Kirk-Othmer Encyclopedia of Chemical Technology.

FINE CHEMICALS, STANDARDS

Fine chemicals are generally considered chemicals that are manufactured to high and well-defined standards of purity, as opposed to heavy chemicals made in large amounts to technical levels of purity. Fine chemicals usually are thought of as being produced on a small scale and the production of some fine chemicals is in tens or hundreds of kilograms per year. The production of others, especially fine chemicals used as drugs or food additives (qv), is, however, in thousands of metric tons (see Pharmaceuticals). For example, the 1990 U.S. production of aspirin [50-78-2] and acetaminophen [103-90-2] was on the order of 20,500 t and 15,000 t, respectively.

Fine chemicals are produced by a wide spectrum of manufacturers, largely because the distinction between different kinds of chemicals is not sharp. There are specialty producers of fine chemicals. Many companies that manufacture drugs also manufacture the chemical substances that are used in preparing the dosage forms. A number of companies manufacture drug chemicals and food chemicals. Some fine chemicals are made by manufacturers of heavy chemicals, and either may be simply a segment of their regular production, or some of that production which has been subjected to additional purification steps. Many fine chemicals are imported into the United States from countries such as Japan, Germany, and the Netherlands.

Over the years compendia have been published in many countries to establish the purity of drug, food, and laboratory reagents available within their borders. For instance, Great Britain, France, Germany, and Japan have long published their own pharmacopeias and, more recently, in the interests of harmonization within the European Economic Community, the *European Pharmacopeia* (1) was issued. Compendia describing laboratory reagent chemicals are not so numerous, but two notable examples are the British *AnalaR Standards for Laboratory Chemicals* (2), and the German *Merck Standards* (3).

The fine chemicals standards discussed herein are primarily those originating in the United States. Much discussion has occurred regarding harmonization of the world's standards. It is not yet clear, however, what impact the International Standards Organization Quality Management Standards (ISO 9000) may have on the manufacture and specifications of fine chemicals.

Standards for drugs are established by the United States Pharmacopeial Convention, Inc. (USPC), and have been published in 21 revisions of the *United States Pharmacopeia* (USP). In the past, standards for many drugs that were not in the USP were established by the American Pharmaceutical Association, and were published in the *National Formulary* (NF). The last edition was published in 1975 (4). In that same year, the USPC acquired the NF, and the USP and NF now are published in one volume (5). In this compendium, drug substances and dosage forms of drug substances are designated USP, and pharmaceutic ingredients are designated NF. The latter substances are used to make the active ingredient(s) into suitable dosage forms for use by patients.

Standards for food-grade chemicals in the United States are set by the Committee on Food Chemicals Codex of the National Academy of Sciences (NAS) which publishes them in the *Food Chemicals Codex* (FCC) (6) (see also Food additives). Standards for laboratory reagents are set by the American Chemical Society (ACS) Committee on Analytical Reagents and are published in *Reagent Chemicals–ACS Specifications* (7). Standards

Table 1. Specifications for Various Grades of Sulfuric Acid

Specification	Technical	NF	FCC[a]	ACS[b]	SEMI standard[c]	SEMI guideline[d]
assay, %	97.5–100.0	95.0–98.0		95.0–98.0	95.0–97.0	95.0–97.0
residue after ignition (RAI), ppm		50		5	3	
chloride, ppm		50	50	0.2	0.1	0.1
nitrate, ppm			10	0.5	0.2	0.15
phosphate, ppm					0.5	0.5
substances reducing permanganate, ppm		40	40	2		
arsenic, ppm		1	3	0.01	As + Sb 0.005	As + Sb 0.005
heavy metals,[e] ppm		5	20	1		
lead, ppm			5		0.3	0.01
iron, ppm	40		200	0.2	0.2	0.01

[a] Also can contain up to 20 ppm selenium.
[b] Also can contain up to 2 ppm ammonium and 0.005 ppm mercury.
[c] 14 other trace metals at 0.01–0.3 ppm.
[d] 31 other trace metals at 0.005–0.01 ppm.
[e] As Pb.

for electronic-grade chemicals, which have extremely low limits for trace ions, are published annually in *The Book of SEMI Standards* (BOSS) by Semiconductor Equipment and Materials International (SEMI) (8).

Standards for sulfuric acid, ranging from technical-grade through drug-, food-, and reagent-grade, to electronic-grade are shown in Table 1. The advances in purity represented by these various grades of chemicals are based on the special uses of the chemicals.

The publications detailing standards (5–8) generally include both specifications and methods of analysis for the substances. The establishment of standards of quality for chemicals of any kind presupposes the ability to set numerical limits on physical properties, allowable impurities, and strength, and to provide the test methods by which conformity to the requirements may be demonstrated. Tests are considered applicable only to the specific requirements for which they were written. Modification of a requirement, especially if the change is toward a higher level of purity, often necessitates revision of the test to ensure the test's validity.

One of the greatest tasks in providing compendial standards is to obtain, adapt, or develop test methods for determining compliance with the standards. Such methods must be capable of routine use in many laboratories by different personnel and equipment. There is a vast difference between a method that can be used in one laboratory by specialists and one that can be used in many laboratories by generalists to determine whether chemicals pass or fail the established specifications. Additionally, the determinations must be reliable, because the results obtained may determine whether a product is safe or legal.

There are no established specifications for the standard reference samples used in general chemical analysis. Many such substances, however, are analyzed and certified by the National Institute of Standards and Technology (NIST), formerly the National Bureau of Standards (NBS). Specific reference standards are required for many of the analyses included in the USP and NF standards for drugs.

The USP and the NF are recognized in the Food, Drug, and Cosmetic Act (1938) as establishing legal drug standards that the Food and Drug Administration (FDA) is responsible for enforcing. The FCC is recognized by FDA regulations, on an individual substance basis, as defining food grade. The ACS reagent specifications have no special legal status per se, but are used by the USP–NF, the FCC, SEMI, and in government procurement, and are referenced in FDA regulations and in American Society for Testing and Materials (ASTM) methods.

Federal regulation of drugs, food additives, and reagents used in *in vitro* diagnostic tests has increased markedly (see Medical diagnostic tests). With increasing consumer concern about the safety of fine chemicals,

especially those used in foods and drugs, the United States government has become increasingly sensitive to the manner in which standards are set. Freedom of information legislation has confirmed the public's right to know, and this has introduced the objective of due process into the development of standards. The USP–NF and the FCC have mechanisms that make possible public participation in setting the standards with which these agencies are involved. Neither ACS nor SEMI has such a formal mechanism, but individuals from industry, government, and academia serve on the ACS Reagent Committee, and committee meetings of both the ACS and SEMI are open to the interested public upon request.

1. Drug Chemicals

Standards for drug chemicals are published in USP–NF. Drug substances are chemicals that have therapeutic or diagnostic uses, whereas pharmaceutical ingredients provide preservative action, flavoring, or fulfillment of a function in the formulation of dosage-form drugs. Examples of drug substances are acetaminophen [103-90-2], ampicillin [69-53-4], aspirin [50-78-2], powdered ipecac, riboflavin [83-88-5], stannous fluoride [7783-47-3], and thyroid. Examples of pharmaceutical ingredients are ethylparaben [120-47-8], lactose [63-42-3], magnesium stearate [557-04-0], sodium hydroxide [1310-73-2], starch [9005-25-8], and vanillin [121-33-5].

Dosage forms include acetaminophen tablets (see Analgesics, antipyretics, and antiinflammatory agents), ampicillin capsules (see Antibiotics), aspirin tablets (see Salicylic acid and related compounds), ipecac syrup, riboflavin injection (see Vitamins), and thyroid tablets (see HORMONES). Stannous fluoride (see Tin compounds) is used in fluoride-containing toothpastes (see Dentifrices). Ethylparaben (see Salicylic acid and related compounds) is a preservative, lactose (see Sugar) is a tablet filler, magnesium stearate (see Carboxylic acids) is a tablet lubricant, sodium hydroxide (see Alkali and chlorine products) is a neutralizing agent, starch (qv) is a tablet binder, and vanillin (qv) is a flavor (see also Flavors and spices).

1.1. The United States Pharmacopeial Convention

The USP was established in 1820 by the assembly of the first United States Pharmacopeial Convention in Washington, D.C. Among the objectives of the meeting was the inclusion in a pharmacopeia of those drugs most fully established and best understood, and standards of pharmaceutical quality for them. The USPC was incorporated as an independent nonprofit organization in 1900, and is headquartered in Rockville, Maryland. A brief history of the Pharmacopeia of the United States is included in the front of *USP XXII–NF XVII* (5). An excellent discussion of the USPC is given in Reference 9, and additional descriptions are available (10–12).

The early USPC was dominated by physicians who selected the best drugs. This prevented inclusion in the USP of a large number of substances that were widely used, particularly elixirs, a popular dosage form in the late nineteenth century. To fill this gap, in 1888 the American Pharmaceutical Association published the first NF, which provided standards for drugs in wide use but not included in the USP. A history of the National Formulary is also included at the front of the NF section in *USP XXII–NF XVII* (5).

When the Federal Pure Food and Drugs Act was passed in 1906, both the USP and the NF were recognized in the act as setting the legal standards of strength, quality, and purity for the drugs described therein. Since the acquisition of the NF, the USPC has as its objective to provide names and standards of pharmaceutical quality for all United States drugs. This inclusion of such standards for all drugs in the USP is being achieved as rapidly as possible.

Tests described in the early compendia were simple analyses that could be performed by a pharmacist using a minimum of laboratory equipment. Tests in the 1990s employ instrumentation such as ultraviolet and infrared spectrophotometers, various kinds of chromatography including gas chromatography–mass spectrometry (gc–ms), x-ray diffraction, nuclear magnetic resonance spectroscopy (nmr), atomic absorbtion (aa), and thermal analysis (see Analytical methods; Chromatography; Magnetic spin resonance; Spectroscopy). Such

tests are no longer performed by pharmacists but are largely used by manufacturers and the various regulatory agencies, eg, the FDA and comparable state agencies.

1.2. The USP Committee of Revision

The work of wholly revising the USP–NF every five years, and making revisions by supplements, is performed by the USP Committee of Revision which now numbers more than 100 experts in the fields of medicine, pharmacy, chemistry, biotechnology, microbiology, etc. The committee members, supported by the Drug Research and Testing Laboratory located in USP headquarters, write the general chapters and product monographs. The *USP XXII–NF XVII* contains well over 3000 monographs.

1.3. The USP–NF

In addition to defining the quality of the reagents used in testing, the USP–NF sets the legal standards of strength, quality, purity, and requirements for packaging and labeling for the articles included in USP–NF. Thus much of the text in the USP–NF represents enforceable legal requirements.

1.3.1. The General Notices

These are the basic requirements for the application and interpretation of the tests and specifications that follow in the USP–NF. Many of the terms used in the text are defined, and the majority of procedural questions that may arise within the monograph for each substance are answered.

1.3.2. The Monographs

A separate monograph is provided for each substance included in the USP–NF. Descriptions and solubilities of the substances are given in a table separate from the individual monographs. The body of the monograph includes a statement of assay, followed by a packaging and storage statement, a labeling statement where applicable, identification tests, and then a variety of tests to establish the strength, quality, and purity of the drug. The tests either provide the methods to be followed or refer to methods in the General Tests and Assays section of the book. Whereas the use of alternative methods, as listed in other compendia described herein is permitted, if there is doubt or disagreement the test in USP–NF serves as the referee method, and only that method is authoritative.

1.3.3. The General Tests and Assays

This section of the USP gives methods for tests that are general in nature and apply to a number of the substances. Procedures are included for such tests as heavy metals, melting point, chloride, sulfate, sterility, bacterial endotoxins, and pyrogens. Also included are descriptions of various analytical techniques, such as spectrophotometry, chromatography, and nmr, and descriptions of tests to be used on glass or plastic containers, rubber closures, etc.

1.3.4. Reagents, Indicators, and Solutions

This section includes the specifications and testing methods for reagents to be used in the tests specified in the USP–NF, and directions for making the various indicator, buffer, colorimetric, test, and volumetric solutions used in the testing. Reagents for which ACS specifications exist are referenced to the ACS book (7).

1.3.5. Reference Standards

Many of the identification tests and assays require the use of reference standards. These standards are available for purchase from the USPC.

1.4. The Standard-Setting Process

Setting USP–NF standards is a continuing, and by no means unilateral, process. The Committee of Revision not only develops monographs for new substances but also continually reviews the monographs, specifications, and testing methods for existing substances. Results are published in one or more supplements each year. A complete review is done every five years and a revision is published.

When a new substance is admitted to the USP–NF, the first step is to locate producers and to obtain their specifications and testing methods. A new monograph is published by the USP for comment in *Pharmacopeial Forum* (PF), which is published every other month. PF includes proposed changes in existing monographs, the general notices, the general tests, or other sections of the USP–NF, proposed new monographs, and proposals relative to policy or philosophy. The public may comment, protest, or make suggestions, and their views receive due consideration. If significant revisions are necessary after this process, a revised proposal is published. Through *Pharmacopeial Forum,* USP–NF standards are openly developed.

1.5. USP Dispensing Information

In the past, USP and NF monographs included information such as the category of use, the usual dose, and package sizes available. This type of information has been greatly expanded, and is now published annually in a four volume book separate from the USP–NF quality standards, entitled *USP Dispensing Information* (USPDI). This information focuses on aspects that enhance the safe and effective use of various medications. It contains information specifically for the health practitioner as well as for the patient, and includes information concerning the dispensing and administration of drugs as well as indications and contraindications related to their use.

2. Food-Additive Chemicals

The FCC is to food-additive chemicals what the USP–NF is to drugs. In fact, many chemicals that are used in drugs also are food additives (qv) and thus may have monographs in both the USP–NF and in the FCC. Examples of food-additive chemicals are ascorbic acid [50-81-7] (see Vitamins), butylated hydroxytoluene [128-37-0] (BHT) (see Antioxidants), calcium chloride [10043-52-4] (see Calcium compounds), ethyl vanillin [121-32-4] (see Vanillin), ferrous fumarate [7705-12-6] and ferrous sulfate [7720-78-7] (see Iron compounds), niacin [59-67-6], sodium chloride [7647-14-5], sodium hydroxide [1310-73-2] (see lkali and chlorine products), sodium phosphate dibasic [7558-79-4] (see Phosphoric acids and phosphates), spearmint oil [8008-79-5] (see Oils, essential), tartaric acid [133-37-9] (see Hydroxy dicarboxylic acids), tragacanth [9000-65-1] (see Gums), and vitamin A [11103-57-4].

Action to compile standards for food-grade chemicals did not take place until after the enactment of the Food Additives Amendment to the Food, Drug, and Cosmetic Act in 1958 (13). This amendment stated that substances added to foods should be of food-grade quality, but it contained no criteria by which such quality could be determined (see also Colorants for food, drugs, cosmetics, and medical devices). The Food Protection Committee of the National Academy of Sciences–National Research Council (NAS–NRC) therefore undertook the project of producing a *Food Chemicals Codex.*

The objective of the FCC is to define food-grade chemicals in terms of the characteristics that establish identity, strength, and quality. It provides specifications in monograph form for some 900 food additives, together with analytical test procedures by which compliance with the specifications can be determined. The third edition was published in 1981; supplements followed in 1983, 1986, 1991, and 1993. The fourth edition is in preparation as of this writing and is to include monographs for almost 1000 food chemicals, including flavors.

Food Chemicals Codex standards are recognized by FDA regulations as defining food grade for many individual chemicals used in foods and food processing. FCC specifications have been adopted by the governments of Australia, Canada, New Zealand, and the United Kingdom. There is extensive international activity in the field of food additives. The FCC is represented at meetings of the Joint Food and Agricultural Organization/World Health Organization (FAO/WHO) Expert Committee on Food Additives (JECFA) and the Food Additive Commission of the International Union of Pure and Applied Chemistry (IUPAC).

2.1. The Food Chemicals Codex

The *Food Chemicals Codex* is developed by the Committee on Food Chemicals Codex, which is a part of the Food and Nutrition Board, Institute of Medicine, National Academy of Sciences, under a contract with the U.S. FDA. The Committee has the responsibility for the development and revision of the FCC. To meet this responsibility, the Committee also contacts manufacturers, trade associations, and other knowledgeable parties to obtain comments and criticisms of monographs proposed by the committee. Broader public input is sought by publication, by the FDA in the *Federal Register,* of current committee activity regarding new and revised monographs proposed for inclusion in the FCC.

3. Reagent Chemicals

Reagent Chemicals—ACS Specifications, in its eighth edition as of 1993 (7), is to reagent chemicals what the USP and the FCC are to drug and food-additive chemicals. The ACS Committee on Analytical Reagents, and its activity relative to specifications for reagents, has a history dating back to 1917, and more tenuously, to 1903 (14). Examples of reagent chemicals are acetone [67-64-1] (qv), arsenic trioxide [1327-53-3] (see Arsenic compounds), barium chloride [10361-37-2] (see Barium compounds), bromine (qv) [7726-95-6], bromthymol blue [76-59-5] (see Hydrogen-ion activity), cupferron [135-20-6] (see Copper; Iron), anhydrous ethyl ether [60-29-7] (see Ethers), hexanes (see Hydrocarbons), hydrochloric acid [7647-01-0] (see Hydrogen chloride), 70% perchloric acid [7601-90-3] (see Perchloric acid and perchlorates), silver diethyldithiocarbamate [38351-46-1] and silver nitrate [7783-99-5] (see Silver compounds), and sodium hydroxide [1310-73-2] (see Alkali and chlorine products).

The ACS Committee on Analytical Reagents is comprised of some 15 members from academia, government, and industry (both manufacturers and users of reagents) and meets twice a year at the ACS headquarters in Washington, D.C. Throughout the year other work is carried out by correspondence. Requirements and details of tests are based on published work, on the experience of committee members in the examination of reagent chemicals, and on studies of test procedures made by committee members.

When a specification for a reagent is first prepared, it generally is based on the highest purity level that is competitively available in the United States. If a higher level of purity subsequently becomes available on a competitive basis, the specification is revised accordingly. An exception to this approach is a need for higher purity in a reagent than is competitively available. In this case the committee sets the standard based on need, presumably stimulating manufacturers to meet that need.

Although the book on reagent chemicals contains many tests for the determination of trace impurities in reagents, it is not intended to be a text on the techniques of trace analysis but rather to provide tests that are reproducible in various laboratories, and which are accurate, economic, and feasible (see Trace and residue analysis).

The usual reagents suffice for many purposes, but the committee recognizes uses for reagents that require a higher purity than that defined by existing ACS specifications. Sometimes reagents must be further purified. However, when there are reasonably widespread uses the committee defines special grades, such as those suitable for use in high performance liquid chromatography (hplc), pesticide residue analysis, or ultraviolet

spectrophotometry. The committee takes into account the practical matters involved in the manufacture of reagents. In general, the higher the purity requirement, the greater the cost. In the combination of high purity requirements with low usage, economics may become an important factor.

3.1. The ACS Book

The ACS book, *Reagent Chemicals—ACS Specifications,* establishes a standard of quality for reagents to be used in precise analytical work, for which purpose it contains both specifications and testing methods for some 350 reagent chemicals.

The book is similar to the two compendia already described. It is published approximately every five years and supplements are published between editions. In addition, notices of changes that need to be publicized after adoption at meetings of the committee are published promptly in the ACS journals *Analytical Chemistry* or, for those of a more urgent nature, *Chemical and Engineering News.*

3.1.1. The Standard-Setting Process

The committee has three main lines of endeavor: the improvement of existing limits for impurities, the improvement of present test methods, and the development of specifications and testing methods for additional compounds.

The ACS committee has a general rule: if two producers meet a given specification, the specification is normally so defined. Usually the methods are checked by several laboratories using samples from various sources. Because of the many different matrices in which impurities are determined, even the simplest impurity tests need to be checked for accuracy in the laboratory.

ACS reagents are specified for tests in the USP–NF and the FCC, and in many ASTM methods of analysis. ACS specifications also are used by government agencies for procurement purposes, and are mentioned in FDA regulations pertaining to the labeling of *in vitro* diagnostic reagents. Although these do not have legal status, as is the case for USP–NF and FCC specifications, these are generally recognized, in the United States and elsewhere, as the definitive standards for reagents.

Most of the common reagent chemicals already are covered by ACS specifications. However, as tests become more highly instrumented and complex, it becomes difficult to write instructions that cover them, and to obtain agreement on tests and results among laboratories. For instance, it became necessary to develop tests for specialized uses for existing reagents, eg, tests on selected solvents to ensure that they are satisfactory for spectrophotometric use or for use in the determination of pesticide residues by gas chromatography (gc) (see Solvents, industrial). Large quantities of such solvents are used to extract pesticides from natural products (see Insect control technology). This means that the solvents themselves must show little or no response to the test, if the reagents are not to overwhelm the substance sought. Testing of such solvents involves a many-fold concentration of possible impurities, followed by a gc examination for peaks that would interfere with the analysis for pesticide residues. Similarly, stringent tests control the suitability of solvents for use in hplc.

4. Electronic Chemicals

Chemicals used in the manufacture of integrated circuits (qv) need to be controlled to even more stringent levels of purity than either USP or ACS grades. In 1973 the Semiconductor Equipment and Materials Institute (SEMI) held its first standards meeting. SEMI standards are voluntary consensus specifications developed by the producers, users, and general interest groups in the semiconductor (qv) industry. Examples of electronic chemicals are glacial acetic acid [64-19-7], acetone [67-64-1], ammonium fluoride [12125-01-8] and ammonium hydroxide [1336-21-6] (see Ammonium compounds), dichloromethane [75-09-2] (see Chlorocarbons and chlorohydrocarbons), hydrofluoric acid [7664-39-3] (see Fluorine compounds, inorganic), 30% hydrogen

peroxide (qv) [7722-84-1], methanol (qv) [67-56-1], nitric acid (qv) [7697-37-2], 2-propanol [67-63-0] (see Propyl alcohols), sulfuric acid [7664-93-9], tetrachloroethane [127-18-4], toluene (qv) [108-88-3], and xylenes (qv) (see also Electronic materials).

ASTM has published a few selected standards for materials used in the electronics industry, such as gold wire for semiconductor lead bonding, but it does not provide a comprehensive set of standards (see Electrical connectors).

4.1. The Book of SEMI Standards (BOSS)

Of the five (5) volumes issued by SEMI, *Chemicals/Reagents* is the one that pertains to fine chemicals. The committee developing these specifications, originally called Reagent Chemicals, in 1991 changed its name to Process Chemicals. In 1988, to reflect the increasingly global importance of SEMI specifications, the industry body changed its name from Semiconductor Equipment and Materials Institute to Semiconductor Equipment and Materials International. The first chemical standards of 1973 borrowed heavily from ACS specifications with the addition of about a dozen trace metals controlled to the ppm (μg/g) level. The 1993 BOSS contains standards for some 38 chemicals such that the most critical materials contain trace metal limits in the sub-ppm range. In addition, SEMI now offers international standards on-line by its international communications network, SEMICOMM. Furthermore, in response to users' needs for ever lower trace metal levels, a novel approach was instituted in 1990. In addition to the 38 standards of base level purity mentioned above which, in accord with USP–NF, FCC, and ACS practices, include referee procedures, BOSS now also includes guidelines for the 20 most critical chemicals in the industry. Guidelines reflect a chemical purity level typically required by semiconductor devices that have geometries of less than 1 micrometer. Standardized test methods are still being developed for some parameters at the purity levels indicated in the guideline. However, until standardized test methods are published, test methodology must be determined by the user and producer. In general these guidelines limit trace level impurities to 5–10 ppb (ng/g) and also limit particles 0.5 micrometers and greater in bottled liquids. To measure trace metals to the levels required in the guidelines involves the use of state-of-the-art instrumentation such as inductively coupled plasma/mass spectrometry (icp/ms).

5. Chemical and Other Standards Used in Analysis

5.1. National Institute of Standards and Technology (NIST)

The NIST is the source of many of the standards used in chemical and physical analyses in the United States and throughout the world. The standards prepared and distributed by the NIST are used to calibrate measurement systems and to provide a central basis for uniformity and accuracy of measurement. At present, over 1200 Standard Reference Materials (SRMs) are available and are described by the NIST (15). Included are many steels, nonferrous alloys, high purity metals, primary standards for use in volumetric analysis, microchemical standards, clinical laboratory standards, biological material certified for trace elements, environmental standards, trace element standards, ion-activity standards (for pH and ion-selective electrodes), freezing and melting point standards, colorimetry standards, optical standards, radioactivity standards, particle-size standards, and density standards. Certificates are issued with the standard reference materials showing values for the parameters that have been determined.

Some of the standards are fine chemicals in themselves, and others, such as filters for checking spectrophotometers, are of utility in the testing and control of fine chemicals.

5.2. United States Pharmacopeia

Reference standards are required in many USP and NF tests, and in a few FCC tests. The USPC distributes such standards domestically and has authorized international distribution by a number of organizations or companies. There are well over 1000 USP Reference Standards, including several for melting points, and also specimens of narcotics and other controlled substances. New standards are constantly under development as needed in various USP, NF, and FCC testing methods.

6. Impact of the Food, Drug, and Cosmetic Act on Fine Chemicals

6.1. FDA Quality Standards

Although standards for many drugs and biologicals are included in the USP–NF, and for many food additives in the FCC, the FDA also establishes some specifications of its own. In the drug field, specifications and testing methods for antibiotics and biologicals are set by the FDA. Also, specifications and testing methods are prescribed for colorants. Many food-additive petitions are granted with the requirement that certain specifications are met.

6.2. Device Legislation

Regulations covering medical devices define reagents used in *in vitro* diagnostic tests as devices (see Medical diagnostic reagents; Prosthetic and biomedical devices).

6.3. Regulations Concerning Good Manufacturing Practice

Chemicals that are drugs, as defined in the Food, Drug, and Cosmetic Act, are subject to the requirement of the Act that they be made under conditions of Current Good Manufacturing Practice (CGMP). Specific GMP regulations for such chemicals have not been published, but the regulations that have been published for dosage form drugs include many points that should be considered (16).

The primary thrust of GMP is that it is not enough merely to make chemicals to meet USP or other applicable specifications. The chemicals must be made under clean and sanitary conditions, procedures and processes must be validated and documented, and processing and packaging must be carried out under conditions that preclude mixup and mislabeling. Records must be kept of complaints, and the manufacturer must know enough about the storage properties of the products to specify storage conditions and, if necessary, expiration dates on the label.

A manufacturer of drug chemicals is required to register with the FDA, and is subject to FDA inspection at least once every two years. Some manufacturers who make chemicals that incidentally are drugs are impelled to drop the drug designation from their labeling in order to avoid the exposure to inspection that registration entails.

Chemicals used in foods should be made under conditions of GMP similar to those for chemicals that are drugs. Food chemicals specifically are subject to food GMPs (17), which deal mainly with sanitation, but there are no general GMP regulations for food chemicals. For this reason, the FCC includes an informational section, "General Good Manufacturing Practice Guidelines for Food Chemicals," to provide GMP guidance for manufacturers of food chemicals.

Reagent chemicals per se are not subject to any GMP regulations because normally these are not considered to be drugs or devices. However, *in vitro* diagnostic reagents are considered to be devices, and many reagent chemicals can be considered to be *in vitro* diagnostic reagents. Such reagents, to which the *in vitro* diagnostic regulations apply, are subject to the GMPs for diagnostic products (18), and to the labeling requirements

for *in vitro* diagnostic products (19). Thus GMP may impinge on certain reagents, unless the manufacturer specifically declares that they are not *in vitro* diagnostic reagents, and does not sell them for this use. Electronic chemicals are not drugs, food additives, or devices, and thus are not subject to any GMP regulations.

BIBLIOGRAPHY

"Fine Chemicals" in *ECT* 3rd ed., Vol. 10, pp. 338–347, by S. M. Tuthill and J. A. Caughlan, Mallinckrodt, Inc.

Cited Publications

1. *The European Pharmacopeia*, 2nd ed., Maisonneuve, SA, France, 1990.
2. *AnalaR Standards for Laboratory Chemicals*, 8th ed., BDH Chemicals Ltd., Poole, UK, 1984.
3. *Merck Standards*, E. Merck, Darmstadt, Germany, 1972.
4. *The National Formulary XIV*, The American Pharmaceutical Association, Washington, D.C., 1975.
5. *The United States Pharmacopeia XXII, (USP XXII–NFXVII)*, The United States Pharmacopeial Convention, Inc., Rockville, Md., 1990.
6. *Food Chemicals Codex*, 3rd ed., National Academy of Sciences, National Research Council, Washington, D.C., 1981.
7. *Reagent Chemicals—American Chemical Society Specifications*, 8th ed., American Chemical Society, Washington, D.C., 1993.
8. *The Book of SEMI Standards*, Semiconductor Equipment and Materials International, Mountain View, Calif., 1993.
9. L. C. Miller and co-workers, *Anal. Chem.* **32**, 19A (1960).
10. A. Hecht, *FDA Consumer*, 24 (Oct. 1977).
11. W. M. Heller, *Hosp. Formul.* **12**, 883 (1977).
12. D. Banes, *J. Chem. Inf. Comput. Sci.* **17**, 95 (1977).
13. *Public Law No. 618*, 86th U.S. Congress, Washington, D.C., 1960.
14. S. M. Tuthill, *Anal. Chem.* **42**, 30A (1970).
15. *NIST Special Publication 260*, 1992–1993 ed., National Institute of Standards and Technology, Gaithersburg, Md.
16. *Title 21, Code of Federal Regulations*, Parts 210 and 211, Government Printing Office, Washington, D.C.
17. Ref. 16, Part 110.
18. Ref. 16, Part 820.
19. Ref. 16, Part 809.10, particularly section 809.10(d).

SAMUEL M. TUTHILL
NORMAN C. JAMIESON
Mallinckrodt Specialty Chemicals Company

Related Articles

Food additives; Electronic materials; Fine chemicals, production