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Some Transpacific Thoughts on the Regulatory Need for Standardization of Herbal Medical Products

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ABSTRACT

The history and present status of herbal products/neutraceuticals in The United States is briefly reviewed. A case is presented for further, more comprehensive, regulatory oversight than is presently the circumstance under the DSHEA act.

Key words: herbals, DSHEA act, regulation

DISCLAIMER

The opinions expressed in this essay are those of the authors alone and do not necessarily represent the sanctioned official position of any governmental body, scientific society or firm.

Historical Background

Herbal medical products dominated medical practice in the United States and the rest of the world as recently as sixty years ago. Many of these products had been in use in one form or another from prehistoric times and physicians, pharmacists and patients once were quite familiar with them. Their use began to change slowly following the discovery that morphine could be isolated from gum opium and its use as a pure product reproduced many of the desirable pharmacological properties of the plant. Those properties had been known for thousands of years but this revealing discovery did not take place until the first decade of the 1800s. Following this, a succession of pure products from a variety of natural sources were gradually discovered. Medical practice increasingly consisted thereafter of the side by side prescription of both pure chemical entities and crude mixtures.

Some of the many recognized medications that have entered official medicine *via* this route are quinine, atropine, digitoxin, theophylline and penicillin. Many very useful synthetic medicinal agents have structures clearly inspired by these and other natural products and this remains a popular source of important medications to this day.

In addition to these materials, a large commerce existed in unofficial herbal remedies (so called "patent medicines") for which official recognition was denied. Medical use of patent medicines was largely unregulated in the United States until about 100 years ago and the field was characterized by high level and low level science side by side. Indeed, extravagant claims unbacked by reputable scientific studies were

sufficiently common as to color the whole field with a distasteful image which lingers. The industry failed to develop a consensus and regulate itself so that governmental intervention ultimately took place and the grosser abuses disappeared. Regulation required evidence for purity, identity and safety of patent medicines. No requirement exists relating to efficacy. It is important to resist the possibility of a return to the chaotic conditions of an earlier age in which assertion often took precedence over assurance.

The advent of synthetic organic medicinal agents into medicine in the form of single pure entities began only about 100 years ago with the introduction of aspirin and this was followed gradually by the appearance of local anesthetics, barbiturates, and so on. The ever increasing appearance of these synthetic products coupled with dramatic increases in the understanding and application of synthetic methodologies and pharmacology in the years following the Second World War led to a rapid eclipse in the use of crude plant products in favor of the use of single chemical constituents. Within a very few years the majority of herbal products saw very little use by official medicine. It is interesting to note in this context that the United States Pharmacopoeia of today has only about 60 botanical entries (2% of the total of about 2900 articles) whereas the first pharmacopoeia (of 1820) had 425 botanical entries (about 66% of the 633 articles). Among the reasons for this decline in official recognition was the comparative ease of acquisition, standardization and the detection of adulteration of synthetic agents as well as public faith in science and the quality of the new medications. Wherever possible use of bioassay-directed fractionation methodologies led to the discovery of the active constituent and this usually supplanted the use of the crude drug. Pharmaceutical practice rapidly changed from the preparation and dispensing of pills, fluid extracts, tinctures and elixirs to the counting, pouring, and labeling of products bought from pharmaceutical houses. A few botanicals managed to cross the gap and become recognized but most were left behind in the form of patent medicines.

Whereas the plants have undoubtedly elaborated medicinal agents for their own purposes and their structures may

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well have been perfected for this though the operation of evolutionary forces, it is not possible to believe that any energy was expended by the plants in ensuring that these agents would have properties optimal for their ultimate use in man. Some natural drugs, such as penicillin come amazingly close to our image of perfect drugs, but even here allergy, poor stability, difficulty in oral absorption and comparative narrowness of antimicrobial spectrum have resulted in molecular manipulation to solve many of these defects. Thus semisynthetic versions appeared at regular intervals and more than a dozen "unnatural" analogs find very widespread use today. These events, obviously, required the prior identification of the pure active constituent. These options for modification and perfection are generally not available for crude drugs which usually must be used as they are found. The widespread belief among the laity that plant products are intrinsically safe because they are "natural" is a fantasy. One need only think of strychnine and poison hemlock to dispel this notion. This is not to deny that many safe and useful preparations exist but rather to present a more realistic picture and to establish beyond a doubt that safety of herbals is a paramount requirement. A parallel, of course, exists when considering synthetic drugs. The cost of synthetic drugs, however, and continual press reports of significant side effects associated with some of them have contributed to a significant dampening of enthusiasm for them in many segments of the lay public. It is to this segment of society that herbal medicine has its greatest appeal. Perhaps some of this feeling represents cultural overload and a desire to return to a simpler life style.

Comparative Lack of Authoritative Information

Herbal medical products, having largely fallen out of medical favor in the late 1940s, were by and large de-listed from the official compendia and quickly dropped from the curricula of medical and pharmacy schools in the US⁽¹⁾. Indeed, pharmacognosy, the classical pharmacy discipline which dealt with herbals and their preparations, rapidly declined and began disappear from the offerings presented to undergraduate Pharmacy students. One of the important consequences of this was a concomitant neglect in research on these agents leading progressively to increasing ignorance about them. The decline of classical pharmacognosy was much less steep in many other countries because rejection of herbal products there was much less profound. Indeed, in many parts of the world medicine today embraces both single pure chemical entities and herbal medicine side by side and both receive official sanction. The choice between them is frequently made based upon experience, custom and belief as well as upon economic factors.

Herbal medicine is making a strong comeback in the United States. Students in both medical and pharmacy schools are all too keenly aware of their lack of background in this area and are petitioning for the reintroduction of authoritative information on herbal agents into the curricula⁽²⁾. Pharmacists and physicians are also attending continuing education programs in dramatically increasing numbers.

Of course self education is an option however there is an overwhelming mass of literature available, mostly written by advocates with various credentials, and almost every conceivable position is endorsed by someone. There is no wonder, then, that the health professional finds himself at a disadvantage and yearns for a critical analysis of the herbal literature by parties that they trust. The comparative lack of official sanction for these agents fails to provide this reliable crutch.

Almost half of the population now admits to purchasing one or another such product primarily without medical guidance or sanction. Their popularity and an increasing body of scientific data are producing an increasing degree of official acceptance for a number of these products⁽¹⁻⁹⁾. Students who have completed their academic training in the last four decades are, however, not well equipped to deal authoritatively with the questions dealing with these materials that are posed to them by the lay public. This is a dangerous void given that the public finds the pharmacist usually to be the most approachable health professional to whom to pose such questions. If the public cannot rely on governmental regulation or upon the advice of trained health care professionals then they are potentially at the mercy of the providers of these materials not all of whom can be expected to have the highest standards. Certainly they are bombarded by extensive advertisements about herbals.

One may well ask why are herbal products not regulated in the same manner as synthetic drugs? The usual answer is that the cost, even if it were technically possible to standardize all of these products, would be well beyond what the consumer would pay so the manufacturer could not recover the costs. The fact that at least in Germany this has been accomplished and accepted blunts this argument. Furthermore, there is still some argument among experts as to whether a single pure constituent would always faithfully reproduce all of the favorable aspects of the crude or semi-purified mixture from which they would be derived. There are a number of instances in which the pharmacological response obtained from an herbal is greater than what would be expected from the verifiable content of the putative active constituent. It is believed that this can be accounted for by synergy or at least additivity of constituents⁽³⁾. In Western medicine, this argument has largely been resolved by the thought that this does not happen all that often and that the other conveniences of working with single pure entities is justification enough.

The Western reader is reminded, however, that even among officially sanctioned medications there are instances where mixtures are officially approved and are still in use. Some of those which come readily to mind are pregnant equine mare urine preparations (a very widely prescribed estrogen), digitalis extract (a mixture of cardiotonic plant glycosides) and gentamicin (a mixture of closely related basic glycoside antibiotics produced from fermentation of a soil microorganism). Thus there are significant exceptions. The Eastern reader will accept the concept of using mixtures of substances more readily than the Westerner considering that Traditional Chinese Medicine (TCM) often utilizes

blends of different plants whose various constituents are intended to enhance the desired effect and nullify deleterious effects.

In many cases patent protection would be difficult or impossible to obtain for products that have so long been in the public domain. Thus exclusivity which would protect innovative firms from cost competition for a time is unlikely. Firms bearing the expense of leading the way by establishing and adhering to high analytical standards would be put in the unenviable position of effectually donating the research costs to the other manufacturers who could simply adopt the methods and place the findings in their advertising without sharing in any of the associated developmental costs. Complying with a mandated set of standards would prevent this from happening.

Present Usage

The usage of herbal products in the United States and in Europe is primarily for the management or prevention of chronic diseases (especially those associated with aging), to increasing cognitive efficiency, enhancing well being and in increasing longevity. These are complex conditions whose pathophysiology is still incompletely understood and for which the synthetic drugs presently available are rarely preventative or curative.

Commerce in herbal products is estimated to represent at present nearly four billion dollars in the United States and significantly more in Europe. Their use is increasing at an estimated 15-20% yearly. Interestingly, about three-quarters of the usage centers about only a few products (table), some of which are derived from TCM. Many kinds of vendors (principally pharmacies, health food stores, discount stores and supermarkets) deal in these substances and increasingly major ethical pharmaceutical firms now include these agents in their offerings. Legally, these products encompass enzymes, vitamins, minerals and hormones in addition to herbal products. This particular collection of agents represents a market segment primarily defined to encompass practice characteristic of the United States.

These products find use among about half of the U. S. population, approximately half of whom anecdotally report satisfaction with the outcome of their use and about half (not

necessarily the same half) report their use to their health care provider, many of whom are skeptical if not overtly hostile. Interestingly, about 15% mentioned the use of only some of them to their physician and 40% kept entirely quiet about them⁽⁸⁾. It is important that free discussion of herbals between health care providers and patients take place because an increasing literature describes significant interactions between certain botanicals and single chemical agents affecting the clinical outcome of therapy. For instance, a recent study in non-HIV infected humans demonstrated that administration of St. John's wort substantially reduced blood levels of subsequently administered indanavir (a potent HIV protease inhibitor)⁽¹⁾. This undesirable interaction is likely due to the wort's induction of P-450 isoenzyme 3A4, an agent which oxidatively transforms many drugs. Similar interactions with cyclosporin and warfarin are also known. Many other herbal-drug interactions have been tabulated⁽¹⁾.

Regulatory Stance

Today herbals fall under the coverage of the DSHEA act of 1994 (Dietary Supplement Health And Education Act: Public Law 103-417) which redefined dietary supplements to include them. This act specifically exempts tobacco but encompasses products intended to supplement the diet and specifically includes one or more vitamins, minerals, herbs or other botanical substances, amino acids, agents intended to increase or decrease dietary intake, or concentrates, metabolites, constituents, extracts or combinations of these. These are prepared in pill, capsule, tablet or liquid form for consumption by humans. They are not sold for use as a conventional food or as the sole item of a meal or diet. They should be labeled as dietary supplements and may include approved new drugs, certified antibiotics or licensed biologicals marketed as dietary supplements or foods before official approval, certification or licence.

The DSHEA act allows the package or advertisements to make claims as to physiological structure-function in humans but prohibits claims that they can be used to treat, diagnose, cure or prevent any disease. An example of an acceptable claim is that the product reduces cholesterol levels in the blood. This is an ascertainable property and, given the state of present medical beliefs, is widely believed to be beneficial to the cardiovascular system but a claim that this cures, treats, or prevents heart attacks or strokes would be forbidden. Structure-function claims are not required to first pass scrutiny by and gain the approval of the FDA. This last is to be indicated clearly on the label by the statement that "This statement has not been evaluated by the Food & Drug Administration and this product is not intended to diagnose, treat, cure, or prevent any disease". How much attention the lay public pays to such statements on packages and labels is unclear but this is clearly a useful caution for the wary.

The DSHEA act allows the producer to use third-party literature to inform the customer about the properties of the preparation provided that the statements are true and do not promote a specific brand or product to the exclusion of oth-

Table 1. The comparative frequency of purchase of various herbal preparations by US shoppers in 1999

Rank	Herbal	Percentage
1	Echinacea	38
2	Ginkgo	34
3	Garlic	31
4	Ginseng	29
5	St. John's Wort	27
6	Ginger	9
7	Kava-kava	8
8	Vitamins	5
9	Glucosamine	2
10	Saw Palmetto	2
(11)	Other Products	(20)

The numbers result from a survey of households⁽⁸⁾.

ers. Contemporary practice in many health care settings is to provide books and pamphlets dealing with herbal products but to place these materials nearby but not with the herbals themselves.

Products that can be shown to be unsafe or to represent a significant and unreasonable risk of injury to the customer are to be removed from the market by the Food and Drug Administration (USA).

The Need For More Challenging Regulations

The DSHEA act has had its intended dramatic encouraging effect on the herbal industry and the thriving business in them has increased much more rapidly than would have been the case if the act were not in existence. Regulation of nutraceuticals under the act is, however, much looser than regulation of chemical medicines.

We agree that the DSHEA regulations are useful and significantly clarify a previously much more muddy situation but we believe that adherence to these minimal standards is a mixed blessing. Whereas they do allow access to products that the public clearly wants, it permits by default a significant variation in quality and uniformity. The legal requirements, we believe, establish a scientific standard that is less than ideal from an ethical viewpoint. In our opinion, the key need for protection of the public and for the healthy growth of this industry is a requirement for clear clinical validation of the effectiveness of these agents coupled with sensitive chemical or biological assays that accurately reflect the content and intended use of the responsible agents⁽⁹⁾. Undoubtedly this will raise the cost of these materials measurably and thus undercut some of the reasons for which they exist but we feel that it will be worth it. Furthermore, we feel that a move in this direction is both timely and inevitable. It is better to establish such standards speedily and cool headedly rather than in the heated atmosphere generated in response to scandal or in response to instances of harm to patients that could be avoided with application of greater care and good science.

The fact that the scientific base upon which to establish such requirements does not exist as yet in all cases should not prevent the speedy adoption of standards for those where the science is presently adequate. This would lead to two classes of herbals. One would consist of herbals for which adequate science-based standards exist and the package and labeling should state that the contents have met them. This is a higher standard than that which presently exists. The second class would represent those agents for which such standards do not presently exist. Intensive research should be commissioned on the second group with the aim to elevate as many herbals as is justified into the first group when it is possible to do so.

The second group would remain as now or be demoted out of use if they are ultimately shown not to be worthy of use. The packages and the labels of the second group should clearly indicate that convincing evidence for the utility and identity of the responsible agent(s) in the contents is not yet available. The identity of the product itself and its purity

should, however, not be compromised. This plan is closely analogous to that in use in Germany in the form of the Commission E monographs so is not unrealistic or unattainable⁽⁶⁾.

These agents are not powerful medicines by and large so self selection and self dosing is generally believed to be comparatively safe. Given that the active constituent(s) are often unstandardized and, indeed, often unknown, safety is an important consideration.

The potency of different brands varies widely and may well vary widely from batch to batch. Adulteration may be hard to detect.

Almost every scientific issue ultimately becomes one of quantitation. There is a natural progression of knowledge from questions dealing with what these products do, how they do it, how much is needed to cause the effect, how much is safe, and what other things may be safely used at the same time. We suggest that it is time to force the pace of this progression.

The Difficulties

The reasons for present insufficient standardization are comparatively easily understood by scientists and businessmen but not necessarily by politicians or by the lay public. Among the reasons why such products are notoriously variable is the very fact that they are botanical substances present in complex mixtures of plant constituents. The content of active ingredients in such materials has been shown over and over again to fluctuate with the genetic heterogeneity of a plant species, differences in soil conditions, variations in the seasonal cycle, climatic influences, age of the plant, alterations in weather, sun and shade fluctuations, and the like. They also differ depending upon the time and manner of collection or harvest, the method of processing and storage, shelf life, interactions with other plant constituents following harvesting, whether contamination with other plant material or, in particular, microbes, has taken place, and so on. The reader will note that none of these confounding factors imply or represent corrupt practices. These are simply some of the factors that the industry must control in order to produce a reproducibly wholesome and helpful product. These factors can usually be controlled but the problem is exacerbated when the nature of the active ingredients is not clearly known. By comparison, precise standardization of synthetic drugs is almost child's play.

When preparations consist of blends of different herbs standardization, as a practical matter, should take place before blending.

The magnitude of some of these problems is lessened when the material is at least partially purified but one must know what to retain and what to discard during the purification. In these instances, resort to standardization based upon surrogate identity and processing markers is common but risky. The substance upon which the quality of the herbal is established may well in fact not be the active constituent or be only one of the contributing agents or even be without

medicinal value. Analyzing for surrogates is better than nothing but is not ideal.

As an example, our soon to be published work on echinacea convinces us that the active constituents are predominantly among the water soluble high molecular weight carbohydrates as asserted and demonstrated by Wagner⁽³⁾. Commercial preparations, however, are very often standardized based upon their content of low molecular weight solvent soluble polyunsaturated amides and ketones and other solvent soluble metabolites. In our hands, using flow cytometric techniques and vital stains for cytokine production, we find these solvent soluble metabolites to have at best only little immunostimulant activity and, indeed, a degree of toxicity to thymus and bone cells. One can perhaps justify the standardization against these materials as representing a surrogate assay demonstrating that the product indeed contains echinacea extract. However, an examination of the clinical studies performed in the last decade shows that the studies are divided about half and half between those able to show immunestimulation and protection against infection and those which failed to show this. In our hands, the active oligosaccharides are not soluble in alcohol. Those preparations that failed to reveal activity were usually alcoholic preparations. Those preparations that showed activity were usually either expressed juice products or aqueous extracts! This suggests to us that surrogate endpoints have comparatively poor utility from a regulatory standpoint.

Unfortunately their intrinsic complexity and medical hostility has led to a comparative neglect of modern research on herbal products and the all too often resultant substitution of reliance on junk science and anecdotal beliefs. Lack of legal requirements to do otherwise and of public understanding of the need for it makes it economically unrewarding to perform the necessary research to standardize properly and also to regulate properly. Those firms likely to perform the research would not likely be able to recover the investment without a public demand for quality assurance. Although a gratifying number of firms make a strong showing and would have nothing to fear from required standardization, at present the marketplace is dominated by price considerations and advertising assertions. This is not likely to change significantly without the application of external force. Gresham's law of economics suggests that the bad drive out the good. It is clearly in the public interest to avoid this at all costs.

Many manufacturers resist the notion of federal regulation under the belief that this will restrict their freedom to innovate. If the industry would get together and agree consensually to regulate these products along valid scientific lines this would be an entirely healthy development and greatly reduce the likelihood of governmental intervention. In the present environment this seems unlikely to happen.

In some cases only a presumption connects a specific ingredient with the purported use of the herbal. The analysis of ginseng is an example. Ginseng has a plethora of constituents with a variety of effects. Analysis is based about the dozen or so of panaxosides but many more, less abundant, saponin constituents are present. Sorting out which is associ-

ated with what is a major challenge and no single constituent is likely to reproduce substantially the use of the herb and its extracts.

In some cases, it is not clear that certain herbal products work at all, in part because suitable clinical studies have not been done, in part because their use by the public is not closely monitored and because a significant placebo effect is likely to be involved. Where the active constituents are unknown, historically standardization is based upon bioassay. Even here, however, there are vexing complexities. From a (bio)chemical standpoint, for example, what is memory? How would you measure compounds confidently that regulate it if we cannot define and measure it? What sort of animal model would reliably quantitate it? These sorts of problems have vexed workers trying to develop synthetic agents useful in treating Alzheimer's disease and progress has been comparatively slow. The problem is exacerbated when the product to be tested is a complex mixture.

Ginseng is an adaptogen meaning that it produces relief under conditions of stress. This is also hard to measure quantitatively. Lowering cholesterol, lowering blood glucose, or measuring comparative antioxidant power⁽¹⁰⁾ are comparatively simple problems compared to these.

Final Thoughts

Based upon these considerations, it is our thesis that the gap between the highly restricted regulations governing single chemical entity drugs and the comparative permissiveness of the DSHEA regulations needs to be narrowed but not done away with. Doing this is in the best interest of both the public, the medical establishment and the manufacturers themselves. Many vexing questions must find satisfactory answers for this to come about and these answers lie in the realm of good science. In those cases where the necessary science is unavailable today intensive research should be undertaken to remedy this.

We believe that these products should be regulated but in an objective manner using the best of presently available scientific techniques. The magnitude of the task is hinted at in the above discussion. The prospect of hostile regulation intended to inhibit the use of these products by a public that has faith in them should be guarded against. Discouraging scientific exploration of these products is also acting against the public interest. The difficulty of the task should not deter us in starting. To do otherwise would retard the proper development of the field and leave the public insufficiently protected.

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美國草藥製劑標準化管理的需求

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摘 要

本篇簡略回顧美國中草藥製品的現況及其歷史。並針對營養品健康及教育法 (DSHEA) 103-417 條規定內容，提出一種更深入、更廣泛的管理監督。

關鍵詞：草藥，醫藥品健康及教育法，管理