Inspections, Compliance, Enforcement, and Criminal Investigations

Quincy Bioscience Manufacturing Inc. 10/16/12

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Minneapolis District Office
Central Region
250 Marquette Avenue, Suite 600
Minneapolis, MN 55401
Telephone: (612) 334-4100
FAX: (612) 334-4142

October 16, 2012

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Refer to MIN 13 - 0

Mark Y. Underwood
President
Quincy Bioscience Manufacturing Inc.
301 S. Westfield Road, Suite 200
Madison, Wisconsin 53717

Dear Mr. Underwood:

This letter concerns your products Prevagen, which is labeled to contain 10 mg apoaequorin, Prevagen Extra Strength, labeled to contain 20 mg apoaequorin, and Prevagen Professional, labeled to contain 40 mg apoaequorin. These products are labeled as dietary supplements.

FDA reviewed your websites at www.prevagen.com, www.prevagenES.com, www.prevagenpro.com, www.hopetrials.com, www.prevagenreviews.com, www.quincybioscience.com, www.facebook.com/prevagen and www.youtube.com/user/prevagen in August 2012. Based on this review the agency has determined that your products Prevagen, Prevagen Extra Strength, and Prevagen Professional are being promoted for conditions that cause these products to be drugs under section 201(g)(1)(B) of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. § 321(g)(1)(B). The therapeutic claims on your websites (see "Unapproved New Drugs" section below) establish that these products are drugs because they are intended for use in the cure, mitigation, treatment, or prevention of disease. In addition, statements on your www.hopetrials.com website establish that Quincy Bioscience has been sponsoring clinical trials to investigate the use of apoaequorin to treat or prevent disease for which there is no investigational new drug application (IND) in effect. The investigation and marketing of your products for these uses violates the Act.

Under 21 U.S.C. §§ 331(d) and 355(a), a new drug may not be introduced or delivered for introduction

into interstate commerce unless an FDA-approved application is in effect for it. Apoaequorin is not approved as a drug for marketing in the United States, and is not exempt from this requirement pursuant to 21 U.S.C. § 355(i), which governs the use of investigational new drugs. You may find the Act and related regulations through links on FDA's home page at http://www.fda.gov[1].

It has also come to our attention that the apoaequorin used in your Prevagen products is produced synthetically. According to your website www.quincybioscience.com, "Apoaequorin is no longer extracted from the jellyfish, rather rapidly dividing host cells are 'taught' to grow the unique protein. The end result is the exact composition of apoaequorin without any of the heavy metal pollution that jellyfish may be exposed to in the ocean." According to information in documents you provided to FDA, the apoaequorin used in your Prevagen products is produced from **(b)(4)**.

Section 201(ff)(1) of the Act, 21 U.S.C. § 321(ff)(1), defines "dietary ingredient" as a vitamin, mineral, amino acid, herb or other botanical, or dietary substance for use by man to supplement the diet by increasing the total dietary intake, or a concentrate, metabolite, constituent, extract or combination of any dietary ingredient from the preceding categories. Apoaequorin synthetically produced from **(b)(4)** is not a vitamin, mineral, amino acid, herb or other botanical, or dietary substance for use by man to supplement the diet by increasing the total dietary intake. Further, apoaequorin synthetically produced from **(b)(4)** is not a concentrate, metabolite, constituent, or extract of any dietary ingredient, nor is it a combination of dietary ingredients. Therefore, the synthetically produced apoaequorin used in your Prevagen products is not a dietary ingredient as defined in section 201(ff)(1) of the Act.

According to the labels of your Prevagen products, they contain no other dietary ingredient. Therefore, these products do not meet the definition of a dietary supplement, which requires that the product contain one or more dietary ingredient. See section 201(ff)(1) of the Act, 21 U.S.C. § 321(ff)(1). Accordingly, your Prevagen products could not be marketed as dietary supplements even if they were intended only to affect the structure or function of the body and not for use in the cure, mitigation, treatment, or prevention of disease.

Unapproved New Drugs

Examples of some of the claims made in videos posted on your website http://www.prevagen.com/watch/

- "[F]irst and only dietary supplement that…protects the brain cells from death.... If you do just take one supplement, this may be the one to consider to protect and preserve your brain" (Healing Quest video at 2:40).

Regarding the use of pictures and videos on your websites, we remind you that an image may be considered a claim to diagnose, mitigate, treat, cure, or prevent disease if, in the context in which it is presented, the image suggests that the product has an effect on a disease or diseases. See, e.g., Title 21, Code of Federal Regulations (21 CFR), 101.93(g)(2)(iv)(E).

Your **website** www.prevagenreviews.com **also contains claims in the form of personal testimonials, including:**

- "My mother died of Alzheimer's disease…. I thought it was happening to me being too forgetful and so on. When I heard the commercial and them talking about this [Prevagen], it's the first product that I've ever ordered this way…. It proved to be very helpful…in a very short time. This is the first product I guess I've probably ever used that I could absolutely say it's miraculous for the short time I've been on it. I know my thinking and everything is more clearer and so on, just like it says" (testimonial from Rebecca R. from Phoenix).
- "I had a severe car accident that gave me a head injury where I could not remember things at all and Prevagen sounded exactly like what I needed. After about a month…I started noticing that I was recalling things much easier, things that I hadn't before…. Prevagen has made a huge, huge difference" (testimonial from Paul C. from Apple Valley).

Examples of some of the claims observed on your Facebook page at www.facebook.com/prevagen:

- "Prevagen will restore for you the lost protein so that you can gain your dignity back…. Alzheimer's disease is a heartache on any family. Dementia is tough to be around people that have dementia, let alone have it yourself. Prevagen gives you back your dignity and gives you back the proteins that are so precious that we use. No side effects whatsoever, doesn't matter what drugs you're on, this is a safe natural supplement" (Dr. Jan McBarron video at 1:16).

Furthermore, the "Research" and "Science" sections of your various websites marketing these products cit or link to a number of articles about the usefulness of the ingredient apoaequorin (sometimes referred to on your websites as "aequorin")[1] or the Prevagen products in treating and preventing diseases. When scientific references are used commercially by the seller of a product to promote the product to consumers, such references may become evidence of the product's intended use. Under 21 CFR 101.93(g)(2)(iv)(C), a citation of a publication or reference in the labeling of a product is considered to be a claim about disease treatment or prevention if the citation refers to a disease use, and if, in the context of the labeling as a whole, the citation implies treatment or prevention of a disease. The following are examples of citations to scientific references used to market your Prevagen products for disease treatment and prevention on your websites:

- Undated poster accessed via link on http://www.prevagenpro.com/practitioners/science: "Neuroprotective Effects of Aequorin on Hippocampal CA1 Neurons Following Ischemia. Julia A. Detert, Patrick K. Tao, Liviu Bunaciu, Melody L. Schmidt, & James R. Moyer, Jr., Departments of Psychology and Biological Sciences, University of Wisconsin-Milwaukee."
- Study report manuscript accessed via link on http://www.prevagenpro.com/practitioners/science: "Aequorin Protects Adult and Aging Hippocampal CA1 Neurons From Ischemic Cell Death. Julia A. Detert, Melody L. Schmidt, Nicholas D. Kampa, Patrick K. Tao, & James R. Moyer Jr., Departments of Psychology and Biological Sciences, University of Wisconsin-Milwaukee."
- Unpublished abstract accessed via link on http://www.prevagenpro.com/practitioners/science and posted at http://www.prevagen.com/research/apoaequorin-increases-brain-cell-survival: "Neuroprotection of hippocampal CA1 neurons from ischemic cell death using the calcium binding protein aequorin. J. A. Detert, J. D. Heisler, E. L. Hochstetter, T. M. Van Langendon, J. R. Moyer, Jr., Univ. of Wisconsin-Milwaukee. Presented at The Society For Neuroscience; 2009."
- Study report manuscript accessed via links at http://www.prevagen.com/research and http://www.prevagenpro.com/practitioners/science: "The Effects of the Calcium Binding Protein Apoaequorin on Memory and Cognitive Functioning in Older Adults. Mark Underwood, Peggy Sivesind Taylor Gabourie. Alzheimer's & Dementia: The Journal of the Alzheimer's Association, July 1, 2011, Vol. 7, Issue 4, Supplement, Page e65."

Your Prevagen, Prevagen Extra Strength, and Prevagen Professional products are not generally recognized as safe and effective for the above referenced uses and, therefore, these products are "new drugs" under section 201(p) of the Act, 21 U.S.C. § 321(p). New drugs may not be legally marketed in the United States without prior approval from FDA as described in section 505(a) of the Act, 21 U.S.C. § 355(a). FDA approves a new drug on the basis of scientific data submitted by a drug sponsor to demonstrate that the drug is safe and effective.

Your Prevagen products are offered for conditions that are not amenable to self-diagnosis and treatment by individuals who are not medical practitioners; therefore, adequate directions for use cannot be written so that a layperson can use these drugs safely for their intended purposes. Therefore, your products are also misbranded within the meaning of section 502(f)(1) of the Act, 21 U.S.C. § 352(f)(1), in that the labeling fails to bear adequate directions for use. The introduction of a misbranded drug into interstate commerce is a violation of section 301(a) of the Act, 21 U.S.C. § 331(a).

Clinical Investigations Which Require an IND

Statements on your website www.hopetrials.com describe clinical trials you have been conducting to study apoaequorin for use in treating or preventing a variety of diseases:

- "HOPE Trials research consists of a variety of human trials measuring the effect of apoaequorin...a unique compound, originating from a jellyfish, that helps to regulate intracellular calcium levels and alleviate the toxic effects of excess calcium in the brain.… Numerous investigators have linked a variety of medical conditions to ineffectual control of calcium levels. While neurodegenerative disorders, inflammatory diseases, auto-immune conditions and endocrine disorders affect the body ir different ways…they often have a common denominator, a loss of the ability to closely regulate the excessive influx of calcium ions."

FDA regulations (21 CFR Part 312) contain procedures and requirements governing the use of investigational new drugs. Specifically, the regulations require that a sponsor submit an investigational new drug application (IND) to the FDA if the sponsor intends to conduct a clinical investigation with an investigational new drug, 21 CFR 312.20(a), and have an IND in effect before the investigational drug is administered to study subjects, 21 CFR 312.20(b).

A clinical investigation is defined as "any experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects," 21 CFR 312.3(b). Our investigation, including an inspection of your headquarters and warehouse facility at 301 S. Westfield Road in Madison, Wisconsin, between October 24 and December 22, 2011, indicates that you initiated and were responsible for the conduct of clinical investigations of apoaequorin, an investigational drug. Accordingly, you were the sponsor and were required to have an IND in effect before proceeding with the clinical investigations of apoaequorin.

As noted above, the Act provides that a new drug may not be introduced or delivered for introduction into interstate commerce without prior approval, 21 U.S.C. § 355(a). Apoaequorin is not approved as a drug fo marketing in the United States, and is not exempt from this requirement pursuant to 21 U.S.C. § 355(i), which governs the use of investigational new drugs. Therefore, your use of the unapproved new drug apoaequorin in conducting a clinical investigation without an investigational new drug application in effect is a violation of section 505(a) of the Act and prohibited by section 301(d) of the Act. Further, you violated 21 CFR 312.20 by administering the investigational new drug apoaequorin to subjects without an IND in effect.

The violations cited in this letter are not intended to be an all-inclusive statement of violations that exist ir connection with your products. You are responsible for investigating and determining the causes of the violations identified above and for preventing their recurrence or the occurrence of other violations. It is your responsibility to ensure that your firm complies with all requirements of federal law and FDA regulations.

You should take prompt action to correct the violations cited in this letter. Failure to promptly correct these violations may result in legal action without further notice, including, but not limited to, seizure and injunction. The Act authorizes the seizure of illegal products and injunction against manufacturers and distributors of those products, 21 U.S.C. §§ 332 and 334.

Firm's Response to Inspectional Observations on Claims and IND Issues

At the end of FDA's inspection of your headquarters and warehouse facility in Madison, Wisconsin, our investigator issued a list of inspectional observations on Form FDA 483 and met with you and Mr. Mark Roeder, Technical and Quality Manager, to discuss the use of therapeutic claims on your websites and in other promotional materials, among other concerns (see "Comments on Other Inspectional Observations and Firm Response"). You responded on January 13, 2012, promising corrective action; however, a curren review of your websites reveals the continued use of therapeutic claims for your Prevagen products and the continued use of apoaequorin in clinical trials without an IND. Therefore, your response is inadequate.

Comments on Other Inspectional Observations and Firm's Response

Because your products are labeled as dietary supplements, FDA initially evaluated them under the laws and regulations governing dietary supplements, including the adverse event reporting and recordkeeping requirements for dietary supplements in section 761 of the Act, 21 U.S.C. § 379aa-1, and the current good manufacturing practice (CGMP) regulations for dietary supplements in 21 CFR Part 111. As noted on the list of inspectional observations issued to your headquarters and warehouse facility in Madison, Wisconsin, on December 22, 2011, our inspection of that facility revealed that you failed to report serious adverse events associated with your Prevagen products to FDA, as required by section 761(b)(1) of the

Act. Specifically, you failed to report to FDA adverse events like seizures, strokes, and worsening symptoms of multiple sclerosis that had been reported to your firm as being associated with use of Prevagen products. Some of these adverse events resulted in hospitalization. In total, our inspection found records of more than 1000 adverse events and product complaints that had been reported to your firm between May 2008 and December 1, 2011. Some of these involved heart arrhythmias, chest pain, vertigo, tremors, and syncope (fainting), in addition to the seizures, strokes, and worsening of multiple sclerosis already mentioned. As of the beginning of the inspection, only two of these adverse events had been reported to FDA or investigated by your firm.

After our investigators discussed the adverse event reporting requirements for dietary supplements with firm representatives, you submitted two additional reports of serious adverse events to FDA while the inspection was still in progress. We also acknowledge receipt of your January 13, 2012, response to the lis of inspectional observations issued to the Madison, Wisconsin, facility which documented your investigations of a number of additional adverse events reported to you. Your January 13, 2012, response also included adverse event reports on Form FDA 3500A for those adverse events that your investigation determined to be serious, as well as a revised standard operating procedure (SOP) for documenting and grading the severity of adverse events reported to your firm and documentation of retraining that you conducted for employees who take reports of adverse events.

A separate FDA inspection of your manufacturing and laboratory facility at 2010 Pinehurst Drive in Middleton, Wisconsin, between October 24 and December 22, 2011, documented that you failed to comply with the CGMP requirements for dietary supplements in several important respects, as noted on the list of inspectional observations issued on Form FDA 483 (the 483) at the end of that inspection. For example, you failed to perform identity testing for finished batches of Prevagen products manufactured between January 2011 and August 2011; did not complete all steps in the master manufacturing record for certain batches; failed to establish and/or follow written procedures for certain laboratory operations; failed to establish release criteria for several manufacturing steps where control is necessary to ensure that specifications for identity, purity, strength, and composition are met; and omitted required elements from your master manufacturing record.

We acknowledge your response dated January 13, 2012, reporting that identity testing is now being performed on all finished batches of your products, describing updates to your master manufacturing record and existing SOPs and the creation of new SOPs to address other observations from the 483, and reporting the results of batch investigations and testing performed in response to the 483. If your Prevagen products were dietary supplements, we would consider your response with regard to our CGMP and adverse event reporting observations to be adequate, but because the products are drugs, the CGMP and adverse event reporting requirements for drugs apply.

Within 15 working days of receipt of this letter, please notify this office in writing of the specific steps that you have taken to correct the violations cited above. Include an explanation of each step being taken to prevent the recurrence of violations, as well as copies of related documentation. If you cannot complete the corrective actions within 15 working days, state the reason for the delay and when you will complete the corrections.

Your written response should be directed to the attention of Compliance Officer Demetria L. Lueneburg at the address listed above. If you have any questions regarding this letter, please contact Ms. Lueneburg at (612) 758-7210.

Sincerely,
/S/

Michael Dutcher, DVM
Director
Minneapolis District

xc: Mark Y. Underwood
President
Quincy Bioscience Manufacturing Inc.

2010 Pinehurst Drive
Middleton, WI 53562

[1] A review of your websites and other product labeling revealed that you use the terms "apoaequorin" and "aequorin" interchangeably at times to refer to the ingredient that you manufacture and sell in varying strengths in your Prevagen products. In fact, however, apoaequorin and aequorin are distinct chemical entities. Apoaequorin is an apoprotein found in aequorin, which also contains the prosthetic group coelenterazine.

Page Last Updated: 10/19/2012
Note: If you need help accessing information in different file formats, see Instructions for Downloading Viewers and Players.

Links on this page:

1. http://www.fda.gov/