Botanical Products: Drugs and Dietary Supplements

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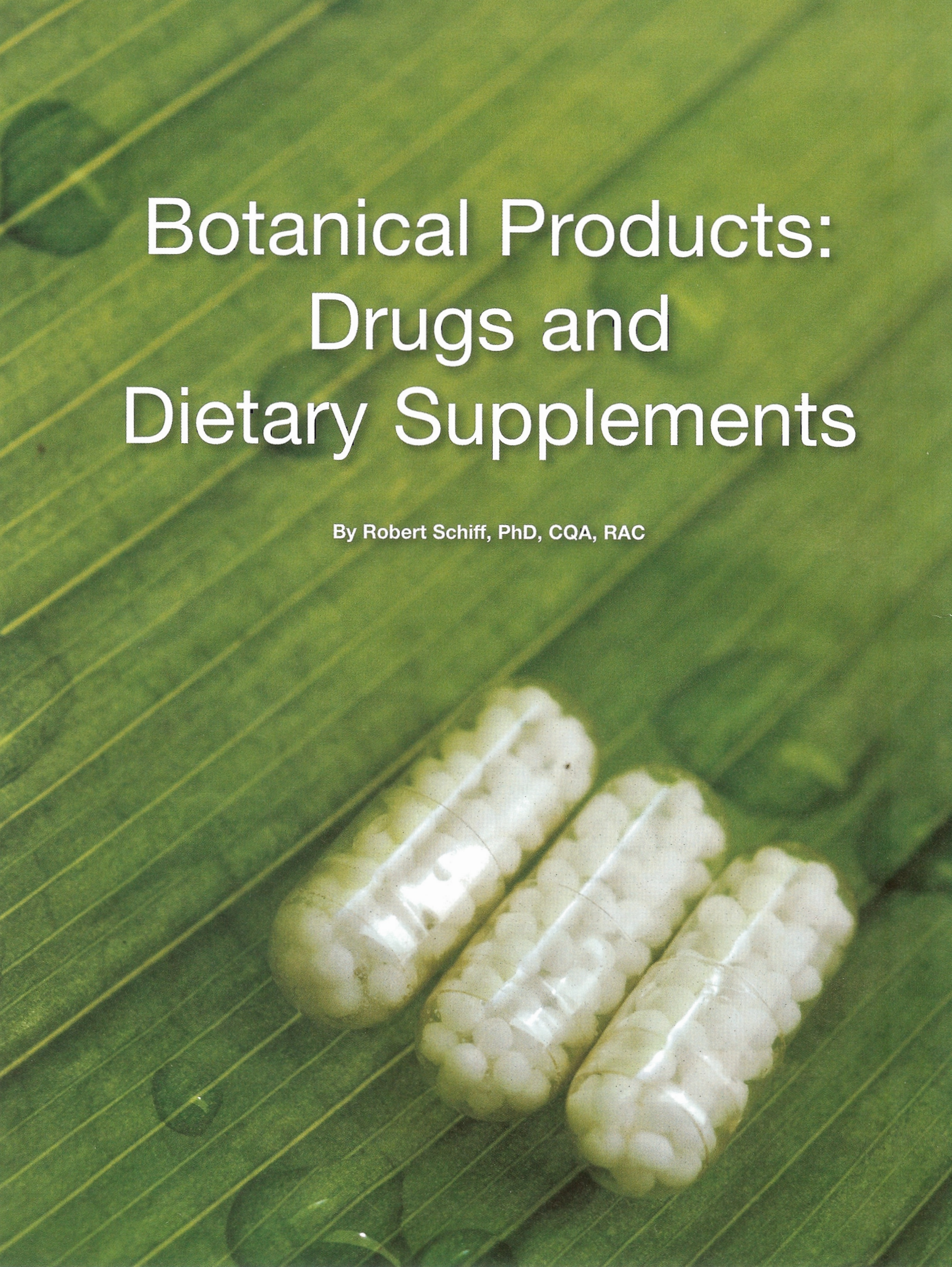

US regulations for botanical products that may be drugs can be confusing. In the author's experience, some botanicals that may have been processed and/or concentrated and have an indicated use for medical treatment are looked upon by the manufacturer as food supplements. Manufacturers take this position to avoid going through the rigors of the drug approval process. There are loopholes in the regulations that manufacturers try to use to eliminate this process.

An examination of FDA Warning Letters[1] clearly shows a large number of Internet advertisements for botanicals to treat various diseases. Either the producers of these ads are unaware of US regulations, or they are attempting to go around the law.

This article explains the differences and similarities between supplements and botanical drugs and their regulatory requirements.

Botanicals

According to FDA's *Guidance for Industry: Botanical Drug Products* (June 2004),[2] botanicals "are finished, labeled products that contain vegetable matter as ingredients... may be a food (including a dietary supplement), a drug (including a biological drug), a medical device (e.g., gutta-percha for dentistry) or a cosmetic. The claims of the manufacturer with respect to the intended use determine the regulatory category of the botanical product."

The guidance makes it very clear that botanicals do not include "genetically modified botanical species," "fermentation products" and especially, "highly purified substances (e.g., paclitaxel) or chemically modified substances."

Dietary Supplements

A dietary supplement may consist of "a vitamin, a mineral, an herb or other botanical, an amino acid, a dietary substance to supplement the diet by increasing the dietary intake (enzymes or tissues from organs or glands) or a concentrate, metabolite, constituent or extract."[3]

The *Dietary Supplement Health and Education Act* of 1994[4] (*DSHEA*) places supplements in a separate category but still under foods. Dietary supplements are not to be considered drugs; they are taken by mouth and are "intended to supplement the diet." Supplements can come in a variety of forms such as liquids, nutrient bars, tablets, capsules and powders. They are not intended to "treat, diagnose, cure or alleviate the effects of disease."[5]

Under *DSHEA*, a "new dietary ingredient" is defined as meeting the requirements of a dietary ingredient and not having been sold in the US before 15 October 1994. Under 21 CFR 190.6,[6] "At least 75 days before introducing or delivering for introduction into interstate commerce a dietary supplement that contains a new dietary ingredient that has not been present in the food supply as an article used for food in a form in which the food has not been chemically altered, the manufacturer or distributor of that supplement, or of the new dietary ingredient, shall submit to the Office of Nutritional Products, Labeling and Dietary Supplements (HFS-820), Center for Food Safety and Applied Nutrition, Food and Drug Administration, 5100 Paint Branch Pkwy., College Park, MD 20740, information including any citation to published articles that is the basis on which the manufacturer or distributor has concluded that a dietary supplement containing such dietary ingredient will reasonably be expected to be safe. An original and two copies of this notification shall be submitted." Later in 21 CFR 190.6, the items specifically needed for acceptance by FDA, including the supplement's history and proof of safety, are described. A point to note is the phrase, "has not been chemically altered." It is not clear if extraction or concentration excludes the item from the supplement category.

In addition, in June 2007, FDA published 21 CFR 111 Current Good Manufacturing Practice (GMP) in manufacturing, packaging, labeling, or holding operations for dietary supplements.[7] The agency has tried for many years to institute GMP for supplements independent of the food regulations in 21 CFR 110.[8] Upon first examination, 21 CFR 111 appears to be an intermediate form of GMP falling between the food regulation in 21 CFR 110 and the drug regulation in 21 CFR 211.[9] However, it more closely resembles the latter, especially with respect to the use of controls to ensure the supplements meet quality standards. These testing controls are certain to add cost to the supplement and may change corporate strategy from marketing a supplement to marketing a drug. Based upon the author's experience, controls are necessary to ensure that the supplement in question

Table 1. Botanical Products and Their Uses

USE	BOTANICALS
Acne	Red clover, Myrrh, Juniper Berries, Calendula, Nasturtium, Tomato, Burdock, Hops, Lavender, Arnica, Lemon, Golden Seal, Lady's Mantle, White Willow, Papaya, Asparagus, Blackberry
After Shave	Aloe Vera, Chamomile, Calendula, Comfrey, Althea, Slippery Elm, Fenugreek, Cucumber, Oats, Milk Thistle, Bay Laurel
Antibacterial	Grapefruit, Echinacea, Lavender, Rosemary, Lemon, Benzoin, Balsam, Sage, Quassia, Bayberry, Sandalwood, Uva Ursi
Antidandruff	Quassia, Artichoke, Birch, Chamomile, Lemon Grass, Nettle, Witch Hazel, Orange Peel, Rosemary, White Willow, Soap Bark, Chaparral, Thyme
Antioxidants	Camellia, Ginkgo
Antiseptic	Echinacea, Indigo, Lavender, Lemon Sage, Thyme, Southern Wood, White Lily, Grapefruit, Hops, Birch, Yarrow, Chamomile, Rosemary, Calendula, Onion, Garlic, Black Walnut, Eucalyptus, Myrrh, Cinnamon
Astringents	Agrimony, Arnica, Oak Bark, Bistort, Bayberry, Witch Hazel, Myrrh, Plantain, Rhatany, Tormentil, Myrtle, Lemon, Raspberry, Rose, Rosemary, Sandalwood, Comfrey, Yarrow, Nettle, Horsechesnut, Corn Flower, Hawthorn
Breath Sweeteners	Angelica, Anise, Cardamon Seed, Rosemary, Thyme, Peppermint, Orris, Parsley
Cellulite	Butchersbroom, Bladderwrack
Red Hair	Beet, Chamomile, Red Henna, Hibiscus, Calendula
Blonde Hair	Golden Seal, Chamomile, Calendula, Southern Wood, Grapefruit, Butchersbroom, Mullein, Elderflowers, Lemon Peel
Brunette	Sage, Chamomile, Rosemary, Black Walnut, Nettles, Southern Wood, Raspberry, Jaborandi, Black Henna
Deodorants	Rosemary, Cardamon, Coriander, Orange Peel, Citrus Bioflavonoids, Orris Root, Patchouli, Rose, Witch Hazel, Chaparral, Parsley, White Willow
Eczema	Cleavers, Comfrey, Fig, Burdock, Red Clover, Golden Seal, Nettle, Yellow Dock, Sarsaparilla, Pansy, Pine, Thyme, White Willow
Emollients	Aloe Vera, Comfrey, Althea, Slippery Elm, Fenugreek, Blue Mallow, Oats, Flax, Orange Flowers, Quince Seed, Various Sea Weeds, Elderflower, Cucumber
Eye	Chamomile, Cucumber, Fennel, Eyebright, Corn flower
Gingivitis	Bayberry, Echinacea, Golden Seal, Myrrh, Oak Bark, Rhatany
Hemorrhoids	Bistort, Witch Hazel, Comfrey, Horsechestnut, Bayberry Bark, Butchersbroom
Dark Hair	Chaparral, Henna, Jaborandi, Nettle, Rosemary, Sage, Southern Wood, Raspberry, Black Walnut
Dry Hair	Chamomile, Red Clover, Quince Seed, Horsetail, Comfrey Root, Elderflower, Orange Blossom, Peach Leaves, Rosemary, Sage, Basil, Southern Wood
Hair, to Add Sheen	Chamomile, Yarrow, Thyme, Rosemary, Sage, Raspberry, Quassia, Lemon Peel, Flax Seed
Hair, Split Ends	Horstail, Comfrey, Fenugreek, Quince, Rosemary, Echinacea, Lavender, Olive, Basil
Hair Stimulants	Jaborandi, Quince, Capsicum, Birch, White Willow, Arnica, Horseradish, Alfalfa, Anise
Healing	Aloe, Comfrey, Horsetail, Yarrow, Pansy, Rose Buds
Insect Repellant	Pennyroyal, Lavender, Citronella, Chamomile, Neem, Eucalyptus, Cedar, Thyme, Pansy, Garlic, Onion, Capsicum
Itching	Chamomile, Chickweed, Calendula, Golden Seal, Cucumber, Echinacea, Plantain
Nails, to Strengthen	Horsetail, Calendula, Aloe, Comfrey
Rubefacients	Capsicum, Cinchona, Pine, Birch, Jaborandi, White Willow
Shingles	Mistletoe, Passion Flowers, St. John's Wort, Valerian
Dry Skin	Aloe Vera, Comfrey, Apple, Chamomile, Red Clover, Dandelion, Elder Flowers, Fennel, Quince, Marsh Mallow Root, Slippery Elm Bark, Sea Weeds, Licorice Root, Oats, Orange Blossom, Orange Peel, Citrus Bioflavonoids, Pansy, Peach, Evening Primrose, Yarrow, Parsley, Violet, Cleavers, Capsicum, Arnica, Ginseng
Oily Skin	Caraway Seed, Cucumber, Dandelion, Dulse, Fennel, Lavender, Lemon, Grapefruit, Lemon Grass, Rose, Witch Hazel
Spots	Cleavers, Echinacea, Fig, Garlic, Thuja
Soothing	Marsh Mallow, Echinacea, Corn Flower, Apple, Colts Foot Comfrey, Calendula, Slippery Elm, Chamomile, St. John's Wort, Cucumber, Red Poppy, Sage, Licorice, Hawthorn, White Lily Pond
Styptics	Bayberry, Bistort
Sunburn	Aloe Vera, Calendula, Lemon, Capsicum, Nettle, Slippery Elm Bark, Comfrey, Sea Weeds, Witch Hazel
Varicose	Golden Seal, Capsicum, Mullein, Horsechestnut, Comfrey, Calendula, Marsh Mallow Root, Hawthorn, St. John's Wort, Witch Hazel, Bayberry, Bistort
Wounds	Milk Thistle, Chamomile, Plantain, Comfrey, Chickweed, Golden Seal, St. John's Wort, Arnica, Calendula, Aloe Vera, Yarrow

contains the ingredients and the amounts noted on the label. Considering that many supplements are imported into the US and in view of recent problems with importation from China, the new GMP requirements for supplements come at an opportune time.

Homeopathy

There are provisions in the regulations for introducing a botanical drug to the market without submission of a New Drug Application (NDA) or Biologic License Application (BLA). Compliance Policy Guide (CPG) 7132.15, Sec. 400.400[10] describes "Conditions Under Which Homeopathic Drugs May be Marketed." Because many homeopathic drugs are biologicals, this mechanism for marketing becomes relevant. According to the *Skeptics Dictionary*, "Classical homeopathy is generally defined as a system of medical treatment based on the use of minute quantities of remedies that in larger doses produce effects similar to those of the disease being treated. Hahnemann (1755-1843) believed that very small doses of a medication could have very powerful healing effects because their potency could be affected by vigorous and methodical shaking (succussion).[11]

FDA defines a homeopathic drug as "Any drug labeled as being homeopathic which is listed in the *Homeopathic Pharmacopeia of the United States* (*HPUS*), an addendum to it, or its supplements. The potencies of homeopathic drugs are specified in terms of dilution, i.e., 1x (1/10 dilution), 2x (1/100 dilution), etc. Homeopathic drug products must contain diluents commonly used in homeopathic pharmaceutics. Drug products containing homeopathic ingredients in combination with non-homeopathic active ingredients are not homeopathic drug products."[12] The *HPUS* contains the standards, composition and monographs for preparation of the drugs. Drugs produced according to the *HPUS* must meet its standards for strength, quality and purity.

Manufacturers of homeopathic drugs must register as drug establishments and must comply with the labeling requirements of 21 CFR 201 and Good Manufacturing Practices as found in 21 CFR 211. However, as indicated in CPG 7132.15, the manufacturer

may not need to comply with expiration dating requirements found in 21 CFR 211.137 and 211.165, which involve testing and release for distribution. FDA proposed in the 1 April 1983 *Federal Register* to change 21 CFR 211.165 to exempt homeopathic drugs from laboratory testing for identity and strength of each active ingredient. Because there is no final rule, FDA has indicated in its CPG that the testing requirement will not be enforced. Considering that drugs and now supplements must undergo finished product testing, it seems ludicrous that a homeopathic drug does not have to be tested prior to release.

Besides a dietary supplement, a botanical compound can be a drug, a food, a device or a cosmetic. The latter will not be discussed in any detail other than to note the definition of "cosmetics" as "articles intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body...for cleansing, beautifying, promoting attractiveness, or altering the appearance."[13]

Figure 1 was taken from the website of the Vege Tech Company of Glendale, CA,[14] and illustrates the botanicals in drugs and cosmetics. For example the botanicals associated with the claims for treatment of acne, antibacterial, antidandruff, eczema, gingivitis, shingles and wounds, to mention a few, are in fact used as drugs or, as in the case of wounds, a device.

If a botanical product is ingested orally, used to improve a classic nutrient deficiency, intended "to affect the structure or function of the human body" and affects general well-being, it probably meets the requirements for a supplement. If not, it is probably a drug.

Marketing Botanical Drugs

There are basically three ways a botanical drug can be marketed in the US. It can be approved via the NDA or Abbreviated New Drug Application (ANDA) routes. The third is the over-the-counter (OTC) drug monograph procedure found in 21 CFR 331-358.[15] However, most of these items are not plant derived. To amend an OTC monograph, a company must file a citizen's petition with FDA under 21 CFR 10.30[16] and meet the requirements of 21 CFR 330. This is a very time-consuming process. As the author has recently discovered, although FDA should respond to a petition within six months, currently there are three petitions older than six months to which the agency has not responded.

Conclusion

Botanical products can enter the US market in several ways. The most obvious, and one that has not been discussed here, is in the food supply. The next is as a dietary supplement, for which the regulations are now under critical review by FDA. A new dietary supplement ingredient must undergo the 75-day "petition" process. The third route of entry is as a drug, either through an NDA, ANDA or OTC monograph or as a homeopathic medicine. Therefore botanical product manufacturers need to exercise caution and prudence when marketing or planning to market a product in the US by understanding which of the confusing regulations are appropriate for the product.

References

1. FDA Warning Letters, available at www.fda.gov/ICECI/EnforcementActions/WarningLetters/default.htm.
2. *Guidance for Industry: Botanical Drug Products* (June 2004).
3. Dietary Supplements, available at www.fda.gov/Food/DietarySupplements/ConsumerInformation/ucm110417.htm#what.
4. *Dietary Supplement Health and Education Act* of 1994 (*DSHEA*).
5. FDA 101: Dietary Supplements, available at www.fda.gov/consumer/updates/supplements080408.html.
6. 21 CFR 190.6.
7. 21 CFR 111.
8. 21 CFR 110.
9. 21 CFR 211.
10. CPG 7132.15, Sec. 400.400.
11. *The Skeptics Dictionary* 2009, available at www.skepdic.com/homeo.html#classical.
12. Ibid 10.
13. *FD&C Act*, sec. 201(i).
14. www.vegetech.com.
15. 21 CFR 330-358.
16. 21 CFR 10.30

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Robert Schiff, PhD, CQA, RAC, is founder and CEO of Schiff & Company, a regulatory affairs, compliance and clinical research organization. Previously, he worked in industry with Warner Lambert Company, Hoffmann-La Roche, Inc., J.T. Baker Chemical Company and the Hyland Division Travenol Laboratories. He also was an Assistant Professor in the Department of Anatomy at Tufts University Schools of Medicine and Dental Medicine. Schiff has authored over 50 publications and holds several patents on medical products. He holds a BS from the City College of New York, MS from Iowa State University, and PhD from the University of California at Davis. Schiff is Regulatory Affairs Certified and is a Certified Quality Auditor, and is a member of RAPS' Board of Editors for *Regulatory Focus*. He can be reached at RSchiff13@aol.com or SchiffandCompany@aol.com.