

USP's Assumption of the *Food Chemicals Codex*: Risks and Opportunities

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ABSTRACT

The *Food Chemicals Codex (FCC)* is a compendium of monographs for food ingredients begun in 1961 following passage of the 1958 Food Additive Amendments to the Federal Food, Drug, and Cosmetic Act. Volunteer experts of the Committee on the Food Chemicals Codex of the Institute of Medicine's (IOM's) Food and Nutrition Board developed and maintained *FCC* through the 5th edition with a single *Supplement*. In August 2006 USP's Board of Trustees purchased *FCC* from IOM and intends to continue its publication as one of USP's four compendia. This *Stimuli* article considers the opportunities and risks associated with the Board's decision.

INTRODUCTION

The United States Pharmacopeial Convention, Incorporated (*USP*, without italics) is unusual among the compendial bodies of the world because it is a private not-for-profit [501(c)(3)] organization begun and continued not by government but by practitioners. Its overarching body is a practitioner-based Convention whose members comprise approximately 400 colleges of medicine and pharmacy and a large number of other national and international organizations. Delegates named by member organizations meet at five-year intervals to adjust USP's Constitution and By-Laws, if needed, and elect an all-volunteer Board of Trustees, the governing body of the organization, and the Council of Experts, the standards-setting body of the organization. These and other volunteer groups are served by a staff of approximately 600 USP employees.

In August 2006 the USP Board of Trustees purchased the *Food Chemicals Codex (FCC)*, a compendium of monographs and allied information for food and color additives and food ingredients from the Institute of Medicine (IOM), one of four National Academies of Science. Food and color additives in the US require premarket approval; other food ingredients must be generally recognized as safe (GRAS) for their intended use. This article uses *food ingredients* for all categories. The Food and Drug Administration (FDA) publishes the safety specifications for food and color additives, which may subsequently be taken up in *FCC*. *FCC* had been developed and maintained for many years by the Committee of the Food Chemicals Codex under

the auspices of IOM's Food and Nutrition Board, with support via grants and contracts from FDA. *FCC* joins USP's *United States Pharmacopeia (USP)*, for drugs and biologics), *National Formulary (NF)*, for excipients), and a web-based series of monographs for articles legally marketed outside the United States (SALMOUS), bringing the total to four. In addition, USP publishes the *Pharmacists' Pharmacopeia*, a resource for compounding pharmacists, which contains both official and reference text.

Elaboration of *FCC* is now the responsibility of a newly formed Food Ingredients Expert Committee of the USP Council of Experts. USP intends to publish the 6th Edition of *FCC* in early 2008 and biannually thereafter, with a *Supplement* in intervening years. Public comment to draft *FCC* documentary standards will occur by means of a Web-based *FCC Forum* (www.usp.org/fcc).

USP's Mission

The mission statement of USP's Board of Trustees is:

USP promotes the public health and benefits practitioners and patients by disseminating authoritative standards and information developed by its volunteers for medicines, other healthcare technologies, and related practices used to maintain and improve health and promote optimal healthcare delivery.

USP's entry into setting food standards arose as a result of the 1994 Dietary Supplement Health and Education Act, which names *USP*, *NF*, and the *Homeopathic Pharmacopoeia* as official compendia for dietary supplements. The Board's decision to acquire *FCC* amplified this opportunity because ingredients for foods

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are sometimes similar to excipients for drugs: i.e., they are added for one or more purposes unrelated to nutrition, just as excipients are added to drug products (medicines) for reasons separate from the safety and efficacy of the drug substance. Thus in US law, dietary supplements may contain one or more food ingredients beyond the dietary supplement itself. *USP* and *NF* speak primarily to practitioners and patients—users and consumers of medicines—and manufacturers and compounding professionals who provide these medicines. In contrast, the dietary supplement standards in *USP* and *NF* and food ingredient standards in *FCC* will speak to a different constituency, namely, to all consumers, manufacturers of food ingredients and foods, and food-control officials.

Terminology

USP, *NF*, and the Web-based monographs for non-US articles contain documentary standards (monographs and allied general chapters) and refer at times to a need for reference materials (RMs). Documentary standards for *FCC* are presented in monographs for use by food ingredient manufacturers (first parties), food manufacturers (second parties), and independent testing laboratories and national and international food-control authorities (third parties) for both quality assurance and compliance purposes, also termed conformity assessment activities (1). Under the name of the ingredient, a monograph contains recognized synonyms, applicable registration numbers (e.g., Chemical Abstracts Service numbers), a description of the substance, properties, tests, and procedures to qualitatively verify its identity, and tests, procedures, and acceptance criteria intended to ensure safety and purity. Beyond this information, the monograph gives brief packaging and storage requirements, and in some cases, labeling requirements.

USP uses specific nomenclature to indicate important aspects of its documentary and physical standards (2). The word *official* is used frequently, and in a draft revision of the *General Notices and Requirements* *USP* has proposed to clarify how the word *official* will be applied with respect to *FCC* (3). For *FCC*, *USP* proposes that *official* text is contained in the General Provisions and Requirements (introductory default statements), monographs, and allied General Chapters. The name of a food additive that appears at the start of a monograph will be its *official* title. After development, public notice, a comment period, and a final decision by *USP*'s Council of Experts, a monograph will be finalized and will become effective with an *official* date. If a reference material (RM) is needed in order for analysts to conduct official monograph tests, the RM is stated to be an official *USP* Reference Standard. A food ingredient with an *FCC* monograph will be termed an *official* article and may be so labeled with the letters

FCC in conjunction with the official title. At times *USP* may create authorized text that is provided as guidance and is not considered required for compliance with the provisions of a monograph.

The terms that *USP* uses are duplicated in terms of the US Federal Food, Drug, and Cosmetic Act (FFDCA); e.g., FFDCA refers in its initial sections to *articles* and cites the existence of a *USP* monograph as one definition of a drug. If *USP* publishes a monograph for a drug substance or product, then that substance or product is a drug and must comply with the standards in *USP* or the label must clearly state how the substance or product differs from the monograph standards (4). Official food articles recognized in *FCC* must comply with standards set by *USP* if the articles are dietary supplements or dietary ingredients or substances intended directly or indirectly for use in foods or food processing and are labeled as conforming to *FCC*. When a food ingredient supplier (first party) puts the letters *FCC* on the certificate of analysis of the container of the ingredient, it signals to a food manufacturer (second party) that the ingredient is official and bears an official title (name) with standards of purity and identity that should be maintained throughout the time the article is in commerce. These quality standards can be tested by third parties (government officials, independent testing laboratories, and others) according to the monograph published in *FCC*, which also requires that ingredients should be prepared according to Good Manufacturing Practices. The terms first, second, and third party are drawn from a nomenclature provided in a guidance from the National Institutes of Standards and Technology (NIST), as is other terminology useful to standards-setting bodies (1).

Via terminology and conjoint activities, food ingredient suppliers and *USP* become joined via an *FCC* monograph in an important communication process—not only to food manufacturers and government—but also to the public at large. The communication speaks to processes whereby a good quality standard in *FCC* is known and is being met. The point of communication is an inherent element of trade and ensures that all parties should be able to know, understand, and utilize independently the documentary and physical standards of an article of commerce to preserve on the one hand the safety and quality for foods and dietary supplements and on the other hand the safety and efficacy for medicines.

The thread that binds supplier, user, compendium, regulatory body, and consumer is a slender one and relies frequently on good-faith efforts. *USP* may seek legal redress if an article purports to be or is represented as an official article in one of *USP*'s compendia and such claim is determined by *USP* not to be made in

good faith. Because of the large number of monographs in *FCC* (1000) and because of the even larger number of food ingredient suppliers and vendors worldwide, USP's ability to monitor good-faith claims of compliance with *FCC* is highly constrained. A risk to USP is thus that a food manufacturer might use the *FCC* letters in bad faith. USP manages this risk by noting that labeling statements or other allusions to *FCC* do not constitute an endorsement and do not represent assurance by USP that the article is known to comply with the relevant standards.

CONFORMITY ASSESSMENTS

In general, any standard has little meaning unless it includes a conformity assessment, i.e., for *FCC* testing by the food ingredient manufacturer to the specifications monograph and so noting the results of this testing for the purchaser on a certificate of analysis. Standards in *FCC* gain force if second parties (e.g., food manufacturers) require conformance to them and also test to them. Under good manufacturing practices for foods, a food manufacturer may qualify a food additive upon receipt by means of some kind of audit and testing program, including testing to *FCC* standards. Although *USP* and *NF* are official compendia of the US, this is not the case with *FCC*, which is variably mentioned not in *FFDCA* but in implementing regulations of the 1958 Food Additives Amendments. USP's view is that *FCC* should be an official US compendium in law. This would bring several advantages, chief of which would be that ad hoc FDA regulations alluding to *FCC* would no longer be needed. Because the agency's procedures for promulgating regulations are labor intensive and time consuming, the reduced burden of rule making would conserve FDA's scarce resources. Equally, if not more important, is the general advantage of compendia that allow frequent updating without a need for regulatory action when safety, or safety and efficacy, is not in question (2). And perhaps most important of all is a general theme appearing in the adulteration and misbranding provisions of *FFDCA*, which allow FDA to take immediate action if an article is labeled to indicate conformity to one of USP's compendia and does not in fact do so. At present, however, inconsistent and incomplete legal references to *FCC* weaken regulatory recourse and thus create a risk for USP that its documentary and physical standards will not receive the attention that they merit as tools for protecting public health.

USP PROCESSES

A key requirement for elaboration of an *FCC* monograph is provision of information in a Request for Revision (5). Requests for Revision usually come from

food ingredient manufacturers who have an interest in providing information to support a monograph and candidate RMs when needed. Updating *FCC* monographs on the initiative of the *FCC* Food Ingredients Expert Committee is also important, and this information too is usually supplied by food ingredient manufacturers in a Request for Revision. Upon receipt, USP staff work with manufacturers to understand the information received [the information can be held in confidence upon request (5)]—specifically the analytical validation for the tests, procedures, and acceptance criteria for the proposed monograph—and prepare the draft revised monograph standards for publication in *FCC Forum*. After public comments are received, the draft monograph is modified as needed and presented to the Food Ingredients Expert Committee for consideration and then, as appropriate, balloting. A positive ballot promotes the standard to official status in *FCC* or its *Supplement*. Again a thread of cooperation exists among manufacturers who provide information and donate materials to support a Request for Revision and capable volunteers and staff who evaluate this information independently and create public official standards for official articles. Risk to USP arises if this thread of cooperation is attenuated. In addition to the elaboration of the documentary standard, USP laboratory staff characterize candidate RMs for *FCC* procedures and, by means of collaborative testing, assign a level of purity. In a manner similar to the work with the documentary standard, USP laboratory staff carry out their work and then present data to the Reference Standards Expert Committee of the Council of Experts, who evaluate the data and, if appropriate, endorse the candidate material as an official USP Reference Standard.

These various activities create risk for USP, specifically:

- (1) that manufacturers won't donate needed information or materials,
- (2) that capable volunteers won't be available, and
- (3) that USP will lack resources to conduct the necessary studies to support Expert Committee decisions. USP is heartened by the early enthusiastic response on the part of food ingredient manufacturers and their associations and by the willingness of highly capable volunteers to become members of the Food Ingredients Expert Committee (Appendix). USP is especially pleased to note that many of the distinguished volunteers on the Expert Committee came from the IOM's Committee on Food Chemicals Codex.

FCC USE

A compendium must be used, and all relevant parties must appreciate its value. Consumers should be educated to look for the mark of a compendium and understand its value in ensuring the quality of a food

ingredient. For *FCC* the monograph and its mark are thus highly important. These approaches exist in a series of requirements and steps that result in a good quality food being available in the US and elsewhere. For example, the International Conference on Harmonization has articulated the following elements needed to ensure good quality medicines: 1) characterization during development; specifications, process validation, raw material testing, in-process testing, stability testing, and good manufacturing practices (6). Suppliers of food ingredients must be willing to test to *FCC* specifications and to use official *USP* Reference Standards in this testing. Purchasers must be willing to conduct additional qualifying tests. The joint display of the *FCC* mark to purchasers and consumers signals a commitment to quality that is critical to both groups—and to *USP*, given the latter's non-profit private character. Unlike many other compendial bodies, *USP* does not receive government (ministerial) funding and relies on the sale of its documentary and physical standards to gain resources for its standards-setting activities. *USP* is proud of this fact, which allows independence from government, which can respond at times to commercial interest. *USP* rigorously separates its standards-setting activities from its business activities by careful application of conflict-of-interest and other rules and procedures. This separation is and will continue to be important to the new Food Ingredients Expert Committee so that it sets its standards unfettered by any kind of influence—either external or from *USP*'s activities that make its products and services available to purchasers. Failure to achieve these specific objectives—or perceptions about *USP*'s objectives—is a continuing risk for *USP* because public understanding not only is needed but also is difficult to achieve.

SCIENCE

Advancing the science of a compendium is an exciting opportunity for *USP* because it carries on the distinguished efforts of IOM's Committee of the Food Chemicals Codex. A compendium of quality standards is necessarily a living document. It must account for new ingredients, for changes in the manufacturing process of ingredients, development of new analytical procedures, and for new safety concerns that may arise. Measurement science has advanced remarkably in the past 50 years. This science evolves in many locales, including perhaps especially national metrology institutes (NMIs). The US NMI is NIST, which works collaboratively with other national NMIs. The overall system is a remarkable one that was established by the Treaty of the Meter in 1985 with the goal of establishing consistent and harmonious approaches in support of world trade. A key goal of measurement science is the maintenance of the international system (SI) units, which is pertinent to *FCC* given that its ar-

ticles are usually measured in terms of mass. The SI unit for mass is the kilogram, the international artifact of which is maintained by the Bureau international des poids et mesures (BIPM) in Sèvres. *USP* is expanding application of modern measurement science (metrology) approaches to both its documentary standards and RMs (7), and this expansion will include applications to official articles in *FCC* and food ingredient RMs. This expansion brings risks as well as opportunities. As always, compendial science can advance more rapidly than a country's manufacturers and its policy makers are willing to allow, because modern analytical techniques can rely at times on extremely expensive equipment that can be difficult to purchase, operate, and maintain. Beyond this particular challenge lie challenges arising from increasing analytical sensitivity that allows detection of very low levels of moieties that may or may not have relevance to food safety.

NEED FOR FCC

The question may arise if *FCC* is needed anymore in view of the comprehensive food ingredient monographs developed by the Joint World Health Organization (WHO)/Food and Agriculture Organization (FAO) Expert Committee on Food Additives (JECFA) (8), along with their allied safety evaluations (9). Standards promulgated by JECFA may be adopted by the Codex Alimentarius Commission; Codex food standards are recognized by the World Trade Organization. This is not an option for *FCC* standards. Despite the fine work of JECFA and the cachet of its output, *USP* believes that *FCC* is indeed needed, primarily because JECFA's Terms of Reference are restricted to "food additives." This means that JECFA will not address an enormous number of food ingredients that are not considered additives by either JECFA or Codex, such as ordinary sugar (sucrose) or high-fructose corn syrup (HFCS). In fact, many JECFA food additives are considered GRAS in the US. A universe of substances used in foods thus exists for which only the *FCC* Food Ingredients Expert Committee could be expected to address specifications standards. The broader scope, as well as the quality, of *FCC*'s standards developments is a prime reason for the acceptance nationally, as well as internationally, of *FCC* specifications.

CONCLUSIONS

FCC is an experiment with risks and opportunities that *USP* is proud to undertake. It speaks clearly to *USP*'s public health mission and draws *USP* beyond its primary focus on drugs further into the realm of documentary and RM standards for foods. In part this extension is logical because of Congressional decisions. Further, *USP*'s practitioner-based approaches for foods can speak to consumers' interests not only

in the US but in other countries as well. USP notes that *FCC* is an official compendium of food additives for Australia, Canada, and New Zealand, and it may be used by other countries as well. In advancing *FCC* into this century, USP wishes to thank and congratulate IOM and its Committee on the Food Chemicals Codex for their remarkable efforts. Manufacturing and measurement science and technology for foods and food ingredients are advancing rapidly, yet at the same time so too is the risk of contaminated and adulterated

foods. Safety nets to protect consumers from dangerous foods need strengthening, and USP intends that *FCC* will be an important part of the series of approaches needed to ensure good quality foods and food ingredients. USP looks forward to working with all constituencies—manufacturers, regulators, academicians, policy makers, and others in the US and elsewhere in making *FCC* as valuable to food ingredient and food manufacturers, regulatory bodies, and food consumers as it can be.

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APPENDIX

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