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The National Institutes of Health Investment in Research on Botanicals

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Abstract

The Office of Dietary Supplements (ODS) and the National Center for Complementary and Alternative Medicine (NCCAM) were both established by Congress in the 1990's. ODS aims to strengthen knowledge and understanding of dietary supplements (DS). NCCAM promotes exploration of complementary and alternative medicine in the context of rigorous science. Together, they developed the Botanical Research Centers Program to promote interdisciplinary study of botanicals, particularly those found in DS, by supporting research activities ranging from plant and characterization to preclinical and early-phase clinical studies. These Centers are part of the coordinated efforts of ODS and NCCAM to enhance botanical research.

1. INTRODUCTION

The National Institutes of Health (NIH), an agency of the US Department of Health and Human Services, is the largest biomedical research funding agency in the world. Since 1999, the NIH has funded a network of interdisciplinary research centers devoted to the study of herbs and other botanicals [1]. This has been a joint effort of two components of the NIH – the National Center for Complementary and Alternative Medicine (NCCAM) and the Office of Dietary Supplements (ODS). At various times during the life of the NIH Botanical Research Centers Program (BRCP), other NIH components have participated. The BRCP is the largest, but not the only, component of the botanical research portfolios of ODS and NCCAM. As described below, these agencies are committed to fostering the highest quality botanical products used in research and – by extension – in commerce.

Both ODS and NCCAM have a longstanding interest in and commitment to research with botanicals. In the US, most botanical ingredients are marketed as dietary supplements, hence the interest of ODS. In addition, US data from the 2007 National Health Interview Survey (NHIS) reveal that approximately 40% of the American public uses CAM therapies and nearly 20 % of the adult population uses natural products, including botanicals [2]. NCCAM is committed to supporting this research, in view of such widespread use of botanicals in the US. Together, these two organizations fund a considerable amount of research with botanicals, ranging from basic botanical and phytochemical characterization through

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preclinical studies aimed at understanding mechanisms of action to clinical investigation examining efficacy and safety. It should be noted that other components of the NIH, as well as other federal agencies such as the USDA and the FDA, continue to invest in research with botanicals. Details of this funding from 1999 to the present can be found at the Computer Access to Research in Dietary Supplements (CARDS) database that was created by ODS (http://ods.od.nih.gov/Research/CARDS_Database.aspx).

There are three primary areas in which NCCAM and ODS have invested in botanical research, mostly in collaboration. These areas include extramural grant support for botanicals, in particular the NIH BRCP; the NCCAM Product Integrity Process; and the ODS Analytical Methods and Reference Materials Program.

2. ODS & NCCAM SUPPORT FOR BOTANICAL RESEARCH

2.1 THE BOTANICAL RESEARCH CENTERS PROGRAM, 1999 – 2010 AND BEYOND

In 1999, Congress attached language to the appropriation for ODS that “calls on ODS to establish a botanical research initiative with major research institutions in the United States”. The then-Office of Alternative Medicine, also at NIH and predecessor to NCCAM, found this to be of considerable interest to them and joined ODS in publishing the first Request for Applications (RFA) for two multidisciplinary Centers that were funded at the end of 1999. Shortly thereafter, a second RFA released by ODS and NCCAM led to the addition of three more Centers. Both the National Institute of General Medical Sciences (NIGMS) and the Office of Research on Women’s Health (ORWH) at NIH participated in funding these Centers. A sixth Center was added in 2002 with support from the National Institute of Environmental Health Sciences (NIEHS). The Centers were called upon to conduct the full range of studies from botany to the clinic, create training opportunities, and perform public outreach. An evaluation of the program at the end of this first funding period led to a more focused RFA in 2004, with an emphasis on basic, pre-clinical, and early clinical studies. This decision was based on the realization that major clinical studies were beyond the scope of what could be reasonably accomplished in a five-year funding period and that other NIH mechanisms existed to fill this need. Furthermore, it was recognized that much work needed to be done at the earlier phases of investigation before full-scale clinical trials of botanical extracts would be appropriate. Training, while a valuable component of a Center’s activities, could also be funded in other ways and Centers were encouraged to take advantage of other mechanisms at the NIH (e.g., pre- and post-doctoral training awards) to meet this goal.

Over the first two rounds of the BRCP, the NIH has invested a total of approximately $90 million. The Program has been a sound investment for NIH and has been responsible for significant contributions to the field of research on botanical dietary supplements [3].

Awards for the third round of the BRCP were issued in the summer of 2010 (http://www.nih.gov/news/health/aug2010/od-31.htm).

2.2 OTHER ODS AND NCCAM SUPPORT FOR RESEARCH ON BOTANICALS

In addition to the NIH BRCP, NCCAM has developed a robust portfolio of investigator-initiated research on botanical extracts and compounds. Many of the research grants funded by NCCAM in this area are supported with co-funding from ODS. NCCAM’s botanical research portfolio also includes Small Business Innovation Research (SBIR) projects, as well as mentored training and fellowship grants to support projects of young investigators in training. The research scope of NCCAM-funded botanical research includes both basic and mechanistic studies, as well as early-phase clinical work.

In considering what data are required prior to implementing clinical research on a given botanical, NCCAM encourages investigators to focus on critical gaps in the understanding of product biology before embarking on human trials. Such gaps typically include data on absorption, distribution, metabolism, and excretion, as well as toxicity. Data on appropriate dosing or dose frequency are also frequently lacking. Although markers of biologic effect, and efficacy, are also scarce, it is important that such markers be sought for a specific botanical of interest. An understanding of appropriate study outcome measures and target population are similarly important for ultimately planning a large clinical trial of a botanical product.

It is also important to recognize that other Institutes at the NIH support botanical research, including NIEHS; the National Cancer Institute (NCI); the National Heart, Lung and Blood Institute (NHLBI); the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK); and the National Institute on Aging (NIA). In view of the broad research scope funded across the NIH, and their strong interest and commitment to funding outstanding botanical research, both NCCAM and ODS work with staff from other NIH Institutes to organize and support scientific meetings on botanical research, and co-fund many projects that are supported primarily by other NIH Institutes.

3 THE NCCAM PRODUCT INTEGRITY PROCESS

With the expansion of the botanical research portfolio, NCCAM has developed a standardized process for assessing study product information in NCCAM-funded botanical projects. This process began formally in 2005 with establishing a mechanism that resulted in the Product Integrity Working Group (PIWG), and with developing an interim policy and guidance statement for NCCAM grantees. The PIWG comprised staff from both NCCAM and ODS, as well as scientists from the NCCAM National Advisory Council. PIWG efforts provided early structure and definition for product requirements in NCCAM-funded studies. With the expansion of scientific expertise within NCCAM, product assessment, referred to now as the Product Integrity Process, has been modified. The PIWG remains a resource to this process, which is now shepherded by NCCAM scientific staff. The Product Integrity Process focuses on increasing awareness in the research community regarding relevant product issues at the grant application stage, and emphasizes the need for independent product analysis. This process also stratifies product requirements, based on proposed studies (both pre-clinical or clinical). The primary goal of the Product Integrity Process remains ensuring the qualit y and consistency of natural products that are used in NCCAM-funded research.

4 THE ODS ANALYTICAL METHODS AND REFERENCE MATERIALS PROGRAM

The quality of botanical products is one of the greatest challenges that researchers face. Because the inherent nature of these products is that they are, generally, extracts of plants rather than chemically pure compounds, there will always be variability in their composition. The wide heterogeneity in composition has been a subject of continued frustration for consumers, regulators, manufacturers, and researchers alike. Methods to assess the composition of botanical extracts are available for some, but decidedly not most, components. In 2001, Congress included language in the NIH appropriation “calling on ODS to accelerate ongoing collaborative efforts to provide validated analytical methods and reference materials to support chemical analysis for botanicals and other dietary supplements”. ODS created a program that has led to the development of both processes and outcomes for ensuring the availability of these important analytical tools [4]. Over the years, the program has been responsible for enhancing the availability of validated methods (e.g.,

for ephedrine-alkaloid containing dietary supplements) and reference materials that are available to all. Elements of this program are described elsewhere in this volume by Dr. Joseph Betz. These outcomes have only been possible due to the collaboration of government agencies (e.g., NIH, Food and Drug Administration, US Department of Agriculture, and National Institute of Standards and Technology) with outside organizations such as AOAC International, academic researchers, and laboratories in the private sector [5].

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