# Prepared Medicines in Relation to FDA CGMP for Dietary Supplements

By Kevin V. Ergil, MA, MS, LAc and Jason Wright, MS, LAc

## Abstract

The Food and Drug Administration finalized rules in 2007, codified as Title 21, Code of Federal Regulations, Part 111 (21 CFR 111) that apply to all manufacturers of dietary supplements. This article addresses issues regarding the recommendation and sale of prepared forms of Chinese medicines or "patent" medicines distributed under these rules (including the lack of a good conceptual fit between Chinese prepared medicines or "patents" and dietary supplements), rules exempting retailers from these provisions, and the basis for – and approach to – practitioner "due diligence" with regard to sourcing CGMP compliant products.

**Key words:** dietary supplements, herbs, Chinese medicine, Good Manufacturing Practice, FDA

## Introduction

This article discusses some key issues regarding the recommendation and sale of prepared forms of Chinese medicines or "patent" medicines that are now available in the United States as dietary supplements. Several points are important to practitioners whose practice includes the dispensing of dietary supplements are: the lack of a good conceptual fit between Chinese prepared medicines or "patents" and dietary supplements as described under the Dietary Supplements Health and Education Act (DSHEA), the Food and Drug Administration (FDA) provisions exempting retailers from the provisions of the Current Good Manufacturing Practice (CGMP) for dietary supplement products, and the basis for, and approach to, practitioner "due diligence" with regard to sourcing CGMP compliant products. Compounding and preparing formulas from loose herbs or granules in the office setting will not be addressed at this time.

The article in *The American Acupuncturist*, Vol. 51, addressed the history and regulatory impacts of the CGMP rules finalized by the FDA in 2007, which are codified as Title 21, Code of Federal Regulations, Part 111 (21 CFR 111) and are now fully applicable to all manufacturers of dietary supplements sold in the United States. Also addressed was the regulatory enforcement discretion proposed by the FDA in relation to the application of 21 CFR 111 to Oriental medicine practitioners who compounded, i.e., manufactured their own products or herbal formulas.[1] Also discussed were the basic concepts underlying good manufacturing practices, the regulatory domain of the FDA, and the impacts that these regulations may have on our profession (Ergil & Wright 2010).

*"With the passage of DSHEA in 1994, the professional community and product suppliers experienced what seemed to be a regulatory reprieve. There appeared to be a new regulatory category for Oriental medicine products that would allow herbs, and the prepared medicines made from them, to continue to be available for use in our clinics and by our patients.*

## Prepared Medicines as Dietary Supplements

With the passage of DSHEA in 1994, the professional community and product suppliers experienced what seemed to be a regulatory reprieve. There appeared to be a new regulatory category for Oriental medicine products that would allow herbs, and the prepared medicines made from them, to continue to be available for use in our clinics and by our patients. Some members of our professional and manufacturing community assumed that DSHEA specifically encompassed traditional medicinal uses and made allowance for traditional therapeutics. In addition, some Oriental medicine professionals perceived "dietary supplements" as a special category that rescued herbs, herbal medicines, and traditional medicines from the challenge of fitting poorly into either category of food or drugs.

In fact, this is only true for products that adhere to the claims limitations established for dietary supplements by this law. DSHEA's claims provisions place "dietary supplements" in a special category under the general umbrella of "foods," so long as marketers refrain from making any claim that a product is to be used in the diagnosis, mitigation, treatment, cure, or prevention of any disease. This restriction applies both to product labels and to accompanying product literature.

The exact same product, if bearing any of these drug claims,[2] would be considered by FDA to be a drug and subject to enforcement as a drug. Determining whether these products, from a strictly regulatory view, are foods or drugs can be complicated by the tendency of the practitioner community to continue to describe products such as *Xiao Yao San* (Free Wanderer Powder) or *Yin Qiao San* (Forsythia and Lonicera Powder) as medicines: "patent" medicines, "proprietary" medicines, or prepared medicines.[3] The continued manufacture and importation of these products is only possible when they are declared by their manufacturers to be "dietary supplements." The fact that many prepared forms of traditionally prepared and proprietary Chinese formulas are in commerce as dietary supplements is due to the fact that they are appropriately labeled and that no drug claims are made for them. While we can accept the tension between the legal fact of a dietary supplement and the professional concept of a prepared medicine, it is important to recognize that the way in which the professional Oriental medicine community uses dietary supplements may sometimes be more consistent with a "drug" use of these products as opposed to a "dietary supplement" use.

## Retail Sales in Relation to Recommendation and Dispensing

This tension between the regulatory status of dietary supplements and our use of these products in our professional role as practitioners of Oriental medicine extends to our recommendation or sale of these products. In its final CGMP rule governing dietary supplements, the FDA specifically exempted retailers, in that they do not hold, package, label, or manufacture products. When a practitioner sells or dispenses manufactured and packaged dietary supplements that he or she has not compounded or repackaged, that practitioner is essentially engaged in a retail activity. However, our practice is not typical of retail. We do not serve customers seeking a product such as vitamin C or kava root based on their own requirements and information. Rather, we make very specific recommenda-

tions concerning the specific product, dose, and duration of use based on our professional expertise and our assessment of our patient. Even if we do not sell or dispense a product directly to a patient we convey our recommendation for the patient to vendors or distributors, who then dispense the product to the patient. This difference suggests that our responsibilities extend beyond that of a "retailer."

A particularly important point was made at the conclusion of the earlier article, which addressed the question of how FDA CGMP regulations regarding dietary supplements (i.e., 21 CFR 111) affect practice-based dispensaries. "The first and most important point is that both patients and practitioners have a greater assurance of the quality and safety of both traditional and proprietary Chinese herbal formula products that are sold as dietary supplements, assuming that the manufacturer has complied with CGMP. The new standards provide greater assurance of product quality and the identity of the ingredients, and allow practitioners to sell and recommend compliant products with greater confidence. This being said, it may now be incumbent, at least on a moral or ethical basis, on Oriental medicine practitioners to assure themselves that the products they recommend to their patients are compliant with the FDA CGMP." (Ergil & Wright 2010).

This suggests that that careful attention needs to be paid to the CGMP compliance of the products that practitioners recommend to our patients, whether these are dispensed or not. Apart from a purely professional concern with the quality and content of the products recommended, our patients' trust and professional liability involved in recommending products that have not met prevailing standards for product quality and identity needs to be carefully considered.

## Practitioner "Due Diligence" to Assess CGMP of Recommended Products

How can a practitioner be sure that the product that she is selling or recommending is manufactured according to the FDA CGMP for dietary supplements? Theoretically, this process should be very simple. A prepared formula labeled as a "dietary supplement" and available for sale in the United States should now be fully compliant with 21 CFR 111 since this is a legal requirement for such products. As of June 25, 2010, even companies with fewer than 20 employees that are engaged in manufacturing, packaging, labeling, or holding of a dietary supplement are required to be compliant with this regulation.

Based on experience with assessing the compliance of manufacturers of Chinese prepared medicines which are sold as dietary supplements with 21 CFR 111, and in training students to do the same, it is clear that there is tremendous variation in the level of compliance and understanding of these regulations. Based on numerous interviews with representatives of manufacturers, re-packagers, and distributors conducted both by students, and the authors at different times over the last three years, it is accurate to say that while some companies are clearly compliant with the labeling requirements published by the FDA and are able to document their compliance with the CGMP rule, others are not. Some companies continue to sell products with non-compliant labels and find it very difficult to clearly express how their manufacturing methods are consistent with 21 CFR 111.

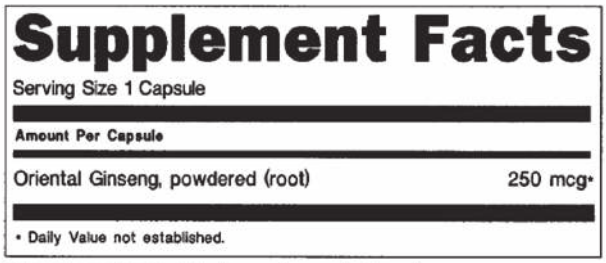
Both compliant labeling and the ability to document CGMP adherence are signs that the company in question understands the requirements and wishes to demonstrate its compliance with these standards to its customers. This means that practitioners and their patients can have confidence that the herbs and other natural products described on the label are present in the product, that steps have been taken to be sure that no misidentified herbs or toxic contaminants have been included in the supplement, and that reliable quality control practices have been followed. Absent compliant labeling and/or the ability to clearly explain how compliance with 21 CFR 111 is established, there is no evidence that the company selling the product understands these rules or has met the standards for manufacturing that they are meant to ensure.

There are two points that practitioners needs to consider. First, how can they assess a product's compliance with label and CGMP standards, and second, how comfortable are they in recommending products for which this compliance is uncertain. This second question is the critical one. When patients are given a pill, powder, tincture, or capsule, the practitioner has absolutely no direct knowledge what the product contains. Trust is implied that the Free Wanderer Powder in pill form actually contains what its label states. The manufacturer is trusted. Even more importantly, the patients trust their practitioners. The Russian proverb "trust but verify" springs to mind.

The purpose of CGMP documentation is to provide the verification for the trust that most manufacturers already receive. It would be one thing to trust a manufacturer's product without checking, but it is quite another when practitioners do so on behalf of their patients. When practitioners fail to take the step of verifying CGMP compliance, has our patients' trust been honored?

## FDA Label Requirements

Familiarity with labeling standards is one simple step in carrying out due diligence. In addition to being clearly labeled as a dietary supplement, five specific statements are required on the label: "1) the statement of identity (name of the dietary supplement), 2) the net quantity of contents statement (amount of the dietary supplement), 3) the nutrition labeling, 4) the ingredient list, and 5) the name and place of business of the manufacturer, packer, or distributor" [21 CFR 101.3(a), 21 CFR 101.105(a), 21 CFR 101.36, 21 CFR 101.4(a)(1), and 21 CFR 101.5]. These labeling standards specify the format seen on a variety of food and supplement products (FDA offers a number of resources to guide label assessment and compliance vm.cfsan.fda.gov/~dms/fdsupp.html). In some instances a very small manufacturer producing small quantities of certain products may be exempt from these standards, however, it will have received an exemption and be able to demonstrate that fact.


**Supplement Facts**

Serving Size 1 Capsule

Amount Per Capsule

| | |
|---|---|
| Oriental Ginseng, powdered (root) | 250 mg* |

* Daily Value not established.

Other ingredients: Gelatin, water, and glycerin.

***Sample label for ginseng as a dietary supplement from 49856 Federal Register / Vol. 62, No. 184 / Tuesday, September 23, 1997***

While product expiration dates are optional on supplement labels and need to be substantiated on the part of the company, it is strongly recommended that the practitioner identify a batch number on the label. This information, overseen by the manufacturer's quality control officers, will allow accurate communication between the seller, the consumer, and the manufacturer about the specific circumstances of the production of the product in that specific container (date, time, ingredients, etc.). This information is critical if there is a problem with the product in question.

## Assessing manufacturer compliance with 21 CFR 111

Assessing manufacturer compliance with FDA's CGMP rule for dietary supplements (21 CFR 111) can be more challenging than assessing a label. In many cases this issue cannot be resolved by an examination of the label and will require a visit to the company's website, a call to the distributor, or communication with a company representative.

The question to answer is: "Is the product manufactured using practices that comply with 21 CFR 111?" If the answer to this question is "yes," the next best question is "How can this be verified?" This is often the point at which receiving a clear answer can be challenging. In some cases the company web site or the representative will clearly state compliance with the regulation of 21 CFR 111 and describe how the company has documented this compliance. Some companies will use third party verification of CGMP compliance. For example, a company may indicate that its products are manufactured under good manufacturing practice (GMP) provided by the State Food and Drug Administration of the People's Republic of China (http://eng.sfda.gov.cn/eng/), by the Taiwanese FDA (http://www.fda.gov.tw/eng/index.aspx), or by the Australian Therapeutic Goods Administration (http://www.tga.gov.au/). The company may then hire an independent agency such as NSF International (www.nsf.org ) to verify that the company's manufacturing operations, and the internal documentation governing them, also meet the FDA standard as established in 21 CFR 111. The use of third party verification to assure compliance provides an established and independent evaluation that can increase the confidence of practitioners in the manufacturing processes used by the company.

In some cases companies will state that their processes are compliant or that the regional GMP (often the case in Taiwan) exceeds the 21 CFR 111. While these statements may be true, the absence of any documentation or independent verification of actual compliance with the requirements of 21 CFR 111 may leave the practitioner with unresolved concerns. In general, one needs to be very cautious with regard to unqualified statements about GMP such as "all products produced in GMP factory" or "we use an international GMP." The concept expressed by "good manufacturing practice" is very broad since the expression does not indicate which GMP standards are being referred to. Only GMPs that are clearly defined by established government agencies are meaningful in this context, but even though these are considered to be excellent standards, there is no reciprocity with the United States. Each manufacturer that meets these foreign standards must also meet all aspects of 21 CFR 111.

The next step is to determine how the GMP applied at the manufacturing site can be established to meet and exceed all aspects of this FDA CGMP rule. Is the product manufactured at one site (in another country) and then packaged at another? In these cases the manufacturer or distributor needs to document CGMP compliance at both sites.

In general, and in the absence of a practitioner having technical or specific knowledge about the company's manufacturing processes, posted documentation of compliance with jurisdictional GMP accompanied by a recognized third party verifier, documentation of compliance with 21 CFR 111 is best. Alternately, clear statements that the company is in compliance with all aspects of 21 CFR 111, including documentation of compliant processes, can be appropriate. As a technical point, registration of a manufacturing facility with the FDA is not a sign of compliance with the required CGMP for dietary supplements under these standards.

Imagine that you are a patient receiving a recommendation for a dietary supplement. Which of the following statements from your practitioner makes you the most confident?

1. "I like this product and trust the people who make it. They tell me it meets GMP requirements."
2. "I have researched this product. It is manufactured under regional GMP, and the company has posted documents to prove it, and has documented independent verification of compliance with CFR 21 111 conducted by a suitable agency. This product meets FDA standards."

There is a wide range of possibility between these two statements. If a company states that its product is manufactured in compliance with 21 CFR 111, you have no obligation to believe that they are misleading you. However, if we give consideration to our patients' trust, we may wish to examine the issue more closely. Professionals taking responsibility for guiding the health-seeking behavior of their patients need to give the same consideration to the manufacturing standards and regulatory compliance of dietary supplements given to the sterility of acupuncture needles or other issues that can have direct impacts on patients and practices.

### References


1. The expression "herbal" is used in the very broad sense used by Oriental medicine practitioners of *yao*, drug, or natural product and not just in reference to medicinal agents of plant origin.

2. Most of the Chinese materia medica and the formulas prepared from them could be considered drugs in that they are applied to treat disease conditions. In fact, the Chinese term "*zhongyao*" which is used to describe the Chinese *materia medica* is properly translated as "Chinese drugs."

3. The term "Chinese Patent Medicines" is a particularly unfortunate one due both to its inaccuracy and its historical association with products sold in the United States as "patent" medicines during the late 19th and early 20th century. Unlike modern pharmaceuticals, these "medicines" were not patented but were proprietary blends that did not, under the laws in place at that time, have any obligation to disclose ingredients. The fact that some of them contained drugs such as opium and cocaine was one of the many factors contributing to the formation of the Food and Drug Administration.

4. Registration of food (including dietary supplements) production facilities is mandated under The Public Health Security and Bioterrorism Preparedness and Response Act of 2002 (the Bioterrorism Act) which directs the Food and Drug Administration (FDA), as the food regulatory agency of the Department of Health and Human Services, to take additional steps to protect the public from a threatened or actual terrorist attack on the U.S. food supply. Because of this, the FDA has established new regulations requiring among other actions that food facilities are registered with FDA. This registration involves no assurance of compliance with 21 CFR 111.

Ergil, K and Wright, J, 2010. How do Food and Drug Administration CGMPs for dietary supplements affect Oriental medicine practitioners?, *The American Acupuncturist*, Vol. 51, Spring, 2010 (http://www.aaaomonline.info/ameracu/vol51.pdf)

Title 21, Code of Federal Regulations, Part 111 Current Good Manufacturing Practice In Manufacturing, Packaging, Labeling, Or Holding Operations For Dietary Supplements Title 21, Code of Federal Regulations, Part 101 Food Labeling


---


Kevin V. Ergil, MA, MS, LAc is a Diplomate of Oriental Medicine (NCCAOM) and an associate professor at the Finger Lakes School of Acupuncture and Oriental Medicine. He has practiced acupuncture and Chinese herbal medicine for twenty years. He is a legislative advisor to the New York State Acupuncture Coalition, chair of the Ad Hoc Committee on TCM Compounding and Dispensing Practice and serves as a consultant to private and government agencies, industry, and law firms on matters pertaining to the production practice, quality, and integrity of herbal products and dietary supplements. His most recent publication is *The Pocket Atlas of Chinese Medicine*.

Jason Wright, MS, LAc is a Diplomate of Oriental Medicine (NCCAOM) and an associate professor at the Finger Lakes School of Acupuncture and Oriental Medicine, where he serves as dean. He has practiced acupuncture and Chinese herbal medicine since 1996. He is co-chair of the Herbal Committee of the Council of Colleges of Acupuncture and Oriental Medicine and a member of the Ad Hoc Committee on TCM Compounding and Dispensing Practice. Mr. Wright has extensive experience in the management and development of herbal dispensaries.