Nutraceuticals and the GMP's

By ***John E. Lincoln***

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INTRODUCTION

Until recently, the taking of vitamin or mineral supplements, and especially herbs, was considered to be at the fringes of respectability by mainstream medicine. However, by 2005 the nutraceutical and dietary supplement industry had become a $182 billion global market, and a $20.3 billion U.S. market, growing at 2.6 % annually.[1]

An important reason for such acceptance is the growing effort to replace anecdotal information on nutraceutical safety and effectiveness with more scientifically based laboratory and clinical studies data. These studies, by their very nature, require the use of products of proven consistency, with repeatable and reproducible ingredients, standardized dosages, and reliable, verifiable documentation. In other words, ingredients, processes, and documentation that are subject to the types of controls defined by current Good Manufacturing Practices (cGMPs).

Nutraceuticals and dietary supplements consist of vitamin and mineral supplements, herbs, essential oils, enzymes, homeopathic remedies, and similar products, with the exclusion of tobacco derivatives. Often listed under alternative medicine, many categories are now, to varying degrees, making inroads into mainstream medicine. These products are widely used by Americans, with an estimated 55 percent of American adults currently taking some form of dietary supplement in any one month and 35 percent taking a multivitamin or multimineral supplement throughout the year.[2]

DSHEA

A discussion of the U.S. nutraceutical industry and the GMPs starts with DSHEA[3], the Dietary Supplement Health and Education Act of 1994 (Public Law 103-417), and the Office of Dietary Supplements (ODS). The ODS was established by DSHEA, at the National Institutes of Health.

Dietary Supplement 'Official' Definition

DSHEA defines a dietary supplement as a product taken by mouth that contains an ingredient that is intended to supplement the diet.[4] This includes: A product (other than tobacco) intended to supplement the diet that bears or contains one or more of the following dietary ingredients:

- Vitamin
- Mineral
- Herb or other botanical
- Amino acid
- Any dietary substance for human use to supplement the diet by increasing the total daily intake; or
- A concentrate, metabolite, constituent, extract, or combinations of these ingredients
- A product intended for ingestion in capsule, tablet, or liquid form
- A product not represented for use as a conventional food or as the sole item of a meal or diet
- A product labeled as a "dietary supplement"
- A product such as an approved new drug, certified antibiotic, or licensed biologic that was marketed as a dietary supplement or food before approval, certification, or license (unless the Secretary of Health and Human Services waives this provision)

Some of these products and/or ingredients may already be classified as "GRAS" (Generally Recognized As Safe) by the U.S. FDA, and officially listed as such.

Food and Drug Administration Regulation

The U.S. FDA regulates dietary supplements under a different set of regulations than those covering "conventional" food and drug products – prescription and over-the-counter (OTC). Under DSHEA, the dietary supplement manufacturer is responsible for ensuring that a dietary supplement is safe before it is marketed. There is currently no FDA 'clearance' or 'approval' process for dietary supplements. Currently, the FDA is responsible for taking action against any unsafe dietary supplement product only after it reaches the market.

The FDA's Center for Food Safety and Applied Nutrition, Office of Nutritional Products, Labeling, and Dietary Supplements (ONPLDS), is responsible for developing policy and regulations for dietary supplements, nutrition labeling and food standards, infant formula and medical foods, as well as for scientific evaluation to support such regulations and related policy development. ONPLDS staff also support compliance and enforcement actions and is responsible for the clinical review, data summaries, and as appropriate, follow-up and research related to adverse events associated with dietary supplements and infant formula.

Unlike pharmaceuticals, manufacturers of dietary supplements generally do not need to register their products with the FDA nor do they get FDA approval before producing or selling their products. However, domestic and foreign facilities that manufacture and process, pack, or hold food for human or animal consumption in the United States are required to register their facilities with the FDA.

There are obvious dangers associated with products that, while currently defined as "food" by the U.S. FDA for purposes of regulation, can often have side effects more in line with OTC drugs. Hence no advertising or labeling can or should minimize the need for the consumer to discuss their anticipated usage with a physician. This is not only due to possible potentially dangerous side effects, but also possible interactions with certain medical pharmaceutical regimens, e.g., antibiotics.

All dietary supplement manufacturers must make sure that product label information is truthful and not misleading. When dietary supplement labeling statements can be construed to assist a bodily function, that labeling must include the caution:

> *"These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease."*

FDA's post-marketing responsibilities include monitoring safety, e.g.: voluntary dietary supplement adverse event reporting, and product information, such as labeling, claims, package inserts, and accompanying literature. The Federal Trade Commission (FTC) regulates dietary supplement advertising,

though there is some overlap with the FDA.

Voluntary Industry Compliance to GMPs

The GMPs, or Good Manufacturing Practices, are the U.S. FDA's codification of the quality and documentation systems required of medical device manufacturers and pharmaceutical or drug companies. Drug products fall under Title 21 of the Code of Federal Regulations (CFR) Parts 210 and 211, while medical devices fall under 21 CFR Part 820. When GMPs and dietary supplements are discussed, it is almost always the pharma/drug model that is assumed. Currently, dietary supplements are not required to adhere to these requirements, but many nutraceutical companies have chosen to comply voluntarily.

Reasons for voluntary compliance generally involve industry's recognition of one or both of the following two basic reasons:

1. The value that compliance with the GMPs offers, in providing –
   - Consistency in manufacturing processes
   - Bases for legitimate studies and clinical trials
   - "Leveling of the playing field"
2. A concern that future FDA regulation of the industry is inevitable

Labeling is a separate issue, and is controlled by the FDA under "foods." The U.S. FTC also monitors advertising claims.

UNITED STATES PHARMACOPOEIA

The United States Pharmacopoeia (USP) is the official authority in setting standards for all prescription and OTC medicines, dietary supplements, and other healthcare products manufactured and sold in the United States. Founded in 1820, the USP is an independent, not-for-profit, public health organization and is committed to developing public standards to help assure good quality in medicines, healthcare delivery, dietary supplements, and related products and practices.

USP - Verified Ingredients

The USP-Verified Dietary Ingredients Program conducts testing to verify active and inactive ingredients used to manufacture dietary supplements to ensure consistent quality. These ingredients include:

- Fine chemicals
- Vitamins
- Minerals
- Amino Acids
- Botanical Extracts
- Non-Botanicals

USP-Verified Ingredient certification means that the ingredients used are of:

- Consistent quality
- Strength, purity, and quality that meet the label claims
- Ingredients and products prepared in accordance with accepted manufacturing processes
- Manufacturing specifications that meet requirements for acceptable limits of contamination

USP standards are enforceable by the FDA. Testing is voluntary and is available to all interested manufacturers. A USP-Verified Ingredient certification seal is displayed on all such verified products.

USP Assessment Process

USP - Verified Ingredient status is obtained through assessment of the following:

- Evaluation of laboratory ingredient samples for compliance with label claims and USP program requirements
- Review of manufacturing and quality control documentation
- Audit of manufacturers quality systems for compliance with Good Manufacturing Practices

NSF INTERNATIONAL

The NSF International is a not-for-profit, non-governmental organization founded in 1944 as the National Sanitation Foundation and committed to public health, safety, and protecting the environment. Serving manufacturers operating in 80 countries, NSF bills itself as *"The Public Health and Safety Company™, providing public health and safety risk management solutions to companies, governments, and consumers around the world."* Now known as NSF International, the company develops standards and criteria for equipment, products, and services that bear upon health, and serves manufacturers operating in 80 different countries. The foundation offers independent testing, certification, auditing, and toxicology consulting services throughout the world. NSF's Dietary Supplement Certification Program is designed to help consumers and healthcare practitioners identify supplement products that have been tested by a third-party organization.

NSF Dietary Supplement Certification

Product formulations and labels are tested to ensure:

- Products contain the identity and quantity of ingredients listed on the label
- Products are free of any undeclared contaminants

Testing for NSF Dietary Supplement Certification is voluntary and available to all manufacturers. Standards for certification were developed by NSF and the American National Standards Institute (ANSI), also known as NSF/ANSI 173.

NSF Certification Process

Third party auditors conduct on-site inspections of manufacturing facilities and provide NSF with copies of all audit and corrective action reports.

To earn NSF Dietary Supplement certification (see also NSF GMP Registration Program below) the program includes:

- Good Manufacturing Practice audits
- Label and formulation review
- Product testing
- Clinical study review
- Toxicological review

The program includes the following elements:

- Inspect manufacturing facility
- Inspect product formulations
- Test contents for quantity of ingredients
- Test contents for contaminants
- Test contents for disintegration
- Open to all manufacturers
- Voluntary participation
- Fee paid for testing

NSF GMP Registration Program

NSF's Good Manufacturing Practices Program (GMP) is designed to provide a system of processes, procedures, and documentation to ensure that the product produced has the identity, strength, composition, quality, and purity that it is represented to possess.

The NSF GMP Registration Program is available to all manufacturers, is voluntary, and is based on a proposed set of GMPs developed by four industry trade associations. The program was submitted to the FDA in 1995. These proposed GMPs are designed to address the unique circumstances of dietary supplement production.

THE NATURAL NUTRITIONAL FOODS ASSOCIATION

The Natural Nutritional Foods Association (NNFA) is a non-profit organization dedicated to the natural products industry. Founded in 1936, the NNFA protects the values and interests of retailers and suppliers in the natural nutritional foods and products industry. It represents more than 1000 manufacturers and 3000 retailers of health foods, dietary supplements, natural ingredient cosmetics, and other natural products.

NNFA GMP Certification Program

The NNFA's Good Manufacturing Practices Program (GMP) was launched in January 1999. It is designed to review all elements of the manufacturing process and ensure that the processes of the manufacturing facility are controlled in order for products to meet their purported quality.

Inspections for cleanliness, equipment maintenance, record keeping, and receiving of raw materials are conducted to identify whether NNFA specified performance standards are met. The standards identified by the NNFA have been through FDA review.

Assessment Process

Third party auditors conduct on-site inspections of manufacturing facilities of NNFA member companies, and provide the NNFA with copies of all audit and corrective action reports. The audits are performed by one of the NNFA approved companies, which utilize former FDA staff to conduct the audits.

Once certified, manufacturers are given a compliance rating. The Performance Rating System is as follows for a member supplier:

- "A": Excellent compliance with NNFA GMPs, with few deficiencies noted
- "B": Good compliance with NNFA GMPs, but several significant deficiencies were noted
- "C": Fair or poor compliance with NNFA GMPs, many deficiencies noted; a re-audit is required

A member supplier who receives an "A" is immediately able to apply for the right to use the certification mark. Those who receive a "B" are able to apply once the problems have been corrected, and those with a "C" rating must submit for a re-audit. Certified companies are audited every three years to verify continued compliance with NNFA GMPs.

Production Methods

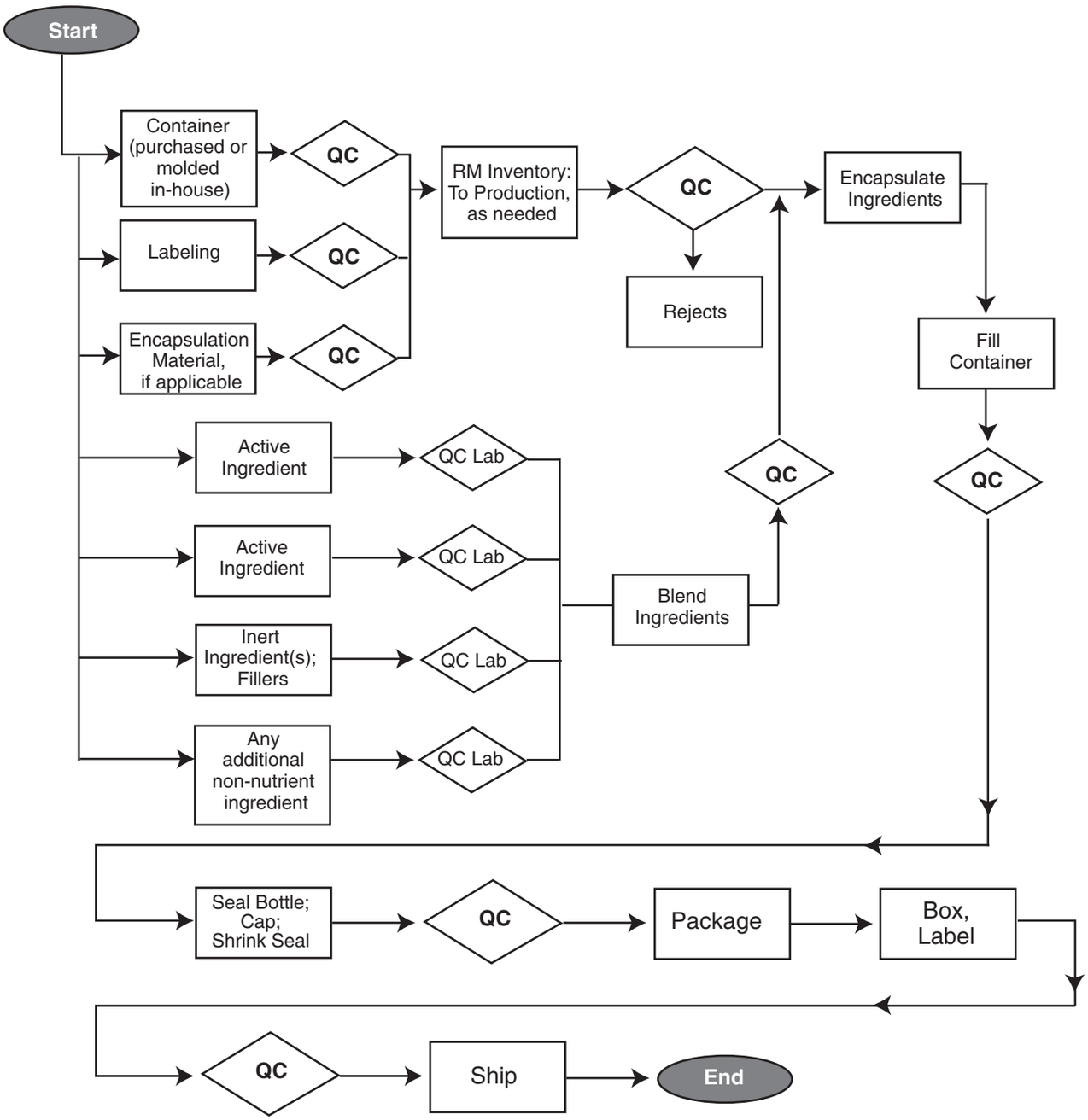
Production of nutraceuticals (see *Figure 1*: Production Steps) generally follows the pharma model as far as tablet formulation, encapsulation of powder or liquid, time release, and other technologies or processes. Key differences include: the lack of mandatory qualification, validation documentation, preventive maintenance, instrumentation calibration, and similar requirements, which are key requirements of the U.S. FDA's GMPs (see 21 CFR Part 210, 211). However, this drawback is changing with the nutraceutical industry's voluntary adoption of the GMPs.

There are many producers who have not yet adopted these strict and somewhat costly GMP systems and procedures. However, several trends are driving changes in this attitude, and are promoting compliance:

- Consumer demand for quality control and standardized product
- The increasing requirement for valid research to support claims and allow targeting of special health concerns, requiring standardized, consistent, known product
- Partial entry into this market by "big pharma"
- Globalization of the market
- Demands by large buying groups, including "Big Box" retailers
- Industry perception of the entry of the FDA into the nutraceutical industry at some point in the future, accompanied by mandatory compliance to a quality system standard
- Company recognition of the inherent advantages of such quality systems
- Business needs for control and monitoring of changes

Figure 1

Typical Key Nutraceutical Production Steps



Change Control – OEM Materials and Production Methods

Change control has always been a big issue with the FDA as it pertains to regulated industries, such as food, medical devices, drugs and cosmetics - especially drugs. It is correctly viewed as a major component in quality maintenance, where its breakdown results in unintended quality problems being introduced after poorly managed control of changes (to product, process or equipment, testing, etc.). It is required to maintain the integrity of costly validations. It is also a key component of the GMPs, ISO 9001, ISO 13485, and similar quality systems standards (see *Figure 2*). Change control requires that no changes in raw materials, formulations, methods of production, packaging, storing, or any other activity that does or could affect product quality take place without proper documentation, including testing, and approvals.

Recognizing its inherent value to stabilize production, failure investigation, product improvement, process and equipment validations, human or clinical trials, and similar advantages, the nutraceutical industry, pushed by various trade associations such as those mentioned above, has been voluntarily adopting these important quality management system principles.

Cleanliness and Sterilization Method Concerns

The industry's move to voluntary compliance to the GMPs, as well as a growing public awareness of "green" issues, and a concern for the quality of products used and consumed, is driving closer review of the inherent variability in the quality of incoming raw materials, and the required processing steps. Large nutraceutical manufacturing companies utilize many elements of the pharma model in the treatment of incoming raw materials, eliminate source contamination, and maintain the cleanliness of production lines. This includes the periodic cleaning of production lines and processing equipment using validated chemicals, methods, and trained personnel.

CONCLUSION

The nature of the industry and its increasing globalization, indicate a wide disparity in the consistency and/or quality of the efforts outlined above. However, as volume increases, and the market shifts to the large producers, use of the pharma model by the industry should increase. It should be noted that countries such as mainland China and India are already utilizing such quality systems in their large industries to offer a regulated production environment and products in a bid to grow their share of the global markets, including nutraceuticals and dietary supplements. Based on these trends and business needs the voluntary use of the cGMPs, or similar quality systems in dietary supplement manufacture, will undoubtedly only increase.❑

ABOUT THE AUTHOR

John E. Lincoln is Principal of J. E. Lincoln and Associates, a consulting company serving the medical device and pharma industries (start-up to Fortune 100 multinationals), with over 25 years industry experience. He specializes in implementing regulatory solutions that make business sense. This includes Device Project Management, Risk Management, Cycle Time Reduction, Quality Systems, and Regulatory issues and submissions. He has held positions as Director of QS/RA, VP R&D, Sr. QA Engineer, and Sr. Manufacturing Engineer, with companies such as Abbott Laboratories, Hospira, and Mallinckrodt Medical.

Additional experience has been with Sperry Univac (Unisys), Hughes Aircraft – Aerospace, U.S. Army Signal Corps / Depot Staff, and the City of Los Angeles' Administrative/Budget Office. He has received several awards for breakthrough project implementation, is listed in Who's Who – Science and Engineering, and has authored numerous peer-reviewed articles on medical device and regulatory issues. He is on the Reader and Editorial Review Boards of MDDI Magazine and the Journal of GXP Compliance, on the board of the IBA (Intermountain Biomedical Association), and is publisher of a medical device newsletter. He is a graduate of UCLA. John can be reached at www.jelincoln.com, phone at 888-882-4655, and e-mail at jel@trilobyte.net.

Figure 2

Comparison between 21 CFR 210, 211 (the Drug GMPs), and ISO 9001:2000 (Quality Management System)

Area of Interest	Drug Good Manufacturing Practice (GMP/CFR)	Quality Management System (ISO/ANSI/OTHER)
Labeling	• 21 CFR 211.122, 211.125, 211.130, 211.132, 211.137, and 211.184	• ISO 9000:2000 5.6, 7.5, and 8.2
Manufacturing Procedures	• 21 CFR 211.130, 211.132, 211.160, 211.184, and 211.204	• ISO 9000:2000 7.5, 7.6, and 8.2
Additional Manufacturing Procedures	• 21 CFR 211.103, 211.110, 211.115, 211.134, 211.165, 211.182, 211.188, and 211.194	• ISO 9000:2000 6.5, 7.5, 7.6, and 8.2
Warehousing and Distribution	• 21 CFR 211.142, 211.150, 211.165, 211.188, and 211.196	• ISO 9000:2000 7.5 and 8.3
Complaint Process	• 21 CFR 211.192, 211.198, and 211.204 • 21 CFR 310.305 • 21 CFR 314.80	• ISO 9000:2000 5.2, 5.3, 7.2, 8.3, 8.4, and 8.5
Calibration Program	• 21 CFR 211.67, 211.68, 211.105, 211.110, 211.182, and 211.194	• ISO 9000:2000 7.5, 7.6, and 8.2
Receipt, Inspection, and Disposition	• 21 CFR 211.82, 211.101, and 211.84	• ANSI/ASQC Z 1.4-1993 • ISO 9000:2000 5.2, 7.2, 7.4, and 8.3
Returns and Salvage	• 21 CFR 211.204, and 211.208	• ISO 9000:2000 5.2, 7.2, 8.3, and 8.4
Containers	• 21 CFR 211.82, 211.84, 211.86-87, 211.89, and 211.94	• ISO 9000:2000 7.2, 7.4, 7.5, and 8.3
Expiration Dating	• 21 CFR 211.125, 211.130, 211.137, and 211.166	• ISO 9000:2000 5.3, 7.5, 8.2, and 8.3
Non-Conforming Material Report (NCMR)	• 21 CFR 211.84, 211.87, 211.89, 211.115, and 211.188	• ISO 9000:2000 8.3, 8.4, and 8.5
Batch (Lot) Records	• 21 CFR 211.188 and 211.192	• ISO 9000:2000 7.5 and 8.2

(CONTINUED ON PAGE 20)

Figure 2 (Continued)

Comparison between 21 CFR 210, 211 (the Drug GMPs), and ISO 9001:2000 (Quality Management System)

Area of Interest	Drug Good Manufacturing Practice (GMP/CFR)	Quality Management System (ISO/ANSI/OTHER)
Master Records	• 21 CFR 211.186 and 211.192	• ISO 9000:2000 4, 5.2, 5.3, 5.7, 7.5, 8.2, and 8.5
Change Control	• 21 CFR 211.100 and 211.186	• ISO 9000:2000 7.3, 7.5, 7.6, 8.3, 8.4, and 8.5
Batch (Lot) Release	• 21 CFR 211.188 and 211.192	• ISO 9000:2000 4, 5.6, 7.2, and 7.5
Personnel and Training	• 21CFR 211.25 (a) and 211.34	• ISO 9000:2000 6.2, 6.4, 6.5, and 8.5 • Applicable state licensing and/or pharmaceutical requirements
Facilities Systems	• 21 CFR 211.42, 211.44, 211.46, 211.48, 211.50, 211.52, 211.56, and 211.58	• ISO 9000:2000 6.4, 7.2, 7.3, and 8.2
Equipment Maintenance and Cleaning	• 21 CFR 211.67, 211.105, and 211.182	• ISO 9000:2000 7.5, 7.6, and 8.5
Product Recall	• 21 CFR 211.115, 211.196, and 211.204 • 21 CFR Part 11.5.1 and Part 7	• ISO 9000:2000 5.2, 5.3, 5.6, 7.2, 8.3, 8.4, and 8.5
Verification and Validation	• 21 CFR Part 11 (Electronic Records and Signatures) • 21 CFR 211.42, 211.63, 211.68, 211.186, and 211.192	• ISO 9000:2000 4, 5.6, 7.2, 7.3, 7.5, 7.6, 8.2, 8.4, and 8.5
Quality Policy	• 21 CFR 211, especially 211.22 (a), 211.100 (a and b)	• ISO 9000:2000 4, 5.4, 5.5, 5.6, 8.4, and 8.5 • Applicable state licensing and/or pharmaceutical requirements. • Industry Best Practices
Outside Audit Policy	• 21 CFR 211.22	• ISO 9000:2000 4, 5.1, 5.5, 5.6.2, 8.4, and 8.5
Site Registration Policy	• 21 CFR 205 and • 21 CFR 211.1	• ISO 9000:2000 1.1(b), 4.1 (Note), 4.2.3, 4.2.4, 5.1 • Applicable state licensing and/or pharmaceutical requirements. • Other applicable requirements, e.g., DOT, OSHA, JCAHO

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2 NTSBS Data, Products and Services Information Services, Stats and Survery, NNFA Consumer Survey, 2001.

3 http://www.fda.gov/opacom/laws/dshea.html

4 "*The Dietary Supplement Health and Education Act of 1994*," U. S. Food and Drug Administration Center for Food Safety and Applied Nutrition, December 1, 1995.

5 JCAHO, Joint Commission on Accrediation of Healthcare Organizations, is a US-based non-profit organization formed in 1951 with a mission to maintain and elevate the standards of healthcare delivery through evaluation and accreditation of healthcare organizations. The Joint Commission employs surveyors who are sent to healthcare organizations to evaluate their operational practices and facilities. Organizations deemed to be in compliance with all applicable standards are "accredited." Hospitals and some other types of healthcare organizations, as accredited organizations are deemed by the Centers for Medicare and Medicaid Services to meet the Medicare and Medicaid certification requirements – necessary for gaining reimbursement from Medicare and managed care organizations – Wikipedia, http://en.wikipedia.org/wiki/Joint_Commission_on_Accreditation_of_Healthcare_Organizations

Article Acronym Listing

ANSI	American National Standards Institute
CFR	Code of Federal Regulations
DOT	Department of Transportation
DSHEA	Dietary Supplements Health and Education Act
FDA	Food and Drug Administration
FTC	Federal Trade Commission
GMP	Good Manufacturing Practice
GRAS	Generally Recognized As Safe
ICH	International Conference on Harmonization
JCAHO	Joint Commission on Accreditation of Healthcare Organizations
NNFA	National Nutritional Foods Association
NSF	National Science Foundation
ODS	Office of Dietary Supplements
ONPLDS	Office of Nutritional Products, Labeling, and Dietary Supplements
OSHA	Occupational Safety and Health Administration
OTC	Over-The-Counter
U.S.	United States
USP	United States Pharmacopoeia