Federal Regulation of Unapproved Chelation Products

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Abstract Chelation products can be helpful in the treatment of metal poisoning. However, many unapproved products with unproven effectiveness and safety are marketed to consumers, frequently via the internet. This paper describes the primary responsibility of the Health Fraud and Consumer Outreach Branch of the United States Food and Drug Administration to identify and address health fraud products. Efforts to prevent direct and indirect hazards to the population's health through regulatory actions are described.

Keywords Chelation products · FDA · Health fraud · FD&C Act · Federal regulatory action

Background

The purpose of this paper is to discuss the Health Fraud and Consumer Outreach Branch of the U.S. Food and Drug Administration (FDA) and highlight health fraud and drug law. This paper will also discuss FDA action against unapproved oral chelation drug products, some representative products, and the specific legal authority for that action, which is provided by the Federal Food, Drug, and Cosmetic Act (FD&C Act) [1, 2].

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The Office of Compliance at the Center for Drug Evaluation and Research within FDA is responsible for protecting and promoting the public health by minimizing consumer exposure to unsafe, ineffective, and poor-quality drugs [3]. As part of this mission, the office is involved in and responsible for encouraging compliance with and enforcement of new drug approval requirements, as described in the FD&C Act. The FD&C Act defines a drug as any article that is used to treat, diagnose, cure, prevent, or mitigate a disease or affects the structure or function of the body. For a new drug to be marketed, one needs to have a premarket review on both safety and effectiveness. This involves rigorous review of controlled clinical trials before any marketing is approved. The FD&C Act also provides regulatory authority over biologics, medical and radiologic devices, foods, cosmetics, and veterinary products [3].

In 2009 and 2010, FDA became aware of an increase in the number of over-the-counter (OTC) chelation products offered for sale over the internet. The products were in violation of the FD&C Act because they were marketed as dietary supplements but claimed to treat and prevent disease. Some of the fraudulent claims included a reduction in cancer mortality, unclogging arteries, and treatment of osteoporosis, among others. In October 2010, FDA issued warning letters to eight firms that were marketing such products. Although they were marketed as dietary supplements, they made drug claims. In addition, some of the products were marketed in dosage forms that were not allowable for a dietary supplement. There was no evidence that any of the products could treat the conditions for which they were indicated. Two firms immediately and voluntarily complied by removing their products from the market. One firm signed a consent decree of permanent injunction. FDA is continuing to pursue additional enforcement actions for the remaining firms.

Health Fraud and Consumer Outreach Branch

The Health Fraud and Consumer Outreach Branch identifies and addresses fraudulent and dangerous drugs that pose a threat to consumers, including direct and indirect health hazards. The FDA defines health fraud as the deceptive promotion, advertising, distribution, or sale of a product represented as being effective to prevent, diagnose, cure, or mitigate a disease. These health claims are part of the regulatory definition of a drug, which requires the extensive premarket studies mentioned above. The Branch investigates websites and works with the FDA field offices to direct field investigations, collect evidence, and coordinate case development. Actions include drafting warning letters, and reviewing and approving seizure and injunction recommendations. Branch agents reach out to the consumer through videos, podcasts, radio, and TV interviews.

Health Fraud Products

While the FD&C Act itself does not include a statutory definition of “health fraud,” there are many examples that meet the FDA’s working definition, as defined above. Examples of health fraud drugs include ineffective or unproven products that consumers might use in place of proven medical treatments, dietary supplements that contain an undeclared prescription drug, or products that are not what they are represented or labeled as being. Counterfeits of approved products also represent health fraud products. Unfortunately, this market is big and lucrative.

Health fraud products are frequently sold on the internet. It is difficult to take action against these online companies because they are often located in undisclosed locations and their contact information typically involves only post office boxes or e-mail addresses. The websites are frequently registered anonymously or by proxy. Sometimes these products are distributed out of individual homes. The companies tend to be “fly-by-night” and can easily change their names and internet addresses and locations. There are minimal costs for these businesses and they never actually have to confront their victims. Health fraud products can be found advertised in newspapers, magazines, and on TV, and they may be found in retail stores as well.

Some specific examples of health fraud that the Branch has addressed include unapproved drug products that have outrageous claims such as curing cancer, HIV infection, diabetes, and autism. Other health fraud products are those tainted with active drug ingredients. These include weight loss products that contain undeclared sibutramine, sexual enhancement products that contain sildenafil, tadalafil, or analogs. The Branch has also addressed a number of body building products that contain anabolic steroids.

The Branch has also confronted homeopathic products that fall outside of the Compliance Policy Guide that defines their appropriate marketing [4]. One example that involved health issues is Hyland’s Teething Tablets, which was associated with belladonna toxicity in infants. A second example is the zinc gluconate-containing Zicam nasal gel, which was associated with anosmia. Homeopathic drugs and their regulation is a separate topic unto itself.

Other products warranting regulatory action include traditional Chinese medicines and Ayurvedic medicines that have been adulterated with heavy metals such as lead, arsenic, and mercury. These products are marketed as dietary supplements but make disease claims. The Branch also deals with street drug alternatives and sometimes with cosmetics that are also unapproved new drugs. There is a broad universe of violative products.

Enforcement Priorities for Direct and Indirect Hazards

The enforcement strategy is based on risk. Highest priority is given to products that pose a direct health hazard. A direct health hazard means that actual harm, adverse event, or serious adverse event is associated with use of the product as labeled. Indirect health hazards are those circumstances where there is no direct harm to the consumer, but use of the product results in not taking standard therapy that might be effective.

There are other factors that may be considered in assessing the enforcement priority of products posing indirect health hazards. These include the severity of the disease, vulnerability of the user group (for example infants), the geographic scope and number of users involved, whether there is actually an approved product for the indication, economic impact, and agency resources.

Outreach activities have included live action and animation videos, articles in the FDA Consumer e-magazine, radio and TV interviews, podcasts, and websites with questions and answers for consumers.

OTC Chelation Products

The FDA action addressed only unapproved OTC chelation products. Use of FDA-approved products in an off-label manner or in a way that is different from their approved indications is generally outside of the FDA’s regulatory authority. Off-label use of FDA-approved products falls under “the practice of medicine” and usually represents an issue for state medical boards and not the FDA.

OTC products are categorized differently from the health fraud products described above. These products are listed in a monograph system, which functions like a menu that defines acceptable specific active ingredients, labeling, dosing, and

warnings. An individual product that is in the OTC monograph may be marketed without prior review as long as the product is marketed under the conditions specified. Drugs not in the monograph that are suitable for OTC use undergo the same new drug approval process with the rigorous review of adequate and well-controlled clinical studies.

Some OTC chelation products are marketed by their manufacturers under the term “dietary supplement.” Dietary supplements are not drugs, but are a category of foods. The organization that is involved in their regulation is the Center for Food Safety and Nutrition. [5]. Dietary supplements do not receive premarket review but, unlike drugs, cannot make disease claims. Anything that is marketed as a dietary supplement that claims to be able to treat, prevent, cure, or mitigate disease is inappropriately marketed and is violative, as its intended use causes it to be a drug.

Categories of Violations Involving OTC Chelation Products

There are two categories of violations of the FD&C Act that are relevant to the FDA action on OTC chelation products. The first relevant category of violations is drug products that are unapproved new drugs. The regulatory definition of a “new drug” is a drug that is not generally recognized by experts in the assessment of safety and effectiveness of drugs as being safe and effective for its intended use (“generally recognized as safe and effective” or “GRAS/E”). There are three criteria that must be met in order to conclude that a drug is GRAS/E. First, the particular drug product must have been subjected to adequate and well-controlled clinical investigations that establish the product to be safe and effective. Second, those investigations must have been published in the scientific literature available to qualified experts. Third, experts must generally agree, based on those published studies, that the product is safe and effective for its intended uses. At a minimum, the general acceptance of a product as GRAS/E must be supported by the same quality and quantity of scientific and/or clinical data necessary to support the approval of a New Drug Application. The standard for “new drug” applies not to the active ingredient or to a class of products. It applies to a specific drug product, including the active ingredient or ingredients, its excipients or inactive ingredients, its labeling, and its container/closure system. The standard is quite high. The FDA believes that there are probably no marketed prescription drugs that qualify as “generally recognized as safe and effective” (GRAS/E). Thus, an active pharmaceutical ingredient cannot be reformulated or marketed as an OTC chelation product. The standard requires the same quantity and quality of evidence that would support the approval of a new drug application, which is more information than what would be found in a published clinical study.

A second relevant violation is misbranding. Drug products can be misbranded in various ways. Products can be misbranded because they include false or misleading information. False information would be, for example, a product represented as being sterile that is not, or a product that declares an active ingredient that is not included. Misleading information includes labeling that has a tendency to deceive by omission, exaggeration, or ambiguity.

Products can also be misbranded when they do not bear adequate directions for their intended use. The FD&C Act defines “adequate directions for use” as directions that a layman can follow to use a product safely. So if a product that is offered OTC for a condition that is not amenable to OTC treatment, then that product is misbranded. Examples might include a product that requires blood level monitoring, requires a physician’s diagnosis, or has a safety profile that requires the practitioner to monitor the patient.

As mentioned previously, dietary supplements are actually categories of foods intended to supplement the diet. They may contain vitamins, minerals, botanicals, or amino acids, but all contain dietary ingredients. Amendments to the FD&C Act through the Dietary Supplement Health and Education Act (DSHEA) in 1994 provided these extra statutory provisions [5]. Since a dietary supplement is a category of a food, it has to be able to be ingested and it has to be in oral dosage form. A dietary supplement cannot be in a suppository dosage form or a topical form.

DSHEA permitted limited marketing claims for dietary supplements to those affecting the normal structure and function of the body. In general, dietary supplements cannot make a disease claim, which is relevant to enforcement action on unapproved OTC chelation products.

Federal Actions Against Online Sale of Chelation Products

There are various categories of enforcement actions that the FDA can take, including advisory enforcement actions, such as warning letters, administrative enforcement actions, such as recalls due to health hazards, and judicial enforcement actions that include seizure of product, injunction, and criminal prosecution.

As noted previously, the FDA became aware in 2009 and 2010 of an increase in the number of chelation products offered for sale over the internet. The products claimed to treat and prevent disease by cleansing the body of heavy metals and toxic chemicals. Although they were marketed as dietary supplements, they were claiming to treat and prevent disease. The language of these claims made them drugs, and therefore was in violation of the FD&C Act. The drugs would need to be approved by the Food and Drug Administration or meet the OTC monograph to be legally marketed. Some of the

fraudulent claims indicated that the product could cause a 90 % reduction in cancer mortality, be an alternative to amputation, unclog arteries, restore cardiovascular function, treat osteoporosis, and treat degenerative diseases.

In October 2010, the FDA issued warning letters to eight firms because their marketed products were violative of the FD&C Act [6–13]. The warning letters were coordinated with a press release, press roll out call, and an article directed at a consumer audience. Not only were the products marketed over the internet as dietary supplements making inappropriate drug claims but they were also available in various dosage forms that were not allowable for a dietary supplement, such as topical sprays, suppositories, and clay baths. These firms targeted patients with serious and incurable diseases and limited treatment options. There was no evidence that the products could treat the conditions for which they were indicated: autism spectrum disorder, high blood pressure, angina, prevention of heart attack or stroke, Alzheimer disease, and Parkinson's disease.

There are no FDA-approved over-the-counter chelation products, and all FDA-approved chelation products require a prescription because they can be used safely only under the supervision of a health care practitioner. As noted earlier, inappropriate or off-label use of FDA-approved chelation products falls into the “practice of medicine” and generally is an issue evaluated by state medical boards. The FDA's primary concern with use of OTC chelation products was the possibility that the patients would delay seeking proven treatment and the potential for serious adverse effects.

The FDA advised consumers to talk with their health care practitioners about prevention and treatment of their medical conditions, and recommended that affected people consider enrolling in clinical trials monitored by an Institutional Review Board and being conducted under an Investigational New Drug application. Individuals should also report any adverse events from use of OTC chelation products to the FDA's MedWatch and Adverse Event Reporting System (<http://www.FDA.gov/safety/MedWatch/HowToReport/default.htm>).

Specific OTC Products

One example was the product PC3x, which claimed to aid in accelerating cellular detoxification. A lot of these products tend to be fairly expensive [9]. This product was sold in a 60-mL vial that normally retails for \$125 and was offered at a discounted price of \$99.99. Disease claims for the component ingredients of this product included autism, Alzheimer disease, allergies, treatment of arteriosclerotic vascular disease, uterine fibroids, herpes, influenza, mad cow disease, and cancer.

Bio-Chelat was labeled as being guaranteed to remove heavy metal ions from the body without removing essential minerals [8]. This product was labeled as containing EDTA. It made additional disease claims for treatment of subacute and chronic heavy metal toxicity, autism, behavioral and developmental disorders, neuropathy, and pollen allergies.

Kids Chelat was claimed to safely remove mercury and other toxic metals and was directed towards use in children [8]. The product claimed to have no harmful adverse effects, that it is able to chelate metals that are tightly bound to tissues and organs, and prevents the metals from being reabsorbed after chelation.

Kelatox was marketed as a dietary supplement even though it was in a suppository dosage form. As noted before, a suppository cannot be a dietary supplement [7]. The firm stated that the CDC recommends EDTA chelation therapy for lead poisoning and other toxic heavy metals, and falsely gave the impression that the use of the Kelatox product was approved or sanctioned by CDC. The product included claims for chronic fatigue syndrome, fibromyalgia, depression, Parkinson disease, macular degeneration, and peripheral neuropathy.

As a result of the enforcement actions, two firms immediately and voluntarily complied by removing their products from the market and disabling their websites. One firm, Artery Health Institute, LLC eventually signed a consent decree of permanent injunction. They consented to remove their claims, hire an expert to certify that all the violative claims have been removed, and that any further violation may result in potential for criminal charges or contempt. The FDA is continuing to pursue additional enforcement actions for the five remaining firms.

Conclusion

The responsibilities of the Health Fraud and Consumer Outreach Branch of the FDA encompass a variety of health fraud products, including unapproved chelation products. Actions are supported by federal regulations, specifically the FD&C Act. There are differences between the types of claims that dietary supplements and drugs can make. Increasingly, these products are sold on the internet. Federal regulatory actions seek to prevent direct and indirect hazards to the population's health.

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