



The NORTH CAROLINA
ARBORETUM

AN AFFILIATE INSTITUTION OF THE UNIVERSITY *of* NORTH CAROLINA

April 23, 2013

To: Karin Szypszak
Legal Assistant to the Vice President and General Counsel
The University of North Carolina

CC: David Lombard Harrison
Associate Vice President for Legal Affairs
The University of North Carolina

From: George Briggs
Executive Director
The North Carolina Arboretum

Re: Request to UNC Umstead Review Panel for Botanical Authentication Program Exception

Please find below a request from The North Carolina Arboretum regarding its continuing engagement in natural products economic development activities through a proposed Botanical Authentication program.

Please contact me at 828.665.2492 or by email at gbriggs@ncarboretum.org if I can answer questions or be of further assistance.

The North Carolina Arboretum Botanical Authentication Program

Contact Information

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Statute Relating to the Proposed Umstead Exemption for the Botanical Authentication Program of The North Carolina Arboretum

G.S. §66-58(b)(8)o - Activities that enable a community in which the constituent institution or other University entity is located or the people of the state to utilize University's facilities, equipment or expertise.

International Context of the Dietary Supplement Market

The international market for herbal supplements and nutraceuticals is both large and proving to be relatively recession proof, averaging 5-8%% annual growth since 2000 in the \$5.3 billion U. S. retail market. This expanding growth curve, based on increasing conventional healthcare costs, consumer natural health and wellness trends, the rise of the middle class in such countries as China and India, and other market factors, is placing increasing pressure on static or compromised botanical supply chains. For example, in certain global regions historically important for herbal production, high levels of pollution are now contaminating fields and their crops with heavy metals, pesticides, and other contaminants, both reducing suitable regions within which to produce quality crops or worse, allowing adulterated or contaminated raw material to enter the market from both domestic and foreign producers. Because many U. S. nutraceuticals depend on public collection of native plants from natural areas, a practice known as wildcrafting, the supply chain is at further risk for contaminated plants mistakenly identified with the target species. All of these factors have yielded recent US studies that have found products on our shelves that contain as low as zero percent of the labeled ingredient. A recent PBS Newshour feature highlighted this troubling phenomena in a recent story aired as "What's really in Herbal Supplements?"

http://www.pbs.org/newshour/bb/health/july-dec10/herbal_10-21.html

Until 2010, the nutraceutical industry was essentially unregulated. Thus its products have been largely unauthenticated except by the most conscientious manufacturers and suppliers. It was not until 2010 that the Food & Drug Administration began to require Current Good Manufacturing Practices for herbal dietary supplements as a category under 21 CFR 111. Now that these are technically in effect, only about 10% of the 2000 U.S. dietary supplement companies so far have been inspected and shown to be GMP-compliant. The level of federal scrutiny and enforcement of GMP requirements is expected to continue to increase dramatically in the future, representing an opportunity for North Carolina.

The Statewide Context

The North Carolina Arboretum, an affiliate entity of the University of North Carolina system, has foreseen the need for increasing product integrity in the botanical dietary supplement industry, and has worked for over 10 years to this end. Positioned in the most biologically diverse region in North America, the Arboretum led the co-founding of the North Carolina Natural Products Association, a means of building networking and education within the state's fledgling industry. The Arboretum hosted the association's original natural product conferences and secured early operating support to sustain the association. To gain access to research support and advanced life sciences, the Arboretum concurrently worked to establish a key relationship with the North Carolina Biotechnology Center, and housed the center's first Western Regional Office. With support and encouragement from these partners, as well as from the UNC system, North Carolina General Assembly, Golden LEAF Foundation, Mission Healthcare Foundation, Buncombe County Commission, and others, the Arboretum has invested substantially in developing the strategic botanical resources necessary for bringing product integrity to the U. S. market.

The University of North Carolina Context

In recent years with significant advances in life sciences, other member institutions of The University of North Carolina system have also recognized the increasing value of our resident biological diversity as an important ingredient in health, wellness, and economic development. From an industry perspective, the nutraceutical and botanical supplement sectors are proving to be areas of economic opportunity for North Carolina. From a health perspective, a majority of U. S. citizens now take some form of dietary supplement in addition to or in place of traditional prescription medications. Consequently, various units of the UNC system have initiated programs to assist the state in conserving and capitalizing on these unique natural resources.

- UNC-Chapel Hill School of Medicine now has an Integrative Medicine program that incorporates complementary and alternative medicine (CAM) -- i.e. therapies such as message, acupuncture, and dietary supplements -- as well as research fellowships in CAM.
- NC State University has a long-standing Specialty Crops Program that has focused on the agricultural aspects of transitioning native woodland and meadow medicinal plants into prospective economic crops under cultivation.
- Appalachian State University has formed a partnership between its Human Performance Laboratory and the North Carolina Research Campus. The mission of the ASU/NCRC Human Performance Lab is to investigate the influence of unique plant molecules (e.g. flavonoids such as quercetin, luteolin, and epigallocatechin 3-gallate or EGCG) on age-related loss of muscle mass (sarcopenia), muscle mitochondrial biogenesis, and exercise-induced changes in immune function, oxidative stress, and inflammation.
- UNC Greensboro, through its Department of Nutrition and Department of Chemistry and Biochemistry, is engaged in a variety of research projects examining various aspects of medicinal plant interaction with the human body for health and wellness purposes.
- Western Carolina University, in its Department of Chemistry and Physics, is engaged in antitumor and antibacterial natural products drug discovery, as well as phytochemical analysis of botanical medicinal products and plants indigenous to Appalachia.

Overview of the Arboretum and the Botanical Authentication Program

The North Carolina Arboretum has been an affiliate institution of the University of North Carolina for almost 27 years. Its mission cultivates connections between people and plants through creative expressions of landscape stewardship including economic development, education, research, garden demonstration, and conservation. The North Carolina Arboretum is committed to the use of its facilities and grounds to support the Arboretum's mission areas and for the general benefit of North Carolina citizens and visitors to Western North Carolina. The Arboretum also has a long-standing and successful record of leveraging unique regional assets for economic benefit to the mountain region and state.

Perhaps supreme among those assets are the exceptional botanical diversity of our mountain region and the region's long heritage of botanical use for health purposes. Ironically, in spite of the expansive growth of the nutraceutical industry in the U.S. and abroad, there has never been established an independent medicinal plant germplasm repository as exists under federal government backing for each of our major food crops. This void has become more important for a variety of reasons. One, natural product research leading to product development from botanicals must now be replicable, given the inherent problems with genetic variability in plant sources from research to manufacturing. The variability in natural products derived from medicinal plants, long unregulated, must now be addressed with new requirements for authentication of product integrity. A reputable scientific source of validated germplasm is essential to the requirement.

The Arboretum has also created as its research focus The North Carolina Arboretum Germplasm Repository for development and storage of botanical seeds and extracts. The repository, following 6 years of field and laboratory work, has now garnered about 2,000 accessions of plant and endophytic fungi that exceed federal curation standards. These materials are now being regularly utilized by a number of significant research partners and grant activities, such as work with the Cherokee on important food crops.

A Bridge to the Dietary Supplement Industry. To make the repository asset more available to industry as they struggle to meet the requirements of Good Manufacturing Practices, the Arboretum led formation and provides continuing leadership of the 501(c)(3) non-profit corporation Bent Creek Institute, Inc. that serves to foster collaboration between the Arboretum's research and commercialization goals. These efforts have been heavily supported administratively and financially by the UNC system, as evidenced by a Collaboration Agreement co-signed by the UNC President, Arboretum Executive Director, and Bent Creek Institute, Inc. President.

The Elements of Authentication

What constitutes proper authentication for plant-based natural products and how does the Arboretum fit into the equation?

Accurate identification of whole plant sources. Easier said than done, the similarity among plants – particularly those of the same genus or family – must be performed by a trained botanist or related scientist. When performed, the subject plant is captured as an exhibit known as a *plant voucher*. The voucher contains the plant's representative parts necessary for proper identification – leaves, stems, buds, roots, flowers, and fruit.

As highlighted in the PBS Newshour feature above, misidentification of plant materials in natural products is an industry-wide problem that poses significant health risks. Consequently,

Good Manufacturing Practices require the presence of a plant voucher by a manufacturer to authenticate that the product is of a validated, credible and properly identified origin.

Though now commercially important, voucher production must occur in a tightly-validated regimen of seed acquisition, plant production and processing, and proper specifications.

Accurate identification of processed plant raw materials. Even more challenging than identifying whole plants is identifying plant parts that have been ground prior to utilization in manufacturing processes. Here, in a similar concept to the voucher for the whole plant, a validated ground material known as a *Botanical Reference Standard* must be on hand, in compliance with GMP, by a manufacturer to validate the identification of ground plant materials at the cellular level by means of a microscope (microscopy). Depending on the final product being manufactured, the BRM must be from both the correct plant and the correct plant part (e.g. leaf, root, fruit) that is being used in the manufacturing process.

The preparation of Botanical Reference Standards is equally as complex as the production of commercial plant vouchers, but also requires a carefully constructed and validated chain of custody and storage system, so that there is no inadvertent mixing of the ground materials which frequently look alike to the naked eye.

Accurate identification of chemical materials. When botanically-derived raw materials or products are handled or manufactured in a liquid state, the manufacturer must also be able to produce a *Chemical Reference Standard* to which the manufactured product must conform. These, of course, must be produced with exacting standards in compliant laboratory facilities.

Accurate testing and validation of raw materials and products. In addition to being required to acquire these components—vouchers, botanical reference standards, and chemical reference standards, natural product manufacturers at all scales must now under GMP standards better account for their raw material and product quality. Thus, producers and manufacturers require tests using various methods to determine the botanical identity of raw materials in various forms. For example, raw materials produced by aqueous solvent may require different testing methods than those produced by other solvents.

Situated within the heart of Southern Appalachian biodiversity and observing these changes in regulation of botanical supplement research and manufacturing, the Arboretum has been uniquely positioned to address these specific requirements of GMP botanical extract and nutraceutical manufacturing. Beginning approximately 8 years ago, the Arboretum began the process of building the only medicinal plant germplasm repository in the United States. By hiring Dr. Joe-Ann McCoy as our Germplasm Repository Director, the Arboretum began the endeavor utilizing cutting-edge standards. For example, because Dr. McCoy has secured permits to collect in over 1,000,000 acres of U. S. Forest Service lands, she has had the unique ability through GPS technology to create a truly “living collection” by precisely pinpointing the location of the specific plant population of plants from which her seeds and extracts were collected. These data are maintained under confidentiality to protect the populations from exploitation or destruction. Consequently, our seed and extract resources are referenced to field populations, our vouchers filed digitally as high definition images, our seeds maintained in state of the art vacuum packaging at cryogenic temperatures and frequently duplicated for back-up deposit in Norway’s underground Svalbard Global Seed Vault, and our extracts and reference materials produced and maintained with leading edge technology. We have also established third-party agreements to assist in these functions, and to validate the quality of our processes and products.

Validation of Vouchers and BRM's

Like any accountable system aspiring to unimpeachable standards, the Arboretum has developed a third-party agreement with the American Herbal Pharmacopoeia (AHP), the “Gold Standard” of American herbal validation for herbs of commerce. Like the U. S. Pharmacopoeial Convention, which is responsible for oversight of prescription drugs in the United States, the AHP has similar responsibility for promoting and validating the responsible use of herbal products and herbal medicines. Consequently, AHP publishes monographs of the most important botanicals, including in-depth descriptions of the quality control criteria needed for ensuring the identity, purity, and quality of botanical raw materials. Each document also presents a complete and critical review of the traditional and scientific literature regarding the efficacy and safety of herbal medicines. They also provide what are called AHP-verified Botanical Reference Standards and AHP-verified Chemical Reference Standards.

The Result and the Umstead Exemption Request

The result of these years of carefully developed planning and execution has been the emergence of North Carolina as a leading state in natural product research and innovation. Within such organizations as the American Herbal Products Association (the only national trade association that is focused primarily on herbs and botanicals and herbal products) and the United Natural Products Alliance (consisting of 40 large companies and 10 laboratories with combined sales exceeding \$4 billion), North Carolina and the Arboretum's programs are viewed as strategically timely and valuable to the future interests of the industry.

This request of the Umstead panel by The North Carolina Arboretum is the endorsement of the Arboretum's Botanical Authentication Program. Because of the significant legwork over many years to locate in Western North Carolina the target plants for voucher preparation, secure necessary collection permits and landowner permissions, collect and process seeds for seed bank preparation and storage, undertake analytical chemistry procedures for extract production, manage the photographic and data systems for high-level validation and documentation, form agreements with third-party partners, and other unique functions, the Arboretum is now uniquely credentialed to supply researchers and manufacturers with all the necessary GMP elements of authentication.

The ability to supply vouchers, botanical and chemical reference standards, and validation testing services to researchers and companies will not only strengthen the state's economy but also stimulate increasing discovery of superior plant varieties and cultivars of commercial importance, assist in identifying new compounds beneficial to human and animal health, and strengthen North Carolina competitively among other states building natural product assets.

With respect to competition for these services, there is none so far as we can discern. Because of the Arboretum's permitting access; regional collecting familiarity and logistical complexity; process requirements for credentialed botanists, chemists, and scientists; third-party agreements in place; substantial capital investment secured; and mountain location in Asheville, we see no existing competition. Were competition to arise in North Carolina, which we believe highly unlikely due to these cited logistical, scientific and capital requirements, it would take a number of years for it to develop sufficiently to satisfy the federal standards now coming to fruition.

While there is no competition, and no quick ability for it to form, the natural products industry in North Carolina requires the products and services of the Arboretum's Botanical Authentication Program now in order to maintain their viability and momentum. Indeed, the Arboretum not only can support emerging

entrepreneurs and existing businesses in the state, but can also assist in attracting new companies. This well-conceived and strategic Botanical Authentication Program will give North Carolina a unique natural advantage in addition to its rich botanical heritage and composition.

Botanical Authentication as an integral component of tourism-based economic development

It is important to note that as a strong partner in regional tourism, the Arboretum with an active Botanical Authentication Program would enhance Western North Carolina as a natural product destination market and support economic development of regional businesses and vendors that engage in this sector. Attracting a new clientele to the region, the Arboretum Botanical Authentication Program will include an educational component that addresses the importance of the industry in the state and the opportunities it is yielding for our future. As it is in all our programs, The North Carolina Arboretum Society, the Arboretum’s supporting 501(c)(3) organization, as it always has been, will be an integral supporter and partner in the execution of the Botanical Authentication Program.

In addition to strong and generous support from the statewide entities cited above, the Arboretum has also has strong backing and support from our regional economic development community. The Asheville Area Chamber of Commerce, the Asheville Hub, and the Advantage West Economic Partnership have all now identified and supported as a priority the natural products sector as an important, vertically integrated economic sector. Five regional partners including the Arboretum’s Germplasm Repository are now implementing a “Blue Ridge Naturally” regional brand that will serve as the “Good Housekeeping” seal of quality for local product integrity, quality, and authenticity. At the recent annual gathering of thousands of natural products companies and organizations in Las Vegas known as Expo West, the “Blue Ridge Naturally” exhibit won the Best Partnership Award, one of only 8 awards given to participating exhibitors.

The regional synergy forming around natural product economic growth is in large part due to the Arboretum’s leadership and coordination of regional interests over the past decade. It is this sectorial growth and attention to authentication standards that are placing North Carolina in a favorable position to compete with Utah, New Jersey, California, and Colorado as traditional national leaders in natural product research and development. Our unique regional advantage, aside from our exceptional botanical diversity and long heritage of use, is the North Carolina Arboretum Germplasm Repository, built from local resources over many years, and its unique capacity to set and validate quality standards for botanical ingredient identity.

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