

# Guest Editorial: The Rise and Fall of PC-SPES: New Generation of Herbal Supplement, Adulterated Product, or New Drug?

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The following article by Geoffrey A. Cordell is an excellent summation and analysis of the published research on the controversial dietary supplement product PC-SPES. Cordell adds his years of experience in pharmacognosy and botanically derived therapeutic agents with his interpretation of the chemical, biological, research, ethical, and legal/regulatory implications of the PC-SPES controversy.

However, for all the time and effort Cordell dedicated to this task—as well as the time expended by researchers conducting clinical trials on this product—one can now question whether it is all moot. Just prior to publication of this journal, on May 15, 2002, the manufacturer of PC-SPES, BotanicLab Inc in Brea, California, quietly announced that it was closing effective June 1. After a product recall in February necessitated by reports that PC-SPES contained the anticoagulant drug warfarin (California FDA), the company found itself unable to produce acceptable new lots of the product. The subsequent loss of revenue, coupled with continued operating costs plus mounting legal costs as a result of suits filed against the company, apparently created untenable business prospects. But the firm's closing may not provide closure to many of the issues raised in the PC-SPES controversy, many of which are covered in Cordell's article, and some of which are summarized below.

To many observers, the news of the “herbal” cancer remedy PC-SPES seemed almost too good to be true. Although the company officially claimed only that the product was “for prostate health,” the unofficial buzz was that the product helped men with prostate cancer (PC). At least 5 published studies since 1998 have demonstrated that the mixture possesses strong estrogenic, antineoplastic, and immunostimulant activity and provides benefits for men with PC, including increased quality of life and longer life with the disease.<sup>1,5</sup>

The first issue that merits discussion is not the product itself but the situation it is intended to ameliorate, PC. PC is a growing public health problem, its

incidence having grown 192% from 1973 to 1992. There are an estimated 190,000 new PC cases in the United States each year, with about 30,000 PC patients dying annually. One in 6 American men is at lifetime risk of PC according to the National Prostate Cancer Coalition.<sup>6</sup> Conventional treatments include surgical removal (prostatectomy), implantation of small radioactive “seeds,” and the use of estrogenic drugs. PC-SPES, although not officially marketed or approved as a drug for PC, is focused on what is generally acknowledged as a legitimate and growing health issue. Clearly, there is a strong public health imperative for natural, relatively safe cures and/or adjunct therapies for PC.

There is also the issue of the composition of the product. This can be seen from 2 aspects, the composition with respect to its chemical/pharmaceutical engineering and what the product may contain with respect to undisclosed pharmaceutical drug adulterants.

Despite early marketing claims and descriptions of the product in published accounts, PC-SPES is *not* a mere mixture of traditional herbs. It is much more sophisticated than blending 7 traditional Chinese herbs and adding a Native American herb (saw palmetto, *Serenoa repens*) to the mix, decocting it in the traditional way to produce a complex phytochemical mixture of the herbs' natural constituents. (Cordell's article provides a detailed description of the herbal ingredients.)

PC-SPES is (or was) reportedly a highly sophisticated, pharmaceutically prepared, chemically complex, highly concentrated mixture of various botanically derived chemical fractions (i.e., groups of related chemical compounds extracted from plants), which were concentrated from 100 up to 1000 times their

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natural levels and made into a unique preparation.<sup>7-9</sup> Presumably, the fractions were identified from the traditional herbs using modern laboratory techniques (e.g., bioassay-directed fractionation, in which specific fractions or individual compounds in plants are identified as having particular biological activity by testing *in vitro* and/or *in vivo*). This complexity and concentration of PC-SPES is probably the reason that the product was not able to be “reverse engineered” by would-be competitors who tried to develop similar products.

On the positive side, PC-SPES may represent a new generation of botanically based remedies. Although its chemical complexity is not novel (herbs and herbal products are by their very nature chemically complex mixtures), its high concentration and presumed design by bioassay-directed fractionation to produce an effective phytomedicine mark perhaps a new era, a new “octave” of medicinal herbal products. As such, it may become a model of what some herb or phytomedicine, or pharmaceutical companies may choose to do (and not to do!) in the future. The validity of this depends on the ability of future batches of PC-SPES, or a closely similar formula, to demonstrate similar biological activity, only after they have been proven to be free of pharmaceutical drug ingredients. Nevertheless, the chemical/pharmacological/pharmaceutical process employed in the development of PC-SPES could be replicated to produce new chemically complex medicines from traditional botanical materials. This model of formulation may be the lasting contribution of PC-SPES and BotanicLab to modern medicinal chemistry and new drug development.

On the other hand, on the down side, PC-SPES can be viewed as a failure of a company to adequately control its quality, the failure to employ appropriate good manufacturing practices (GMPs) in the production of the fractions and extracts in the Chinese facilities from which the company purchased these materials. Or worse, as some have suggested, PC-SPES may represent a worst-case scenario in the herbal dietary supplement industry. This scenario suggests that the company used the concentrated complex herbal materials as a matrix and delivery system for the inclusion of specific conventional pharmaceutical drugs, the combination of which produced desired biological activities—all under the rubric of “dietary supplement”—thereby allowing the company to market a new drug product without the expensive and extensive costs and time required to obtain official approval as a new drug. This cynical view presupposes intentional fraud on the part of the company, something that is difficult

to corroborate at this time and is outside the purpose of this editorial.

At any rate, apparently the economic costs of not being able to sell product for 5 months since the company recalled PC-SPES in February, and presumably the company’s inability to obtain “clean” (i.e., uncontaminated with drugs) product from its suppliers in China, have put BotanicLab in an untenable financial position, forcing the decision to close. Barre Rorabaugh, chief operations officer at BotanicLab, was quoted in a recent article in the *Wall Street Journal*<sup>10</sup> written after the recall: “We don’t have complete control of the supply chain.” Apparently, in the few months since the recall, this situation had not sufficiently improved. Furthermore, the company is reportedly facing a class action lawsuit, which may have also affected the executives’ decision to cease operations.

The impact of the closing will be felt in several areas, beyond the lives of the company’s employees who have lost their jobs and its distributors who have lost a profitable, if highly controversial, product (PC-SPES retailed for \$108 per bottle). PC patients will no longer be able to obtain the product, and several new clinical trials were under way or planned, including one at Johns Hopkins; these will now be halted for lack of product.

Despite the legitimate controversy surrounding the quality control of PC-SPES and whether it was accidentally or intentionally adulterated with pharmaceutical drugs—issues of ethics, responsibility, and business intrigue—the truth of the matter is that PC-SPES did offer a reasonable chance of hope for the PC patients who used it. The *Wall Street Journal* article quotes patients and physicians on both sides of the controversy, noting that the product had gained widespread acceptance among oncologists specializing in PC, with some physicians lamenting the loss of access to the product.<sup>10</sup>

One of the questions that arises when reports of the contamination surfaced is “Was it intentional?” After all, the prescription drugs in PC-SPES were not those with actions outside of the intended activity of the product: diethylstilbestrol (DES) has the estrogenic activity desired for and claimed by the manufacturer, or at least the estrogenic activity reported in clinical research,<sup>5</sup> whereas the presence of warfarin reported in April<sup>11</sup> has the anticoagulant activity that one might suspect would be added to or at least considered desirable for a product that was implicated in several case reports of blood coagulation and emboli.<sup>12,13</sup>

There have been 2 cases reported in the medical literature of bleeding associated with the use of PC-

SPES. A letter to the *New England Journal of Medicine* concerning a patient with bleeding informs of testing by high-performance liquid chromatography (HPLC), which discovered a compound that migrated to warfarin on HPLC, a phytycoumarin that was responsible for the patient's severe bleeding diathesis.<sup>14</sup> Subsequent testing by Richard Ko at the California FDA using sophisticated and valid methods of analysis confirmed the presence of warfarin in PC-SPES (as well as alprazolam in another of the company's products, SPES, used as an immune stimulant).<sup>15</sup>

However, there is no direct evidence of *intentional* contamination or adulteration—at least none that I am aware of. It may be that the company's Chinese suppliers intentionally added the drugs. The company appears to have been incredibly lax in its requirements for GMPs. When I spoke with one of the top executives of BotanicLab in February about the feasibility of testing multiple lots of the product representing production runs over the past several years, he said that the company had no samples available for such testing. In the conventional food and dietary supplement industries, the retention of product samples is required by law for 1 year past the expiration date of such products. This is mandated by law for precisely this reason—to be used for testing in the case of quality control (eg, contamination with mold or, in this case, drugs) or health problems (eg, adverse reactions by customers that may be traceable to a defect in the product). The current GMPs for conventional foods are operative for all supplement manufacturers, at least until the FDA publishes new GMPs designed specifically for the manufacture of dietary supplements, as suggested by the Dietary Supplements Health and Education Act in 1994 (DSHEA). In the case of PC-SPES, the product has a 2-year shelf life; thus, the company should have had access to retention samples reflecting product from 3 years ago.

The lack of GMP at BotanicLab is probably a reflection of other more serious quality control problems, the locus of which resides with the company's suppliers in China. Almost everyone familiar with the importation of Chinese patent medicines is aware of the chronic problems that have plagued many of these products, problems of adulteration with prescription drugs, and, in some cases, contamination with toxic heavy metals.<sup>16</sup> Thus, it would be incumbent upon anyone contracting with factories in China to produce a botanical extract to ensure that both the raw materials and the finished extracts are not contaminated. As shown in testing by the California Department of Health and others as well as unpublished reports from various interested parties, the managers of BotanicLab

and BotanicLab's contractors in China were not able to produce a "clean" product free of pharmaceutical adulterants.

Ralph Moss, a noted cancer activist, was strongly critical of the company in his response to the news of the Sovak study in which warfarin was again found in PC-SPES. He expressed what may be the feelings of many in the alternative cancer community by lamenting the adulteration of PC-SPES:

It is clear now that cancer patients and their advocates have been the subject of a cruel deception. Patients were enticed into buying this high-priced "herbal" product for daily use, whose active ingredients included very low-cost generic drugs. But the monetary loss was the least of it. The patients' health was endangered by exposure to potent drugs in what they were repeatedly assured was a safe, over-the-counter mixture of eight herbs. Many people upheld PC SPES as an example of an indigenous herbal formula that was developed outside the FDA approval process. While the clinical results with PC SPES are not in dispute, their safety and integrity are.<sup>17</sup>

Of the many significant issues raised by Cordell in his article, one deals with the lack of publicly available knowledge about certain aspects of PC-SPES:

The methods of standardization used by the company are unknown. The stability of the product remains unknown. Contraindications and important drug-herb interactions are not known. As a result, development of a long-range plan to investigate the observed clinical efficacy of the product is made substantially more difficult. Yet, that is precisely what is called for. (p 278)<sup>18</sup>

Cordell has raised a difficult issue in the herbal industry. The problems he cites may be due in part to the fact that in general, botanical products are not patentable, and thus the company may not have revealed information that Cordell has presumed is not known. For example, if Sophie Chen's statement at the PC-SPES conference in October 2001 that the product is made of highly concentrated fractions from 8 medicinal plants is credible,<sup>8</sup> which I believe, then it is highly likely that some of the questions raised by Cordell in his final paragraph are already known and answered but have been kept proprietary. However, this raises another compelling issue: if this were the case (ie, if the company had such specific chemical knowledge of its product), then how could the company market a product containing pharmaceutical drugs? That is, how can this product contain levels of DES or warfarin without the knowledge of the chemists or technicians who are producing the complex

material? The question keeps coming up: “How could they not know the contaminants were in the product?”

From a regulatory perspective, there are at least 2 levels to consider in determining whether PC-SPES is a food or a drug: one is the composition, the other is the claim.

As a dietary supplement, PC-SPES cannot make a claim to cure cancer; in fact, neither of the company literature nor the Web site data makes this claim. The marketing language is much more indirect and implicit, consistent with the requirements of DSHEA in the “structure/function” claim (ie, how the product affects the structure or function of the body). DSHEA allows such claims so long as they are truthful and not misleading, are backed by reasonable scientific evidence, do not state that the product will treat or cure a disease, include a mandatory disclaimer that the claim has not been evaluated by the FDA and is not intended to be used as a drug, and meets other requirements of the Food, Drug and Cosmetic Act. This latter condition requires that the product be properly labeled for its contents, is not adulterated, and is manufactured according to current GMPs. In the case of GMPs for dietary supplements, until the FDA releases the long-awaited new GMPs, currently, under federal law, all dietary supplements must meet the requirements of GMPs designed for conventional foods. Even this relatively easy requirement was not met in the case of PC-SPES, as conventional food GMPs do not allow the misbranding of food products.

Charges of adulteration of PC-SPES have plagued the product over the past few years. Before the revelations in February and April of the prescription drugs, there were allegations that the product contained the estrogenic compound DES. An Internet chat room for PC patients has carried allegations from some patients that their prostate-specific antigen (PSA) levels rose after taking recent batches of the product. The allegations charged that PC-SPES formerly contained DES and that recent lots did not contain DES, resulting in rising PSA levels, recurrence of PC symptoms, and so on.

An industry veteran who wished to remain anonymous called the PC-SPES situation “a moving target”; as soon as someone finds something in one analysis, then someone finds something else in the next test. He raised the point that if the company were intentionally contaminating the product, then it makes no sense that it would contaminate with different substances in different batches.

Despite what is revealed as the final outcome of testing of PC-SPES, with respect to the question of adulteration with pharmaceutical drugs, one issue is relatively clear: the product appears to work. That is, there is a significant body of both anecdotal evidence and

evidence from published controlled studies suggesting that PC-SPES works—although it is not clear whether the efficacy arises from specific iterations of its formulation, either with or without DES and with or without warfarin. By “works,” is meant that it appears to help increase quality of life and span of life in men with PC. Is this due solely to the botanically derived concentrated compounds in the formula, as represented to the public by the company, or is it a function of a combination of these complex phytochemical ingredients with the relatively small amounts of prescription medications? To resolve this dilemma, clinical trials must be resumed with a similar product, but only after appropriate analysis of the product to determine that it does not contain DES, warfarin, or any other conventional pharmaceutical adulterants. If the “new,” “clean” product provides the same or similar results as those shown in previous trials conducted with earlier versions of PC-SPES that are now suspect, then this will possibly vindicate the product and presumably the product (or some reasonable facsimile) might be marketable by some other entity.

If, however, the new version of PC-SPES does *not* deliver the results commensurate with earlier studies, then it may be worthwhile for a possible successor to BotanicLab to consider the following scenario: to file for investigative new drug status with FDA for a product containing the herb components *and* DES and warfarin. The real bottom line needs to be the health and longevity of PC sufferers. If the “adulterated” combination product is found to be the most beneficial in future studies, then this mixture should be reviewed and approved as a new drug and made available. However, the obvious prohibitively high costs associated with new drug approval—estimated at up to \$500 million—may very likely preclude this possibility, leaving thousands of men with little hope, at least for the present time.

With the apparent success of PC-SPES with regard to its efficacy, and considering how many deaths are experienced in the United States from PC each year, what might be appropriate is public funding of future research, possibly at the National Institutes of Health, on how to recreate this product, or a similar product. Also, this may be an excellent opportunity for investment by private interests who might purchase the rights to the formula and its manufacturing process and develop this product as a dietary supplement and/or as a drug, depending on whether a drug-free PC-SPES formulation can actually show safe and effective activity. This remains to be seen but is clearly in the interests of the thousands of men who suffer from PC and who are looking for safe, effective treatment options.

There are plenty of victims in the PC-SPES saga. Aside from the PC sufferers, the other losers or victims are the clinicians who have been counseling patients about PC-SPES use, the medical researchers who have invested time, energy, and money to determine the appropriate clinical role for PC-SPES. Also, there are the responsible members of the herbal and phytomedicinal products industry—many of whom manufacture high-quality preparations according to strict GMP and high levels of quality control and quality assurance. Many of these companies—particularly the herb and phytomedicinal producers in Western Europe and many here in the United States—have made significant financial investments in state-of-the-art manufacturing facilities and in basic and clinical research that documents the safety and efficacy of their products. In an industry that is already plagued with adverse publicity about quality control, the PC-SPES debacle may cast an undeserved shadow on these companies that produce ethical, reliable products.

The name PC-SPES is derived from *spes*, the Latin word for hope. BotanicLab's closing and the lack of PC-SPES adversely effects thousands of men who had begun to invest considerable hope that their lives with PC could be extended with the use of PC-SPES. Here is the real shame in the entire PC-SPES drama. For these men, PC-SPES provided relief and hope when no other conventional or alternative therapy did. We can only hope that the essentials of this product can be properly reformulated, that its efficacy can be demonstrated, and that it can be returned to the market, thus restoring hope for these men and the hundreds of thousands of new PC cases that will arise by the time a new version of PC-SPES is available.

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