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Sep 29, 2000

**Dockets Management Branch (HFA-305),  
Food and Drug Administration,  
5630 Fishers Lane, rm.1061,  
Rockville, MD 20852**

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**Subject: Comments on Guidance for Industry Botanical Drug Products  
Docket NO. 00D-1392**

SEP 29 19 55

Dear Sir,

After reading *Guidance for Industry Botanical Drug Products* distributed for comments, we hereby elucidate our points of view as follows:

- **Integrative Medicine [1] is a direction of medicine in the future, and eventually it will become the Unified Medicine[2][3].**

"As we approach the twenty-first century, medicine finds itself in great trouble. An economic crisis of unprecedented proportions has engulfed healthcare institutions. ... conventional medicine has become too expensive. ... By rolling back infectious disease, the major killer in the early twentieth century, it left us to deal with chronic degenerative illness, a much more stubborn and costly problem. ... Another reason for the expense of conventional medicine is its extreme dependence on technology" [1].

Although "the three-stage, randomized, controlled clinical trial remains the most reliable way to judge the efficacy and safety of new drugs and medical devices, ...the necessary trials may require more than a decade to complete and cost hundreds of millions of dollars. ...Trials that fail to show that a treatment works outnumber substantially those that prove that one does work, but both can cost the same"[4].

"And money — who pays for the research and who takes home the profits — looms over every clinical trial. For many years, the pharmaceutical companies have done most of the work of clinical trials themselves. As a result, no one should be surprised that drug companies want to recover their costs as expeditiously as possible" [4]. But "diminishing returns are the norm in the clinical trial process. Only about 20

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percent of Investigational New Drug (IND) applications filed with the FDA make it to the final step, many years and many tests later; approval of a New Drug Application (NDA), which clears a treatment for marketing to the public" [4]. This may be one of the reasons of the economic crisis.

"Consumers are very clear about their desires for natural, complementary, and alternative therapies. ... It should be obvious by now that this is not a passing fad but rather a worldwide sociocultural trend with deep roots and great economic significance. Surveys consistently show that close to 40% of US citizens are now using alternative medicine of one sort or another" [1].

"Alternative medicine is a rich mixture of wisdom and folly. ... But many conventional practices are also unproven and not a few dangerous as well as ineffective and costly. The challenge is to sort through all the evidence about all healing systems and try to extract those ideas and practices that are useful, safe and cost-effective" [1]. Then "we must try to merge them into a new, comprehensive system of practice — integrative medicine that has an evidence base and also address consumer demands"[1]. We believe that this new system will eventually become a Unified Medicine.

"Congress of US has now mandated the teaching of integrative medicine. ... Like it or not, these changes are coming to medicine, forced by economic necessity and consumer demand. ... Designing a new kind of medical education for a new millennium is an urgent priority" [1].

### ● Beyond reductionism

"Although reductionism has been the key to gaining useful information since the dawn of Western science and is deeply embedded in our culture as scientists and beyond, shortfalls in it are increasingly apparent. ... Mostly these arise from information overload. ... Another problem is oversimplification"[5]. "So perhaps there is something to be gained from supplementing the predominately reductionist approach with an integrative agenda. ... No longer content to inventory cells' molecular parts, biologists are teaming up with physicists and engineers to study how all the different cellular players work together in complex tasks" [6].

A study on retinoic acid receptors (RARs) indicates that downregulation of RAR  $\alpha$  in mice by antisense transgene leads to a compensatory increase in RAR  $\beta$  and RAR  $\gamma$  and development of lymphoma. Coarse fur, male sterility, and low body weight are other abnormalities observed in these mice. Thus, "it supports the hypothesis that a balance among the RARs is necessary for appropriate response to various homeostatic needs" [7]. This is only one of the evidences that understanding how part of a biological system interact is just as important as understanding the parts themselves.

Botanical drug products, especially the multi-herb, are usually prepared as complex mixtures. Their chemical constituents are not always well defined. In many cases, even the active constituent in a botanical drug is not identified, nor its biological activity well characterized. But as a whole, some of them really take effect on curing, mitigating, treating or preventing diseases, particularly some chronic degenerative diseases, or improving subhealth state and enhancing the quality of life.

For instance, water-soluble ingredients of the herbal decoction sho-saiko-to inhibited the proliferation of a human hepatocellular carcinoma cell line (KIM-1) and a cholangiocarcinoma cell line (KMC-1) more strongly than did each of its major ingredients, *i.e.* saikosaponin a, c and d, ginsenoside Rb<sub>1</sub> and Rg<sub>1</sub>, glycyrrhizin, baicalin, baicalein, and wogonin. "Because such ingredients are barely soluble in water, there could be synergistic or additive effects of the ingredients in sho-saiko-to" [8].

To sum up, more resources should be devoted to evaluating the safety and effectiveness of the entire final botanical product, which contain the interaction of different parts of constituents, rather than the attribute of a single constituent of the botanical product.

#### ● The Optimization of Pharmacotherapy for Individual Patients

"There are very large differences among individuals in how they dispose of and react to a particular medication, *i.e.* in pharmacokinetics and pharmacodynamics" [9].

Single nucleotide polymorphisms, or SNPs, the most significant outcome of the Human Genome Project (HGP), are the most common type of polymorphisms; they can have significant effects on both susceptibility to diseases and drug responses. "Because of these tiny genetic variations, many drugs work only on 30~50 percent of the human population. In extreme cases, a drug that saves one person may poison another"[10]. As a result, the biotechnology and pharmaceutical industries have recently focused attention on the discovery of SNPs. The emerging ability to correlate drug responses with SNPs promises to enable doctors to prescribe appropriate drugs to patients with the goal of maximizing drug response and minimizing side effects [11].

An era in which drug therapy can be safer, more effective and better understood by applying the power of SNPs analysis and its role in disease and drug response is now approaching. The growing ability to identify and profile SNPs will enable pharmacogenomics to become an increasingly powerful tool in drug discovery and in clinical practice. A test that could distinguish poor responders from good responders to drugs in which more than one therapeutic alternative exists could significantly reduce health care costs. And pharmacogenomics may allow pharmaceutical components to include a genetic component in the design of clinical trials so that the

candidate drug is targeted to individuals with a specific genotype, and thereby improving results and reducing the costs of clinical trials.

And another new approach, called "toxicogenomics" is also going on, "which pharmaceutical industries are among the most enthusiastic about the vision in finding ways to speed the process of toxicological testing to keep pace with new R&D techniques" [12].

Now many companies "hope to cash in on pharmacogenomics" [10]. Although "personalized medicine is still on the lab bench, but some business analysts say it could become an \$800-million market by 2005"[10].

Given the latest development of pharmacogenomics, toxicogenomics and the trend of individualized or personalized medicine, the choice would be absolute between taking advantage of the achievements of modern science to optimize the usage of botanical drug product and excluding it merely because of deriving from different culture.

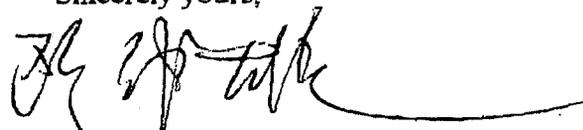
● **Our Target and Suggestion**

According to current research, development and application of botanical products, especially Chinese medicine, we are proposing the launch of some botanical drugs marketed under an OTC monograph. We are also planning to carry out randomized and controlled clinical trials of some botanical drug products by computerized systems to prove their safety and effectiveness with self-selection criteria. Relevant protocols will be sent to you soon.

Based on our points of view mentioned above, there is some suggestion on *Guidance for Industry Botanical Drug Products*. Details are to be found in the attached file.

Thank you for your kind consideration.

Sincerely yours,



William Au  
President,  
GIBI

Encl. 1. Comments on Guidance for Industry  
Botanical Drug Products  
2. Reference



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**Comments**  
**on**  
**Guidance for Industry**  
**Botanical Drug Products**

**Docket NO. 00D-1392**

**September 2000**

## **I. About fermentation products**

On page 2, line 4, "It does not include fermentation products ---". Fermentation is one of the methods for preparation of Chinese herbs in common use, just like preparation with water *et al*, which could enhance curative effect, reduce toxic effect, change properties of herbs and expand their uses. For example, *Prepared Soybean* is fermented by steaming *Glycine max (L.) Merr.*. We hold that fermentation products should be included in botanical products.

## **II. About safety and effectiveness**

Safety and effectiveness are always the two focuses on new drugs, including botanical drug products and synthetic or highly purified drugs. And in *Guidance for Industry Botanical drug product*, safety and effectiveness of botanical products are mentioned for many times, *e.g. Sec.III.C. CMC and Toxicology Information to Support Initial Studies, Sec.VI.A. IND Information for Different Categories of Botanicals, Sec.VI.B.7. Pharmacological and Toxicological Information, Sec.VII.E. Clinical Considerations, et al.*

### **1. Two major differences between botanical drug products and synthetic or highly purified drugs.**

#### **a. Botanical drug products have abundant human use experience.**

Botanical drug products, especially Traditional Chinese Herbs have been used by human for thousands of years, their safety and effectiveness are proved directly in human rather than in mice. "Humans are not simply large mice" [13]. Can anything else be more convincing than human use experience for thousands of years? We suggest that the long history of human use should deserve more substantial consideration.

#### **b. Botanical drugs are usually prepared as complex mixtures.**

In *Sec.III.B.CMC Information for Botanical Drug Products*, the guidance indicates that, "Their chemical constituents are not always well defined. In many cases, even the active constituent in a botanical drug is not identified, nor is its biological activity well characterized." So we should not determine the safety and effectiveness of the botanical drugs as we do on synthetic or highly purified drugs. There may be synergistic action to enhance curative effect and inhibitory action to reduce toxic effect among different components in one of the botanical drug, especially a multi-herb one.

In *Sec. III.D. Applicability of Combination Drug Regulation*, the guidance indicates, "botanical drugs composed of multiple parts of a single plant species, or of parts from different plant species, currently are subject to the combination drug requirements, which should demonstrate that each component or active ingredient makes a contribution to claimed effects. However, FDA intends to propose revisions to its regulations to allow for the exemption of such botanical drugs from application of the combination drug requirements under certain circumstances."

And in *Sec. VI.B. Basic Format for INDs* (on page 8, line 9), "A sponsor need not differentiate the clinical effects of each molecular entity in a botanical product derived from a single part of a plant. Even where the components of a combination product must be studied, initial controlled studies could be used to evaluate the entire combination product."

So it is ambiguous between determination of the effect of each component and evaluation of the entire combination product. We suggest that we should lay stress on the safety and effectiveness of the entire combination product while being conscious of the interaction among the components.

**2. Individualized or personalized therapy — the common trend in use about both botanical drug products and synthetic or highly purified drugs.**

On page 8, paragraph 7, "For botanical as well as for synthetic or highly purified drugs, absolute safety does not exist for any therapeutic intervention ..."

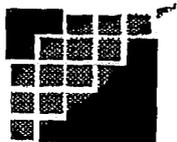
And one of the good annotations is --"There are very large differences among individuals in how they dispose of and react to a particular medication, i.e. in pharmacokinetics and pharmacodynamics." [9] It is also one of the reasons for the trend of developing individualized or personalized medicine.

By the research of pharmacogenomics and toxicogenomics, we understand that safety and effectiveness of drug depend on the genotype of the individual. The development of technology in SNPs assay in current genotype and phenotype will make it possible to conduct individualized or personalized therapy, which is safer and more effective.

Consequently, individualized or personalized therapy should be taken into substantial consideration in evaluating the safety and effectiveness of botanical drugs, especially Traditional Chinese Herbs.

## Reference

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<b>DATE:</b> September 29, 2000	<b>TOTAL NO. OF PAGES(INCL.COVER):</b> 9
<b>FROM:</b> Hong Zhao, Ph.D.	<b>SUBJECT:</b> Docket NO. 00D-1392

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