Drug and Supplement Regulation in America: Divergent Systems Lead to Health Dangers

By

Heather Barr

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Abstract

Dietary supplements consumed by many in the United States can seriously interact with other drugs and/or medications having potentially lethal side effects. Such supplements are marketed with little regulatory oversight from the United States Food and Drug Administration (FDA). As many supplements are taken for their health effects, as are drugs and medications, the regulations imposed by the FDA on drugs should be examined and comparative regulation developed for supplements. A comparison of the two systems of regulation leads to the logical conclusion that supplements should be regulated in a manner similar to over-the-counter drugs.

Dietary Supplement Background

The dietary supplement industry, growing at a 7% annual rate, had sales over $30 billion in 2012 (Nutrition Business Journal, 2012). This is not surprising considering that over half of adults in the United States report taking one or more dietary supplements. The Centers for Disease Control and Prevention (CDC) found that supplement use by U.S. adults increased from 42% in 1988 to 53% in 2006. Multivitamins are the most popular supplements and were used by 39% of adults in 2006 (Park, 2011). The term dietary supplement refers to a wide array of products, including: vitamins, minerals, herbs and other botanicals, amino acids, and other substances found in the human diet, such as enzymes (U.S. Food and Drug Administration, 2009). A study published in the Journal of the American Medical Association Internal Medicine (JAMA Internal Medicine) found that adults over age 60 and non-Hispanic whites are most likely to use supplements. The study found that the main reason for use of supplements was to improve or maintain overall health. The authors comment, “As seen in this study and others, the use of dietary supplements is associated with lower BMIs (Body Mass Index), moderate alcohol use,
more exercise, abstinence from smoking, and having health insurance. Previous research also suggests the supplement users have higher intakes of most vitamins and minerals from their food choices alone than nonusers,” (parentheses mine). The study also showed that 77% of the users of dietary supplements do so by choice and only 23% were actually using them following a recommendation by their physician (Bailey, Gahche, Miller, Thomas & Dwyer, 2013). The American Dietetic Association (ADA) states that dietary supplements can never take the place of a healthy diet but could be useful for the following groups of people: pregnant women, nursing mothers, strict vegetarians, people with food allergies or intolerances, senior citizens and those with kidney, cardiovascular, or bone disease or cancer (Zelman, 2009). Supplements are often used to help with asthma, insomnia, depression, chronic gastrointestinal disorders, pain, memory problems, and menopausal symptoms (Gardiner, Phillips & Shaughnessy, 2008). The American Cancer Society noted several misconceptions that surround supplement use including: “more is better; natural means it is safe; if it has been used for thousands of years it must be good; it cannot hurt to take supplements with regular medications; and, if it could hurt you they would not be allowed to sell it” (American Cancer Society, 2011). Unfortunately these beliefs may lead to mega dosing, naïve use of products, and not informing their physicians of use.

**Ingredient Dangers**

Dietary supplements like other medications and drugs can have associated side effects. Consumer Reports® has a list of ingredients, referred to as the dirty dozen, that they recommend people avoid due to side effects. These include aconite, bitter orange, chaparral, colloidal silver, coltsfoot, comfrey, country mallow, germanium, greater celandine, kava, lobelia, and yohimbe. Dangers associated with these supplements include toxicity, nausea, vomiting, kidney damage, liver damage, low blood pressure, respiratory paralysis, heart arrhythmias, fainting, heart attack,
stroke, bluish skin, mucous membrane discoloration, neurological problems, cancer, coma, rapid heart rate, and even death. Bitter orange and country mallow have now been officially banned by the FDA. In addition, yohimbe actually contains a prescription drug, yohimbine (Consumer Reports, 2010). Yohimbine is used for pupil dilation and increasing peripheral blood flow and should only be available by prescription (Micromedex, 2011). Prescription drugs should never be used without the guidance of a physician. The FDA features advisories about certain products. Some products being sold for arthritis and bone cancer contain remoufan plus and other ingredients found in prescription drugs (U.S. Food and Drug Administration, 2012d). Even when the ingredients in a supplement are not believed to cause side effects unregulated manufacturing processes employed by supplement makers could result in the inclusion of harmful contaminants.

**Mega-Dosing**

Consumers who are often misled are known to believe that more of a good thing must be better. Knowing this the supplement industry markets mega dosages. Mega doses of fat soluble vitamins A, D, E, and K can be especially dangerous as can iron supplements. Nausea, vomiting, diarrhea, and rash often accompany acute and chronic vitamin toxicity. Other symptoms of toxicity vary by type of vitamin, for instance, high doses of vitamin A may promote development of osteoporosis (Rosenbloom & Tarabar, 2011). It is therefore, important to follow the recommended dietary allowance (RDA) for these substances.

**Potency**

The actual content of the supplements may not be as claimed on the label. This can result in a shortfall in people who need a recommended intake of the vitamin in question. A study published February 11, 2013 in JAMA Internal Medicine found that in a 12 bottle sample, each from a
different manufacturer, the content of Vitamin D in the supplements ranged from 9 to 146% of the content listed on the label. Dr. Pieter Cohen, an Assistant Professor of Medicine at Harvard Medical School and a General Internist at Cambridge Health Alliance in Boston commented, “It leaves patients in the dark about how to replete their Vitamin D.” (Rettner, 2013). Malnutrition associated with lack of certain vitamins can also be dangerous. For instance, Vitamin D deficiency may lead to rickets or osteomalacia. Muscle weakness and bone pain are more subtle symptoms. Vitamin D deficiency could also be a risk factor for osteoporosis and cancer. (National Institutes of Health, Office of Dietary Supplements, 2011a).

**Reported Adverse Events**

The American Association for Poison Control Centers (AAPCC) has kept records on all poisonings including those from dietary supplements since 1983. In 1983 there were 14,006 reports regarding vitamins, minerals, and essential oils. The number grew to 125,595 reports by 2005. The 260 nonvitamin, nonmineral supplement associated deaths reported to the FDA between 1989 and April 2004 are believed to represent serious under reporting. According to Dr. Alexander M. Walker of the Harvard University School of Public Health, “A best estimate is that less than 1 percent of serious adverse events caused by dietary supplements are reported to the FDA.” Unfortunately poison control centers report that nearly three fourths of the reported injuries related to exposure are in children under age 6 (Hurley, 2007). Clearly there has been an increase in adverse events since the passing of the Dietary Supplement Health and Education act (DSHEA) in 1994.
Drug Interactions

As noted dietary supplements may be dangerous when taken by themselves. These dangers are often multiplied when supplements are taken in conjunction with prescription drugs. This is especially true when they are not taken under the supervision of a physician. For instance, Vitamin K can reduce the effectiveness of blood thinners, St. John’s Wort can speed the breakdown of antidepressants and birth control medications, and antioxidants including Vitamins C and E may reduce the effectiveness of some types of cancer chemotherapy (National Institutes of Health, Office of Dietary Supplements, 2011b). Many people do not consider supplements to be medicines and therefore have not consulted their health care provider regarding their use. It is estimated that one in four people taking a prescription medication also take a dietary supplement (Gardiner, Phillips & Shaughnessy, 2008). In a survey the American Association of Retired People (AARP) found that of those over age 50 taking supplements fewer than half had consulted with health care providers regarding their use (Jaret, 2012). The American Academy of Family Physicians reports that 2 out of 3 patients taking a prescription medication and supplements do not inform their doctor of their supplement use (Gardiner, Phillips & Shaughnessy, 2008).

Drug Regulation

In the United States the regulation of drugs is a complex process involving various departments within the FDA. The system focuses on reviewing and licensing new drugs. However, they must also keep up with a growing counterfeit drug market. Throughout this process the FDA promotes safety through accurate labeling, advertising, and communication. A reporting system for adverse events, investigation regulations, and the ability to withdraw medications also help
ensure the safety of the American public. As the system encounters new challenges changes and amendments are made. In order to stay up to date and continue to move forward with new medical breakthroughs the FDA participates in consortiums, conducts new research, and looks for areas in drug regulation that must be strengthened. Unfortunately the efforts of the FDA to protect consumers from supplements fall short of the activities and time spent on other drug regulation.

Center for Drug Evaluation and Research

The FDA states, “Our goal is to protect and promote the health of Americans.” The FDA Act of 1997 clarified the mission and called for the FDA to: “promote the public health by promptly and efficiently reviewing clinical research and taking appropriate action on the marketing of human drugs in a timely manner, protect the public health by ensuring that human drugs are safe and effective, participate through appropriate processes with representatives of other countries to reduce the burden of regulation, harmonize regulatory requirements and achieve appropriate reciprocal arrangements, and carry out its mission in consultation with experts in science, medicine and public health and in cooperation with consumers, users, manufacturers, importers, packers, distributors and retailers of human drugs” (U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research, 2007). The FDA’s Center for Drug Evaluation and Research (CDER) regulates both Over-the-Counter (OTC) and prescription drugs to include fluoride toothpaste, antiperspirants, dandruff shampoos and sunscreens. The CDER evaluates new drugs, ensures that they work as claimed, and that benefits outweigh the risks to consumer’ health (U.S. Food and Drug Administration, 2010a). OTC drugs may be prescription drugs that are subsequently approved as OTC drugs. The FDA has regulations requiring labeling of OTC drugs be written in a way that can be understood by
average people. These regulations require the label include intended use/s of the product, results expected, adequate directions for proper use, and warnings against unsafe use. Side effects and adverse reactions must also be included. Toxicity, as well as the possibility of self-diagnosis are other areas to be considered when authorizing a drug for OTC distribution. With regard to toxicity, the FDA considers the overall safety of the drug. OTC drugs are evaluated on an individual basis in regard to ability of consumers to self-diagnose. Ultimately OTC drugs must benefit while not sacrificing safety (U.S. Food and Drug Administration, 2010a).

**Drug Testing**

Drugs must be tested in a different ways prior to sending the FDA a New Drug Application (NDA). The drug must undergo laboratory, animal, and finally human testing. If the drug is a biologic agent a Biologics License Application (BLA) must be submitted. Drug test results, manufacturing information to demonstrate the company can properly manufacture the drug, and the company’s proposed label for a drug must all be included in the application for manufacture and distribution (U.S. Food and Drug Administration, 2010c). Generics, while not requiring the clinical trials done for new drugs, must prove bioequivalence to the brand name drug (U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research, 2007). It is important to note that the FDA does not test drugs but instead relies on the studies submitted by drug companies. The FDA relies on evidence from supplement companies when a claim is being made. The CDER has physicians and scientists that review this data. While the FDA is not permitted to provide information about drugs that are under investigation, there are programs that allow patients access to these developmental drugs if they have an immediately life threatening condition. People may participate in clinical trials or seek expanded access outside of a clinical trial. Immediately life threatening is defined by the
FDA as “a stage of a disease in which there is a reasonable likelihood that death will occur within a matter of months, or in which premature death is likely without early treatment (U.S. Food and Drug Administration, 2010a).

**Prescription Drug User Fee Act**

The Prescription Drug User Fee ACT (PDUFA) provides resources to CDER to conduct comprehensive drug reviews and other drug safety activities. PDUFA is an act which helps with fulfilling the first part of the FDA mission, promote the public health by promptly and efficiently reviewing clinical research and taking appropriate action on the marketing of human drugs in a timely manner (U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research, 2007). In 2011 PDUFA enabled review of the following: 105 original NDAs and BLAs, 64 resubmitted NDAs and BLAs, 131 NDA and BLA efficacy supplements, 36 resubmitted efficacy supplements, and 2,548 NDA and BLA manufacturing supplements (U.S. Food and Drug Administration, 2012h).

**Clinical Trials**

Clinical trials are important to determine safety and whether the benefits of new pharmaceuticals outweigh the risks associated with their use. The FDA began developing guidance to facilitate innovations in study design and analysis in 2007. Pharmacogenomics is another important area being used by the FDA. It allows for identification of differences in people’s response to drugs. Through this identification the best form of treatment for the patient may be predicted. The FDA issued Draft Companion Guidance to the Pharmacogenomics Guidance on Recommendation for the Generation and Submission of Genomic Data. They also posted Valid Genomic Biomarkers in Drug Labels on the genomics web site, and co-authored *Guidelines and Recommendations for*
Laboratory Analysis and Application of Pharmacogenetics to Clinical Practice. The FDA is focusing on creating a tighter scientific linkage between non-clinical and clinical studies, enhancing methodology for assuring product quality, building databases for improved drug development and review, and providing regulatory support through laboratory testing. To accomplish this they are identifying biomarkers for organ damage, identifying biomarkers for inflammation, establishing scientific research capabilities in analysis of medicinal plants and herbs, and developing a standardized approach to provide better use of exposure-response data.

Research Programs

The FDA is even involved in research in biotechnology. According to the FDA, scientific research helps them understand how pharmaceutical products are developed and manufactured thus helping to ensure quality and safety. They contend that scientific research helps them to make sound scientific and regulatory decisions, set standards for specific products based on scientific evaluation, develop appropriate methodology for complex and novel products, determine how best to label products, address various public health issues, and study new technology to determine regulatory requirements. Microbiology is another area of FDA research. They review product sterility, maintenance and safety. They also look at controls used for drug development and manufacturing. They maintain that their research is being done to support regulatory decision making. This includes research in the following areas: application review, regulatory policy, product testing, new technology, manufacturing, formulation changes, process analytical technologies, mechanism of action and biomarkers. Counterterrorism biotechnology research is another area. This research includes identifying bio warfare agents, finding neutralizers of biological toxins and developing strategies to defend against anthrax (U.S. Department of Health and Human Services Food and Drug Administration Center for Drug
Evaluation and Research, 2007). The FDA must conduct this research to stay up to date with new threats and protect the public.

**Labeling and Advertising**

Another part of the FDA mission is to protect the public health by ensuring that drugs intended for human use are safe and effective (U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research, 2007). This mandate is accomplished through monitoring drug safety, ensuring accurate advertising and truthfulness of drug information, and monitoring quality and safety. The FDA monitors drug safety and informs health-care providers and the public while also developing policies, guidance, standardized drug labeling, current manufacturing practices, clinical and laboratory practices, and industry practices. The FDA ensures accurate advertising and drug information by regulating information accompanying OTC drugs and making sure drug advertisements are accurate as to effectiveness, side effects, and circumstances that may require drug avoidance. The FDA issues regulatory letters citing violations in advertising. Fifty-nine such letters were issued in 2007 along with 655 letters about drug promotion. As drug advertising continues the FDA performs ongoing research in the areas of new tactics in direct consumer advertising, ongoing direct consumer advertising, and direct to consumer promotion letters.

It is of note that supplement advertising is not monitored in the same way leading to advertising which is often misleading. It is the opinion of this author and others that supplement advertising should be regulated in a similar manner in order to ensure accuracy of information, understanding of the ingredients, and possible side effects (U.S. Department of Health and
Human Services Food and Drug Administration Center for Drug Evaluation and Research, 2007).

**Communication**

Communication is essential to public health as well as major areas of work by the FDA. Their work in enhancing communication involves public participation, stakeholder participation, and consumer and industry outreach. The FDA seeks to raise public awareness in the following areas: antibiotic resistance, benefits vs. risks of medication use, cautions of buying drugs from outside the U.S., buying prescription drugs online, using medicines safely in children, counterfeit drugs, generic drug quality, medicines and the elderly, misuse of prescription pain relievers, OTC medicine labels, and the hazards of use of sedatives and driving. In keeping with this goal their messaging reportedly reached 200 million Americans in 2006 (U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research, 2007). The CIA world fact book estimated the population of the U.S. to be approximately 313 million as of July 2012 (Central Intelligence Agency, 2013). Using this figure means the FDA public health messages are estimated to be reaching 2/3 of the population.

**Adverse Events Reporting and Investigation**

Concerning protecting quality and safety, the FDA looks carefully at who will be using a drug, how it is to be used, what side effects it may cause, how it is to be administered. The FDA also reviews the seriousness of side effects to see if that outweighs the benefits to cure of the disease. According to the FDA their professional staff spends about half their time addressing the following: watching for adverse events, overseeing clinical trials, evaluating new therapies and
expanded uses, overseeing manufacturing, overseeing distribution, overseeing promotional activities, preventing medication errors, and developing risk management strategies.

**Post Approval Monitoring**

Safety and quality must also be monitored after a drug enters distribution. Health care providers are not required to report adverse events to the FDA, a fact that this author considers unfortunate. Consumers, however, have the opportunity to report problems directly. The FDA monitors drugs on the market for risk categories that include product quality defects, known side effects, avoidable side effects, unavoidable side effects, medication errors, and other uncertainties. Population-based data, data mining, and an adverse events reporting system (AERS) aid in monitoring drugs that are on the market. AERS receives reports to their MedWatch system directly from individuals and, more so, from health-care practitioners, from 15 day expedited reports from manufacturers, and from manufacturer periodic reports (U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research, 2007).

**Investigatory Activities**

Investigation is an important duty of the FDA and that is necessary to keep the public safe. All adverse reactions require a FACTS consumer complaint report and follow-up report. Details provided include the brand name and an identity statement which includes label and code marks. The item which caused the problem and its place of origin are identified through this information. The FDA must investigate how the product was used which includes questions about frequency, amount, other treatments being taken, allergies, and history of previous reactions. The FDA must identify all medical research that a reporter of an adverse event used. A
sequence of events and symptoms must be established. If injuries are significant, photographs may be collected. Other people involved should be listed and interviewed for their account of the incident. Any other consumer complaints or reports made to the manufacturers are also investigated. Finally, distribution information should be gathered from the manufacturer along with lot numbers. The FDA states that “Drug injuries or reactions, either human or veterinary, result from the use of products which: 1). Vary markedly from declared potency; 2). Contain deleterious substances; 3). Are mislabeled as to identity, warnings, or instructions; 4). Have been mistaken for other drugs despite proper labeling; 5). Have changed composition, or become contaminated after shipment; 6). Are dangerous when used according to directions. 7). Have not been used in accordance with label directions or directions from the prescriber; 8). Have been improperly administered, or administered without the necessary precautions; 9). Have been contaminated with objectionable microorganisms, soaps or cleaning solutions; 10). Have been misidentified; 11). Have been labeled as sterile drugs, but are found to be non-sterile; and/or, 12). Have adverse effects that were not identified prior to marketing.” These are all problems that are addressed by the FDA (U.S. Food and Drug Administration, 2012j). The FDA also reviews proposed brand names, labels, and packaging to help prevent medication errors. They review approximately 2,000 post-marketing reports on errors each month (U.S. Food and Drug Administration, 2012b).

**Counterfeit Drugs**

Today, through the internet people have easy access to drugs without a prescription. As a result there is a growing concern regarding counterfeit medications coming into the U.S. The FDA works with other agencies and the private sector to combat the acquisition of counterfeit drugs and provides information for the public on precautions when buying drugs online (U.S. Food and
Drug Administration, 2012b). Under some circumstances it is legal to import drugs for personal use that have not yet been approved by the FDA. The FDA states that it does not object to personal importation of an unapproved drug provided, “The drug is for use for a serious condition for which effective treatment is not available in the United States; There is no commercialization or promotion of the drug to U.S. residents; The drug is considered not to represent an unreasonable risk; The individual importing the drug verifies in writing that it is for his or her own use, and provides contact information for the doctor providing treatment or shows the product is for the continuation of treatment begun in a foreign country; and ,Generally, not more than a 3-month supply of the drug is imported.” The FDA warns that it cannot ensure safety or effectiveness of these drugs so individuals must take responsibility and be vigilant (U.S. Food and Drug Administration, 2010b).

**Withdrawal of Drugs**

The FDA may require product recalls or withdrawals when safety is a concern (U.S. Food and Drug Administration, 2012j). The FDA assists in coordination of recalls and informing the public. The top reasons for drug recalls include correctly labeled products in incorrect packaging, temperature abuse, subpotency, chemical contamination, impurities/degredation, failing dissolution test requirements, illegible labeling, marketing without an approved NDA, lack of assured sterility, label mix-up, expiration dates not supported by stability data, and microbial contamination of non-sterile products.

**The Food and Drug Administration Amendments Act**

Many changes took place at the FDA in 2007. Among these was the establishment of the Risk Communication Advisory Committee on June 4, 2007. This committee was suggested by the
Institute of Medicine (IOM). George W. Bush signed a new law into effect September 27, 2007 called the Food and Drug Administration Amendments Act (FDAAA). The FDAAA endorsed the Risk Communication Advisory Committee. The FDAA provides the FDA with authority by expanding PDUFA. The expanded PDUFA allows the FDA to adjust user fees based on inflation and workload, expand implementation of Good Review Management Practices (GRMPs), and work toward strengthening drug safety especially in the area of full life cycles of drugs. The FDAAA also reauthorized the Medical Device User Fee and Modernization Act, Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA). The Medical Device User Fee and Modernization Act gives the FDA authority to make improvements in the medical device review program. The Best Pharmaceuticals for Children Act, and Pediatric Research Equity Act work together to promote activities leading to the development of treatment for children. There are many times when a drug approved for adults might be helpful for children; unfortunately doctors with no information may be unwilling to prescribe them or may prescribe them improperly. The FDA has regulations requiring some manufacturers to provide information on safety if taken by children, newborns or adolescents. This, however, is not the case for all drugs. The FDA can only require children’s studies for drugs already approved in circumstances when pediatric information can help avoid serious risks to children (U.S. Food and Drug Administration, 2010a). Some of the changes made by the FDAA include: authorization of an internal review committee, and making information on clinical pharmacology, statistical review and adverse event reporting available to the public. In October 2007 a new initiative called Safety First/Safe Use began building on authorities provided by the FDAAA (U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research, 2007).
Consortiums

The FDA has many teams and participates in many consortiums that provide research.

**Maternal Health Team**

The FDA has a Maternal Health Team with the mission to increase knowledge about the safe and effective use of medicine during pregnancy and breastfeeding. This team encourages research and provides scientific guidance in their area of interest. The FDA ensures that information available on the use of a medicine during pregnancy and breastfeeding is updated on medicine labels. The scientific guidance provided includes determining the appropriate dose of a drug for pregnant women, evaluating study results on approved drugs when used during pregnancy, lactation studies in women, and pregnancy exposure registries.

**Serious Adverse Events Consortium**

The FDA also participates in the Serious Adverse Events Consortium. The Serious Adverse Events Consortium is a nonprofit consisting of pharmaceutical companies and academic institutions as well as the FDA. In 2007 they began research programs to identify genetic markers to help predict risk for drug-related adverse events. The initial areas of focus include liver toxicity and Stevens - Johnson syndrome, a serious skin condition.

**Predictive Safety Testing Consortium**

The FDA is part of the Predictive Safety Testing Consortium which includes the CPath Institute and pharmaceutical partners. The Predictive Safety Testing Consortium has a goal validation of the predictive value of new preclinical biomarkers of toxicity and qualifications of their use in specific regulatory contexts. Biomarkers of nephrotoxicity were set in 2007.
The Biomarker Consortium

The FDA also collaborated with a public-private research group, The Biomarker Consortium, which is working on discovery, development, and qualifying of new biological markers to support drug development, preventive medicine and medical diagnostics (U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research, 2007).

Areas to Strengthen in Drug Regulation

Science, communications, and operations are areas that the FDA is looking to enhance their efforts toward assuring the safety of drugs. The IOM issued a report at the request of the FDA titled *The Future of Drug Safety: Promoting and Protecting the Health of the Public*. The FDA completed their review of the recommendations and responded in 2007 by improving drug safety communication channels, prescription drug information, medication guides, and early public health advisories (U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research, 2007).

Supplement Regulation

In 1993 Senator Orrin G. Hatch, Republican of Utah, stated that, herbal remedies, “have been on the market for centuries,” he added: “In fact, most of these have been on the market for 4,000 years, and the real issue is risk. And there is not much risk in any of these products.” (Hurley, 2007). This and other comments led to decreasing regulation over supplements creating what this author believes to be a dangerous situation for consumers. Myths, misconceptions, and misinformation surround the use of dietary supplements. The passage of the DSHEA in 1994 by the FDA has led to consumers having access to and using substances that are assumed to be safe
until proven otherwise. However, with the enactment of the DSHEA of 1994 the FDA is allowed to have a separate system to regulate dietary supplements (Brackett, 2009).

**Supplement Labeling**

There are requirements for the label on supplements ensuring that such labels are not misleading. First labels must have the product name and labeling that identifies it as a dietary supplement. Labels must bear a supplement facts panel delineating nutrition information. Ingredients not found in the supplement facts panel must also be listed. Additionally labels must list the net quantity of contents provided as well as names and addresses of the manufacturer, packager, and/or the distributor. Possibly the most important difference between drug and supplement labeling is the information that must be placed on the label if claims are made. If a label includes claims about an effect on health, well-being, body function, or nutrient deficiency there must also be a disclaimer stating that the FDA has not evaluated the claim and that the product is not intended to diagnose, treat, cure, or prevent any disease. The FDA also requires companies to have evidence substantiating health claims and requires notification of the claim on the label within 30 days of marketing (U.S. Food and Drug Administration, 2012c).

**Supplement Safety**

Supplements are assumed safe and therefore not required to provide evidence of product safety to the FDA. However, if a supplement contains a dietary ingredient that was not marketed prior to October 15, 1994 the manufacturer must give a 75 day pre-market notification to the FDA. The manufacturer must also supply citations of articles proving that the new dietary ingredient is reasonably expected to be safe (U.S. Food and Drug Administration, 2012c).
Regulation Enforcement

Enforcement of dietary supplement laws is a joint effort between the FDA and Federal Trade Commission (FTC). The FTC regulates advertising of products while the FDA regulates safety, manufacturing, and labeling. Enforcement is accomplished through inspections which may result in voluntary compliance, voluntary recalls, warning letters, seizure, and injunctions. The FDA and FTC co-chair a health fraud steering committee including agencies in the U.S., Canada, and Mexico. The group has worked to find fraudulent marketing of health care products on the internet. The Drug Enforcement Agency (DEA) also works with the FDA in the area of illegal steroid products marketed as dietary supplements. In 2004 the Anabolic Steroid Control Act (ASCA) classified many steroids as controlled substances.

The Office of Criminal Investigation (OCI) is responsible for conducting and coordinating criminal investigations. They liaise and cooperate with federal, state local, and international law enforcement agencies. The OCI works directly with federal and local prosecutorial offices and participates in grand jury proceedings and other necessary judicial actions as well. The FDA conducted 588 domestic inspections of manufacturers, issued over 350 warning letters to marketers, and seized products worth over $13.4 million from October 2002 through February 2006. During this same time period they also supervised voluntary destruction of over $3 million worth of products that were either marketed with unsubstantiated claims, were unapproved drugs, or were found to be unsafe. The FDA also issued permanent injunctions to five distributors of misbranded or unapproved drugs being marketed as dietary supplements. Over 4,000 shipments of foreign dietary supplements have been refused because they were potentially unsafe or misbranded. The FDA publicizes actions against supplements in order to warn health care professionals and the public. The FDA evaluates, literature, and reports that are published to
assist in evaluation of supplements and to remain informed on safety. The FDA collaborates with the National Center for Natural Products Research (NCNPR), the National Institutes of Health (NIH), and the National Center for Toxicological Research (NCTR) in their effort to stay current on safety of supplements. These partnerships allow them to test natural and synthetic ingredients in supplements and identify possibly unsafe ingredients or amounts of substances that may be unsafe. In addition to the above there is a Center for Food Safety and Applied Nutrition (CFSAN) and a CFSAN Adverse Event Reporting System (CAERS) that work with dietary supplements and food. Health care providers and individuals report adverse events from supplements on a voluntary basis. CAERS began operation in June 2003. Since 2003 approximately 1,145 adverse events have been reported. The FDA alerts manufacturers about reported adverse events, when the reporter of the event appropriately identifies the product (Brackett, 2009). Manufacturers must alert the FDA of any reports of serious adverse events related to their products (U.S. Food and Drug Administration, 2012e).

A thesaurus of botanically-derived ingredients is being compiled to enable easier search of the CAERS database. The FDA regulates supplements with the current Good Manufacturing Practices (cGMPs) as well (Brackett, 2009). The cGMPs help to ensure product quality. The practices include all firms involved with activities of testing, quality control, packaging and labeling or holding regardless of whether that firm is foreign or domestic. Provisions are related to the design and construction of physical plants that facilitate maintenance, cleaning, proper manufacturing operations, quality control procedures, testing final products, or incoming and in process materials, handling consumer complaints, and maintaining records. Manufacturers are also required to do the following: employ qualified employees and supervisors; design and construct their physical plant in a manner to protect dietary ingredients and dietary supplements
from becoming adulterated during manufacturing, packaging, labeling and holding; use equipment and utensils that are of appropriate design, construction, and workmanship for the intended use; establish and use master manufacturing and batch production records; establish procedures for quality control operations; hold and distribute dietary supplements and materials used to manufacture dietary supplements under appropriate conditions of temperature, humidity, light, and sanitation so that the quality of the dietary supplement is not affected; keep a written record of each product complaint related to cGMPs; and retain records for 1 year past the shelf life date, if shelf life dating is used, or 2 years beyond the date of distribution of the last batch of dietary supplements associated with those records. The cGMPs help prevent production of dietary supplements that contain ingredients in amounts that are greater or less than those listed on the label, contain the wrong ingredient, contain other contaminants, contain foreign material in a dietary supplement container, or have improper packaging, or are mislabeled (U.S. Food and Drug Administration, 2012c). The cGMPs are currently being reviewed by the Office of Management and Budget.

The Consumer Health: Information for Better Nutrition Initiative was started by the FDA to provide consumers with scientifically accurate information about foods and supplements. There are two complementary goals of the initiative: encouraging marketers of conventional foods and dietary supplements to make accurate, science-based claims about the health benefits of their products, and bringing enforcement actions against those who make false or misleading claims (Brackett, 2009). There are no standardized servings for nutrients in a supplement. The manufacturer makes this decision and is not required to receive approval from the FDA. The FDA states “In that FDA has limited resources to analyze the composition of food products, including dietary supplements, it focuses these resources first on public health emergencies and
products that may have caused injury or illness. Enforcement priorities then go to products thought to be unsafe or fraudulent or in violation of the law. The remaining funds are used for routine monitoring of products pulled from store shelves or collected during inspections of manufacturing firms.\textsuperscript{7}(U.S. Food and Drug Administration, 2012e).

**Office of Regulatory Affairs**

The Office of Regulatory Affairs (ORA) is responsible for conducting inspections, collecting and analyzing samples, initiating enforcement, and conducting follow-up to assure compliance. The ORA has over 179 offices across five regions and twenty districts. In 2008 offices were opened in China. Most of the ORA’s work is with post-market inspections of food, human drug, biologics, animal drug and feed, and medical device manufacturers. The ORA also conducts post-market inspections to assess compliance with cGMPs. In addition the ORA participates in radiological health activities such as inspecting certified mammography facilities. The OCI is called in when there are allegations of criminal misconduct. Otherwise the ORA may propose formal warnings, reinspect firms to see if corrections have been made, initiate an import alert, and propose a seizure or an injunction (U.S. Food and Drug Administration, 2009). In 2011 the following enforcement was done: 15 seizures, 16 injunctions, 1,720 warning letters, 3,640 recall events, and 9,288 recalled products. These statistics include the Centers for Devices and Radiologic Health (CDRH), CDER, the Center for Biologics Evaluation and Research (CBER), the Center for Veterinary Medicine (CVM), the Center for Tobacco Products (CTP), and CFSAN. CFSAN had 11 of the 15 seizures, 12 of the 16 injunctions, and the most class 1 recalls 963 products and 276 events. Class 1 is defined as a situation in which there is a reasonable probability that the use of or exposure to a violative product will cause serious adverse health consequences or death (U.S. Food and Drug Administration, 2012f).
Discussion

As seen in the above the regulation of drugs in the U.S. is a complex process. Pharmaceutical companies must complete many tests and perform a great amount of research. Evidence of effectiveness and safety from these tests allow companies to apply to sell the newly created drugs. The FDA has great responsibility in this process. Reviewing applications is only a small portion of the duties involved. The FDA requires staff to look through the evidence provided by companies ensuring the safety of the public. The FDA must monitor and investigate reports of adverse events. Advertising has become a larger issue that requires monitoring now so that messages are clear and do not mislead consumers. The FDA also has the burden to carry out inspections of drug manufacturing facilities guaranteeing recommended and appropriate processes are followed. The FDA responsibilities include assisting in recalls as well. In addition to all of these tasks the FDA performs research on drugs, and participates in various coalitions for drug regulation. The FDA is an invaluable resource to the American public providing excellent, up to date information on all drug related matters.

Supplements as OTC Drugs

Unfortunately supplements, although often having effects similar to drugs, do not come under the same careful regulation the FDA provides for pharmaceuticals. The FDA does nothing to regulate dietary supplements until they prove harmful, putting the public at peril. CFSAN had the largest number of class 1 recalls out of any of the FDA’s regulatory bodies. The fact is supplements can and are causing serious health implications and in some cases their use has even resulted in death. Supplements should be treated the same way that OTC drugs are treated. Applications for supplements would be submitted to the FDA with evidence of safety and efficacy. Currently manufacturers must only provide evidence of efficacy when an effect is
claimed on their label. There is a great amount of available research data as well as ongoing investigation of the various ingredients found in supplements. Some companies may simply be able to site existing research. By treating supplements as OTC drugs labeling requirements would be more stringent. Labels would be written so that average people can understand them. Labels would include intended use and results expected, adequate instructions for proper use, and warnings against unsafe use and noted side effects and adverse reactions just like OTC drug label inclusions (U.S. Food and Drug Administration, 2010a). Labels would also be restricted to only including conditions that multiple studies have found they are effective against. Medline plus, a service of the U.S. National Library of Medicine from the NIH, contains information on herbs and supplements. Many of these supplements have conditions listed under effective, likely effective, possibly effective, possibly ineffective, likely ineffective, and insufficient evidence to rate effectiveness (Natural Medicines Comprehensive Database, 2012). When conditions the supplement is effective against are listed on the Medline plus site, these same conditions could be placed on labels. As research grows supplements would be found to be effective or ineffective against more conditions. Requiring evidence of safety, efficacy, and application in order to market supplements would reduce the number of dangerous and ineffective products that are produced and sold. Any supplements that may contain ingredients found in prescription drugs would never be sold.

As with any drug or supplement there will always be cases of adverse events but the FDA should do everything within its power to protect the public. Research in the area of supplements will need to continue just like research into new drugs and their effects/efficacy continues.
Cost

The FDA requested $1,258,614,000 for all the activities necessary for regulating human drugs in 2013 (United States Food and Drug Administration, 2012i). Food, cosmetics, and supplements are covered by the same budget. The FDA requested $1,083,939,000 for regulation of all these items (United States Food and Drug Administration, 2012g). It is unclear how much of the budget for food, cosmetics, and supplements is actually spent on supplement regulation. Food regulation is most likely the main focus of this budget due to the numerous foodborne outbreaks that have occurred in recent years. A budget increase would clearly be needed to implement changes in supplement regulation. Taxation of supplements could help provide the necessary resources. Federal excise taxes on tobacco raised $15,101,077,000 in 2011 (RJ Reynolds, 2013). This is almost 12 times the FDA requested budget for regulation of drugs in 2013. Supplements could be taxed far less than tobacco and still provide enough income to cover all federal regulation activities. Numerous studies show lower use of tobacco as taxes increase. Although taxes on supplements should not be as high as taxes for tobacco any tax may cause consumers to pause and examine their use of them. Consumers may study their effectiveness before taking supplements, or may consult their doctors to determine if dietary supplements are necessary or which types would have any benefit. Therefore, taxation may not only lead to income to pay for regulation but more careful use of supplements by consumers.

Public Health Campaigning

Production and marketing of new drugs is a lucrative business so they are often the subject of much research. There is growing demand for natural and homeopathic treatments which may help to drive more research. However, the public also should take responsibility in protecting themselves. The average American has little time or energy. They seek a quick fix for everything
and often a drug or a supplement fits. This leads to trying products without investigating properly. A great deal of information is available through the NIH or the FDA on efficacy and safety related to dietary supplements. There is, however, also a great deal of misinformation and marketing to mislead the consumer. More public health campaigns could be done to circulate trustworthy information.

The FDA regulates labeling for supplements and ensures claims on labels are backed by evidence. However, advertising for pharmaceuticals is much more stringent. The FDA could do more to regulate print and television ads for supplements. Along with taking the responsibility to do research the public also needs to thoroughly inform their physicians about what they are taking. Every year people take supplements and neglect talking with their doctor about them because they have been led to believe they are harmless. Supplements causing negative drug interactions could be at the root of a medical complaint or problem. At the same time a doctor may be able to help you with a health problem by prescribing a supplement and recommending the proper dosage. As 53% of the adult population took a supplement in 2006, physicians should make every effort to educate themselves about dietary supplements and maintain current knowledge of availability, efficacy, and possible side effects (Park, 2011).

In a study by the Journal of the American College of Sports Medicine in which health care providers from the Department of Defense (DoD) and alumni from the Uniformed Services University (USU) were interviewed, the authors found that only 5% of the physician respondents from USU reported that they were extremely comfortable handling questions about dietary supplements. Five percent reported that they were extremely uncomfortable when handling questions about dietary supplements. The rest of the USU respondents were neutral. A reliable source of information was another concern of the USU respondents and 65% reported that there
was not a reliable source of information. Concerning adverse events more than half of the USU physicians reported that they had encountered a patient with a possible adverse event caused by dietary supplements. Only 16% of those encountering an adverse event reported it whereas 74% did not know how to report it (Cellini, Attipo, Seales, Gray, Ward, Stephens & Deuster, 2012). The above study supports this author’s contention that resources on supplements need to be made available and promoted as do means of reporting adverse events. Some medical schools are beginning to offer training in Complementary Alternative Medicine (CAM). Such classes on CAM should be included in all medical school curricula. More opportunities for continuing education in CAM should also be created. This knowledge has become increasingly important and as the population taking supplements grows, the knowledge will become invaluable.

**Conclusion**

Supplement use will continue to increase. The FDA must take on more authority to regulate supplements in order to accomplish part of its basic mission ensuring that human drugs are safe and effective. As supplements may interact with the body like drugs they should be regulated in a similar manner. The lives of the American population are too important to disregard this issue.
Glossary

AAPCC- American Association for Poison Control Centers

AARP- American Association of Retired People

ADA- American Dietetic Association

AERS- Adverse Events Reporting System

ASCA- Anabolic Steroid Control Act

BLA- Biologics License Application

BMI- Body Mass Index

BPCA- Best Pharmaceuticals for Children Act

CAERS- CFSAN Adverse Event Reporting System

CAM- Complementary Alternative Medicine

CBER- Center for Biologics Evaluation and Research

CDC- Centers for Disease Control and Prevention

CDER- Center for Drug Evaluation and Research

CDRH- Centers for Devices and Radiologic Health

CFSAN- Center for Food Safety and Applied Nutrition

cGMPs- current Good Manufacturing Practices
CTP- Center for Tobacco Products

CVM- Center for Veterinary Medicine

DEA- Drug Enforcement Agency

DoD- Department of Defense

DSHEA- Dietary Supplement Health and Education Act

FDA- United States Food and Drug Administration

FDAAA- Food and Drug Administration Amendments Act

FTC- Federal Trade Commission

GRMPs- Good Review Management Practices

IOM- Institute of Medicine

NCCAM- National Center for Complementary and Alternative Medicine

NCNPR- National Center for Natural Products Research

NCTR- National Center for Toxicological Research

NDA- New Drug Application

NIH- National Institutes of Health

OCI- Office of Criminal Investigation

ORA- Office of Regulatory Affairs
OTC- Over-the-Counter

PDUFA- Prescription Drug User Fee Act

PREA- Pediatric Research Equity Act

RDA- Recommended Dietary Allowance

USU- Uniformed Services University
References


http://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/CounterfeitMedicine/default.htm


