Safety Assessment of Dietary Supplements Marketed to Enhance Male Sexual Performance

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INTRODUCTION

Many dietary supplements claim to benefit men seeking to enhance erectile function and performance. These supplements often claim to be safe and effective yet often are adulterated with approved pharmaceutical ingredients (API) or their analogues (e.g., sildenafil). This practice is not only illegal but can place consumers at risk of significant serious side effects because they may not know that these API's are present in the adulterated product and/or that those API's prescribed for the treatment of erectile dysfunction (ED) can interact with certain medications and dangerously lower their blood pressure.

According to the U.S. Food and Drug Administration (FDA) the problem of adulteration of such products is wide spread [1-3]. The vast majority of products found to be adulterated were either intentionally adulterated or whose origin came primarily from China, where the practice of adulteration of Traditional Chinese Medicine (TCM) products with API's prescribed for erectile dysfunction is now widespread.

In a study carried out by the Consumers' Foundation of Taiwan in 2005 of sexual performance supplements produced in China, 33 of 122 such products contained API's, including the ED API's, sildenafil and tadalafil.[4] In addition, some adulterated products were found to contain anti-inflammatory and analgesic drugs, such as indomethacin.

Although it is tempting to believe that conducting a series of toxicological and analytical studies might suffice, of equal importance is the need to establish and enforce standard operating procedures (SOPs) focused on quality assurance that can eliminate the possibility of API's entering products of this nature that can pose a risk to consumers.

Our intention was to evaluate a model developed by a company that claimed to have SOP's able to discover product adulteration that supported its concern for product safety by also performing preclinical toxicology studies prior to placing its male sexual performance product into the marketplace. We learned that Life Span Labs, LLC (Portland, OR, USA) [5-6], claimed to perform quality assurance procedures and conduct preclinical toxicology studies for its product "112 Degrees™ ", for men.[7] The product,112 Degrees™, contains 5 vitamins, 4 minerals, 1 amino acid, and 5 botanicals, which in combination at the dosage indicated and per usage directions would according to the company, "support sexual performance in healthy men."[7]

TOXICOLOGY STUDIES

Prior to marketing 112 Degrees™, the company performed the preclinical toxicology studies as shown in Table 1.

An evaluation of these studies determined that each study had been performed in a Good Laboratory Practices (GLP) and US FDA compliant laboratory.

Table 1. List of Preclinical Toxicology Studies

1 Acute oral toxicity study (OECD 423) in the rat at 100 times the recommended human dose.
2 Bacterial reverse mutagenicity assay (OECD 471) using 5 tester strains with and without S9 activation, and a confirmatory repeat assay, to measure gene mutations in cell DNA.
3 Cytotoxicity study, to measure ability to damage or kill cells.
4 Immortalized human hepatocyte assay to measure the effect on liver detoxification enzymes (i.e., CYP1A2/CYP3A4) involved in 1st phase drug metabolism.
5 Two-week preliminary study to assess efficacy and safety *in vivo* in the rat, including histopathologies of reproductive-related organs and blood/urine chemistries.
6 Mouse peripheral blood micronucleus assay (OECD 474) to measure any potential clastogenic effect by measuring its ability to induce micronucleated reticulocytes.
7 Chromosome aberration assay (OECD 473) in Chinese hamster ovary (CHO) cells to measure the effect on chromosomes in mammalian cells.
8 Inducible nitric oxide synthase assay to measure ability to induce iNOS enzyme in cells *in vitro*.
9 iNOS vs. endothelial nitric oxide synthase (eNOS) assay, to measure *in vitro* ability to induce eNOS enzyme in cells, NO production, inhibition of COX-2 enzyme, and inhibition of human lipoxygenase enzyme activity.
10 12-week study of the product's sexual effect and behavior in the rat at 10 times the human dose, to measure the effect on sexual behavior, penile size, intracavernous pressure, testosterone level, sperm density, organs (testes, epididymis, prostate gland, seminal vesicle), endocrine glands (pituitary gland, adrenal gland), liver, kidney, spleen, blood/urine chemistries.

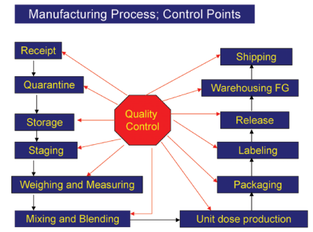
STANDARD OPERATING PROCEDURES FOR PURITY

The company conducted numerous quality assurance assays and tests for ingredient and product purity for pilot batches and commercial lots, based on production records of both the manufacturer (VitaTech International, Tustin, CA, USA) and the distributor (Life Span Labs) as shown in Table 2.

Table 2. List of Quality Assurance Assays and Tests of Ingredients and Formulation

1 Developed a fingerprint and commissioned analytical methods for validation for any botanical ingredient lacking a validated method.
2 Analytical (e.g., HPLC, LC/MS, GC/MS) determination of each ingredient to validate conformity to ingredient specification and supplier's certificate of analysis.
3 Analysis for ED adulterants: analytical assay for erectile dysfunction (ED) API's and known analogues.
4 Analysis for API's: assay of 168 API's in 19 drug categories.
5 Heavy metals: assay for lead, mercury, arsenic, cadmium, and copper levels.
6 Pesticides: test for pesticides residues using both US FDA and State of California pesticide panels.
7 Microbiology: test for total plate count, yeast and molds, *E. coli*, salmonella, *S. Aureus*, staphylococccus, and aflatoxins.
8 Selection of third-party certified manufacturing facility compliant with FDA's dietary supplement cGMP's regulations.[8]
9 Legal review of label conformity to FDA's dietary supplement labeling requirements.[9]
10 Oxygen radical absorbance capacity (ORAC) assay to measure lot-to-lot consistency.
11 Finished product analysis for presence of ED adulterants or analogues.
12 Rho-kinase II inhibition assay for lot-to-lot consistency. (Myosin phosphate [MP] activity has been shown to be involved in penile erection. MP is regulated by cytosolic Rho-kinase. Phosphorylation of MP by Rho-kinase maintains myosin light chain phosphatase (MLCP) in its inactive state. However, inhibition of Rho-kinase allows dephosphorylation of MP, which prevents intrinsic contractile tone, and allows relaxation of the cavernous smooth muscle.)

Figure 1.



DISCUSSION

Dietary Supplement cGMP's become effective June 24, 2008 through June 24, 2010, depending on the size and/or annual sales of companies engaged in the distribution and/or manufacture of such products.[9] These cGMP's will be legally binding on those involved as manufacturers, packers, labelers and holders of dietary supplements.

Under the new dietary supplement cGMP's, the FDA has defined quality as: Quality means that the dietary supplement consistently meets established specifications for identity, purity, strength, composition and limits on contaminants, and has been manufactured, packaged, labeled and held under conditions that prevent adulteration.[10] Figure 1., above illustrates each of the critical control points that support quality controls during the manufacturing process.

Although these regulations, or any other regulations promulgated by FDA do not require assessment of safety, it is commendable that Life Labs elected to perform a series of preclinical toxicology studies and assays prior to marketing its product. It is unknown how prevalent such a practice is in the dietary supplement industry without performing similar evaluations of other companies. Life Span's program of safety testing could raise the bar for this category of products, as most companies in this category seem more interested in making claims of efficacy, rather than also substantiating safety.

Of particular interest was the degree to which Life Span Labs checked for the presence of both API and ED adulterants, including the finished product, as part of its in-process testing and SOP program. Such procedures should make it highly likely that testing of its product would reveal the kinds of adulteration that seems to be pandemic for these types of supplements.

CONCLUSION

Life Span Labs was found to have an active quality assurance and analytical program in place able to discover the kinds of adulteration of male sexual performance supplements FDA has expressed concern with, which, combined with an extensive array of preclinical toxicology studies, could serve as a model for how dietary supplement companies and distributors could ensure the absence of ED API's in such products.

It is the opinion of the authors that despite the added cost of implementing such SOP's, the importance of such quality assurance procedures, combined with toxicological evidence of safety, is a worthwhile model that all dietary supplement companies can and should adopt.

References

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8 Final Rules for CGMPS for Dietary Supplements. Federal Code of Regulations, 21 CFR Part 111, pp. 34,712-34,942; June 25, 2007.
9 Final Rules for Nutrition Labeling of Dietary Supplements. Federal Code of Regulations, 21 CFR Part 101.36, pp. 49,849-49,852; Sept. 23, 1997.
10 Federal Code of Regulations, Federal Food, Drug and Cosmetic Act, 21 CFR Part 402(a)(1),(a)(2),(a)(3), and (a)(4). Quality attributes are named in 21 CFR 111, and include: identity, purity, strength, and composition.

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