

CHAPTER 7

PHARMACOGNOSY IN ACTION. INDUSTRY

The Role of the Pharmaceutical Industry

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Given the strong confluence of their basic themes, one might expect the Pharmaceutical Industry (Pharma) and the ASP to have a tremendous influence on one another, and indeed they have, but perhaps less than might have been expected. Gordon Svoboda, an alkaloid chemist at Eli Lilly, served as the Society's 4th president in 1963, but it was not until 1997 before a second full-time Pharma employee filled this position again, with the election of Bob Borris, a researcher at Merck, as the 38th President. Jim McAlpine as the 45th president and Guy Carter as the 49th president-elect, as we go to press, will be the third and fourth from industry.

The genesis of ASP coincided with the later "Golden Years" of antibiotic research. The miracle of penicillin had been rapidly followed by discovery and commercialization of chloramphenicol, streptomycin, erythromycin and tetracycline, and Pharma which had risen to the war effort with the production of penicillin by virtually every company, now found itself in a frenzy to discover antibiotics. Abbott, Eli Lilly, Upjohn and Warner Lambert signed the "Midwest Agreement" in which they cooperated in the discovery of antibiotics and shared the spoils. However, ASP and Pharma, although both studying natural products, were somewhat out of synch. ASP had grown out of the Plant Science Seminar, and its emphasis in the early years was almost entirely on plant-derived natural products. Industry was not uninterested in plant derived pharmaceuticals. (Abbott Laboratories grew out of The Abbott Alkaloidal Company, Lilly developed the vinca alkaloids), but plant derived natural products have not been a major focus in any large American Pharma in the last 50 years. Moreover by the time microbial natural products started to receive significant attention in ASP the industry was losing interest in them. Antibiotic screening in the '60s and '70s, prior to the introduction of robots and automation, was a very labor-intensive operation and the cost of labor in the US became prohibitive for US Pharma. Many of them chose to, either abandon antibiotic discovery programs (e.g. SmithKline), or move major parts of them overseas. (Merck to Spain; Abbott, Bristol Myers, Eli Lilly to Japan) In the 1980s many of these operations were repatriated to the US and pharmacognosy graduates looked to Pharma for their careers. The 1980's also saw the genesis of the Biotechnology companies with pharmaceutical goals, many of which had a natural product approach, e.g. Kosan (combinatorial biosynthesis), Phytera & Esca Genetics (plant cell culture), Diversa (metagenomics) Napro (phytochemistry). However, by the end of the millennium the number of career positions in the industry for pharmacognosy graduates was undergoing a severe reduction, with three factors contributing; i) the trend in large Pharma to use acquisitions (or mergers) as a means of growth (e.g. Pfizer of 2007 is the result of amalgamations of 14 different companies over 25 years) has reduced the number of this group of employers. ii) a move by large pharmaceuticals away from antibiotic research and natural products as a source of NCEs, (as we go to press, Wyeth[†] is the only large US Pharma with viable natural product discovery programs) and iii) the burst of the "Biotech Bubble" with less venture capital going to small biotechs.

Natural Products Drugs Introduced into Major Markets in the Last 25 Years¹

Drug	Indication	Introduced	Company
Chenodiol	Gallstones	1983	Rowell
Cyclosporin	Transplant rejection	1983	Sandoz
Prostacyclin	Platelet function	1983	Burroughs-Wellcome
Aztreonam	Antibacterial	1984	Squibb
Epirubicin	Anticancer	1984	Erbamont
Leuprolide	Anticancer	1984	Abbott
Imipenem	Antibacterial	1985	Merck
Fortimicin	Antibacterial	1985	Kyowa Hakko
Miokamycin	Antibacterial	1985	Meiji Seika
Pseudomonic acid	Antibacterial	1985	Beecham
Ivermectin	Onchocerciasis	1987	Merck
Lovastatin	Hypercholesterolemia	1987	Merck
Plaunotol	Anti-ulcer	1987	Sankyo
Simvastatin	Hypercholesterolemia	1988	Merck
Teicoplanin	Antibacterial	1988	Merrell Dow
Vinorelbine	Anticancer	1989	Pierre Fabre
Acarbose	Antidiabetic	1990	Bayer AG
Idarubicin	Anticancer	1990	Erbamont
Romurtide	Immunostimulant	1991	Daiichi
Paclitaxel	Anticancer	1993	Bristol Myers Squibb
Tacrolimus	Transplant rejection	1993	Fujisawa
Irinotecan	Anticancer	1994	Daiichi Seiyaku
Mycophenolate mofetil	Transplant rejection	1995	Roche
Lepirudin	Anticoagulant	1997	Hoechst Marion Roussel
Miglitol	Antidiabetic	1998	Sanofi
Orlistat	Obesity	1998	Roche
Colforsin Daropate	Cardiac failure	1999	Nippon Kayaku
Eptifibatide	Cardiac failure	1999	Cor Therapeutics
Rapamycin	Transplant rejection	1999	Wyeth
Dosmalfate	Anti-ulcer	2000	Faes
Arteether	Antimalarial	2001	Articef BV
Caspofungin	Antifungal	2001	Merck
Fondparinux	Thrombosis	2002	Sanofi Synthelabs
Micafungin	Antifungal	2003	Fujisawa
Daptomycin	Antibacterial	2003	Cubist
Tygecycline	Antibacterial	2005	Wyeth
Ziconotide	Chronic pain	2005	Elan
Anidulafungin	Antifungal	2006	Pfizer

¹In compiling this list, semisynthetic penicillins, cephalosporins, macrolides and rifamycins were excluded, and multiple examples of the same structure type were only included if they incorporated a markedly different feature. Major markets considered are the US, Europe and Japan.

Advances in technology, particularly in spectroscopy, screening methodologies and genomics hold the promise of reversing this trend. Certainly Pharma, and indeed humankind, have benefited mightily by discoveries in pharmacognosy over these 50 years, and as our understanding of the various roles secondary metabolites play in their producing organisms grows, and how these relate to *Homo sapiens*, it is certain that Pharma will build on this knowledge, and we must expect a larger role of industry scientists in the Society in the future.

Natural product drugs introduced onto major markets (US, Europe, Japan) in the last 25 years are shown in the Table above. In compiling this list, semisynthetic penicillins, cephalosporins, macrolides and rifamycins were excluded, and multiple examples of the same structure type were only included if they incorporated a markedly different feature.

† Editor's Note: A merger between Pfizer and Wyeth Pharmaceuticals was announced on January 26, 2009

The U. S. Herbal Industry: A Perspective[†] **Steven Dentali^a, Renuka Misra^b and Ramesh C. Pandey^b**

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The American herbal industry arose from the ashes of the large scale abandonment of the use of crude botanical drugs in medicine, as reflected by their general disappearance from the *United States Pharmacopeia* (USP) and *National Formulary*.¹ At about the time that the American Society of Pharmacognosy was founded, pharmacognosy was on the decline, gradually becoming a course artifact for US pharmacy students' medicinal chemistry classes to remind them whence medicines had evolved. Pharmacists no longer needed the tools to establish the quality of crude drugs purchased from botanical supply houses, because pharmacists had stopped preparing such medicines.

While official uses of herbal medicines diminished during the middle and latter half of the last century, herbal practices did not fall away completely. Traditional uses rooted in cultural practices continued and were supplemented by a renewed interest in herbs arising from social movements in the late 1960s. Historically, US medical practice included many movements that had a strong botanical component. Of necessity, pharmacognostic skills would have been employed by the Thomsonians² and Eclectics. The Eclectic medical system left behind a vast repository of direct herbal experience as documented in the *Eclectic Medical Journal* published from 1849 to 1937, and many other publications.³ Echinacea and other botanicals were familiar remedies in American households a hundred years ago, due to the Eclectics and especially John Uri Lloyd, who, with his brother Curtis Gates, founded the Lloyd Library and the publication that eventually became the American Society of Pharmacognosy's *Journal of Natural Products*.⁴ John Uri Lloyd himself was twice past president of the American Pharmaceutical Association,⁵ and was elected as an ASP Honorary Member in 1961.

The Lloyd Library remained an undiscovered treasure trove until the latter part of the 20th century as far as the herbal industry was concerned,⁶ for the Eclectics had died off and no one remained to pick up that thread. Lone voices in books by Edward⁷ and lectures and books by Dr. Christopher⁸ championed the practice of botanicals as medicine, while the professional need for

classic pharmacognosy dwindled. Botanical microscopy classes, for example, vanished from pharmacy curricula altogether.

The 4th to 7th editions of *Pharmacognosy* published in 1961, 1965, 1970, and 1976 respectively,⁹ accurately reflect the diminution of interest and focus on crude botanical medicines. The fourth edition contains standards and tests, descriptions and photographs, uses and doses for many plants. Rhubarb received four photographs and four pages in the fourth edition, while sarsaparilla warranted a four page coverage including species from over five countries; drawings of microscopic structures appear there and in the fifth editions. By the seventh edition, sarsaparilla was allotted two short paragraphs, rhubarb less than a page and microscopy references had disappeared altogether.

As a reflection of the times, the cover for the fifth edition featured images of *Digitalis purpurea*, the structure of digitoxigen, crystals of digitoxin and a drawing of what appears to be a distillation apparatus. By contrast, the editions immediately following present images of a cannabis leaf (treatment of this plant moved from the resins and resin-combinations chapter to that on poisonous plants!), *Amanita muscaria* mushroom and rye ergot with associated chemical structures. The mushroom image on the cover of the sixth edition emanates alternating green and blue psychedelic “vibes”, while the seventh edition appears to have settled into a red-yellow-orange avant-garde presentation of intersecting geometric images. The irony is that as the contents of these texts reflected the reduced mainstream concern with botanical preparations, the covers paid homage to the counterculture influence that had a significant impact on the re-emergence of botanical products as viable health care options.

Herbal adherents from that time read the available contemporary texts, of which there were precious few of any substance, dusted off pre-1950s USP’s, the 20th edition of the *US Dispensatory*, and rediscovered pharmacognosy. Companies were started. Among the first of the contemporary botanical industries to emerge were tea companies such as Celestial Seasonings and Traditional Medicinals, which celebrates its 35th anniversary this year. A few of the US herbalists of the 1960s and 1970s actually made a living by opening herb shops, teaching classes, helping individuals address health issues and selling herbs and herbal preparations, some of which were facsimiles of USP tinctures. The recently deceased Michael Moore, credited with being the godfather of American herbalism,¹⁰ wrote three seminal herb books,¹¹ trained legions of herbalists and left a treasure of a website¹² that still holds thousands of plant images and dozens of classic reproduced texts. Michael trained students how to collect, prepare, and use botanical preparations, much as had been done throughout the history of the US herbal industry.

New enterprises arose as herbal enthusiasts purchased powders for encapsulation and tincture making. Old time collectors found new markets, with new collectors and growers springing up with small enterprises. Many focused on proper identification following basic taxonomic principles and employed organoleptic skills to evaluate quality. Tinctures made with fresh material appeared on the market, as did many other types of preparations, such as freeze-dried fresh herbs, salves, and liquid hydro-ethanolic macerates and percolates as both single herbs and extracts. A few US extraction houses opened or gained new life, including Madus a long time ASP sponsor, and a trade association, the American Herbal Products Association (AHPA) was born.

As the nascent US herbal industry grew, a few companies began to employ HPLC analysis for so called standardized extracts from Europe (actually registered phytomedicines), which were later copied by African, Indian and Chinese suppliers. Botanical microscopy is seeing a resurgence following FDA workshops on the topic. Few laboratories offered analytical testing for botanical raw materials in the early 1980s. Responding to an increasing demand, herbal testing was added to the repertoire of existing laboratories, and start ups specifically focused in this field opened their doors. The use of HPTLC grew as one equipment supplier developed and provided botanical methods to industry.

A host of agencies joined the movement, beginning with the USP returning to botanical monograph creation. The US government provided additional development through the Office of Dietary Supplements (ODS), which supported projects at the Association of Analytical Communities (AOAC) for analytical methods and the National Institute of Standards and Technology (NIST) for certified reference standards. Ascertaining botanical quality became a priority for government funded research, with the National Center for Complementary and Alternative Medicine (NCCAM) releasing guidelines to assure botanical integrity in clinical trial study materials.¹³ Industry released a standardized protocol for suppliers to provide dietary ingredient information,¹⁴ as the need for botanical specifications and identity testing becomes more acute, with dietary supplement specific GMPs coming into force. Educational organizations were founded and developed by traditional herbalists, including the American Herbal Pharmacopoeia (monographs, modern text on microscopy) and the American Botanical Council (HerbalGram, informational website).

Throughout these developments, the academic world of pharmacognosy that had not heard of “echinacea” in 1978 was mined by the herbal community for the tools and expertise that could be uncovered there. Whether or not classical pharmacognosy returns to colleges of pharmacy remains to be seen. What is certain is the opportunity and need for the growth of pharmacognosy within the herbal industry and the job opportunities for adequately trained individuals in the herbal industry.

Estimated herbal dietary supplement sales through all channels (based on surveys of manufacturers, distributors, and companies involved in sales through retail, network marketing, mail order, and internet, as well raw material and ingredient supply companies) were reported to have risen by 4.1% and 4.4% in 2006 and 2007, respectively, with total sales estimated as \$4.59 billion and \$4.791 billion, respectively.¹⁵ The top ten selling supplements in 2007 in order of decreasing sales were soy, cranberry, garlic, ginkgo, saw palmetto, echinacea, black cohosh, milk thistle, ginseng and St. John’s wort.¹⁵

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† Dedicated to Michael Roland Shaw Moore (1941-2009)

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- (13) <http://nccam.nih.gov/research/policies/bioactive.htm>; see also the NIH Office of Dietary Supplements in the US Government Section of Pharmacognosy in Action in this volume.
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