an "LIB" and were validated for routine use by AOAC or other procedures.

Finally, a publication which has proved useful to petitioners for a regulation for indirect food additives is the leaflet "*FDA Guidelines for Chemistry and Technology Requirements of Indirect Food Additive Petitions*", first published in 1966 and revised this year. It outlines the types of extraction tests and analytical data required for polymers and similar components of containers and their adjuvants (antioxidants, plasticizers, lubricants, defoamers, etc.) if the petitioner is to avoid the submission of incorrect data, possibly requiring repetition and expensive toxicological studies.

To summarize, the FDA issues informal publications where it has unique expertise, or where because of its advantageous information gathering position, it is the only organization which has the necessary information required by the regulated industry.

IV. OTHER METHOD VALIDATING MECHANISMS

By far the greatest single source of methods used by FDA arises through the validation procedures conducted by the AOAC.

The special role that the AOAC has played in the establishment of official methodology deserves particular attention. This organization of government chemists was established in 1884 to solve the problem of disagreements among analytical results between the government and industry. It has developed to a very high degree of refinement the principle of approving only those methods which demonstrate a satisfactory degree of reliability and practicality when tested on unknown samples by a representative group of laboratories.

The mechanism of AOAC approval begins with the appointment of an interested scientist as an Associate Referee with the responsibility for choosing a method and validating its performance by conducting an interlaboratory collaborative study. Such a study must be designed to provide information on the basic analytical attributes of accuracy (recovery of known amounts), precision (reproducibility both between and within laboratories), and specificity (exclusively measuring the desired component in the system of interest). In addition, depending on the nature of the problem, the collaborative study may include additional features such as number of false positives, number of false negatives, magnitude of the blank, limit of detection, sensitivity, speed, and economy.

The Associate Referee makes the initial recommendation as to the suitability of the method for its intended purpose, based upon its performance in this blind study. This recommendation is reviewed by a General Referee who is in charge of a number of Associate Referees in a major subject area, such as chlorinated pesticides, egg products, or fertilizers. The decision of the General Referee is further reviewed by one of seven subcommittees devoted to general categories such as agricultural products, drugs, foods, pesticide residues, and

microbiological methods. The final recommendations of the subcommittees are voted upon by the Association as a whole. This voting, however, is restricted to those organizations, federal or state, who exercise official control over the commodity under consideration.

Although this mechanism may appear rather cumbersome, it usually works very smoothly, since disagreements are worked out at the preliminary stages before it becomes necessary to take a formal vote. The restriction of voting privileges to government officials has not proved objectionable in practice to either industry or consumers, since reports of projected and completed projects are delivered at the annual meetings and published in the *Journal of the Association of Official Analytical Chemists* to provide an opportunity for comment and second guessing by all who are interested.

The insistence of the AOAC on a demonstration of the practicality and reliability of the methods it approves has clearly placed its methods in a position to obtain legal endorsement. At a meeting of an ad hoc FAO/WHO Committee of Experts on the selection of Referee Methods for the determination of contaminants in foods,[4] AOAC methods were chosen for endorsement almost exclusively, since they were the only methods in the world providing a published basis for judging suitability that were available to the scientific and legal professions. As an outgrowth of the experts' meeting, the methods that were selected can be used to develop a set of criteria which may serve as the basis for selection of referee methods at trace levels which are suitable for use in preventing or settling disputes in international trade: These are:

Accuracy: at least 70% recovery at the 10 ppb level

Precision: less than 40% coefficient of variation between laboratories

False positives and false negatives: not more than one incorrect decision per unit of 10 decisions (samples and/or laboratories)

Further discussions are required to develop criteria for: (1) ratio of a measurement to that of the *blank* (as either a signal-to-noise ratio or an absolute magnitude of the blank relative to the measurement); (2) *sensitivity* of measurements (discrimination between measurements or measurement per unit concentration); and (3) *limit of detection*—lower limit of reliable measurement.

The FDA also utilizes the methods of other organizations, usually in more specialized areas. With polymers, the extensive American Society for Testing and Materials specifications are useful in characterizing physical and chemical properties. The methods of the American Oil Chemists' Society and the American Association of Cereal Chemists also provide useful methods in their areas of expertise. These organizations attempt to maintain uniformity in method of analysis where common methods are required for their individual memberships.

To summarize this final section, FDA utilizes the collaborative study mechanism of the AOAC to provide validated methods of analysis needed by governments for the enforcement of the law and by industry for compliance with the law.

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Application of Tolerances, Standards, and Methodology in the Enforcement of the Food, Drug, and Cosmetic Act†

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The FDA quality assurance program for its 20 field laboratories, the use of standards established by officially recognized organizations, the national check sample program, and the quality assurance audit visit program are described.

At first glance it would appear that there is not very much that needs to be said under this topic. The Food and Drug Administration as a regulatory agency covering the interstate commerce of foods, drugs, and cosmetics, as well as medical devices and diagnostic products, is a scientific information-consuming agency. As such, it utilizes the analytical methods and standards developed both by itself and the outside scientific community for obtaining data to determine whether any regulatory action is indicated. Nearly every action which FDA takes is based on data provided by its laboratory personnel—in large measure by its analytical chemists. FDA employs some 900 chemists, at least half of whom are analytical chemists.

Having said the above, what remains to be said? Actually a great deal, not in terms of volume but in terms of importance. A former commissioner of FDA has said, "The public interest simply cannot be served if our regulatory decisions are not supported by sound science". Properly validated, sensitive analytical methodology and published standards are essential for the proper administration of the Food, Drug and Cosmetic Act. The question always has to be asked—how reliable are the data coming in from various laboratories? How comparable are the data from one laboratory with those from another? The mercury–seafood contamination problem was an outstanding example. The discovery of mercury in Great Lakes fish was made by the University of Western Ontario utilizing neutron activation analysis. By this time it was known that it was not elemental mercury that posed the problem in fish, but rather the monomethylmercuric ion formed by biological conversion. By this time, it was also obvious that older analytical procedures such as the dithizone colorimetric method were not adequate, and a flurry of analytical reports utilizing

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