DALMIA CENTER FOR RESEARCH & DEVELOPMENT

FORMERLY **DALMIA CENTER FOR BIOTECHNOLOGY**

Registered under the Societies Registration Act
(Recognized by Department of Scientific & Industrial Research, Government of India)

DCRD/DRD/FDA/411/01 May 24, 2001

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

Kind Attention of Yuan-Yuan Chiu, 301-827-5918

Sir / Madam

We are here with enclosing our comments and suggestions in connection with the draft guidance for industry circulated by the Food and Drug Administration for Botanical Drug Products.

Thanking you

Yours truly,
For Dalmia Center for Research & Development

Dr. P. M. Murali
Director R & D

Encl: As above

00D-1392 C28

9/369, Siruvani Main Road, Kalampalayam, Coimbatore - 641 010. India.
Tel : + 91 - 422 - 807987 • **Fax :** + 91 - 422 - 807688
E.Mail : dalmiabiotechnology@vsnl.com • dalmiabiotechnology@usa.net
Website : http:\\www.dalmiaindia.com

Background

The objective of circulating this note is in response to the Guidelines of August 2000 by the U. S. Department of Health and Human Services, the Food and Drug Administration and the Center for Drug Evaluation and Research in which the broad principles that are likely to be followed in the future on Botanical Drug Products is outlined and suggestions solicited from the Industry and Public.

A similar document has also been prepared by the European Agency for the Evaluation of Medicinal Products through its Committee for Proprietary Medicinal Products who have also come up with a detailed Guidance on specifications for Test procedures and acceptance criteria for Herbal Drugs, Herbal Drug Preparations and Herbal Medicinal Products as of November, 2000.

About our Institution

Dalmia Center For Research and Development is an organization that has been actively working in the area of Medicinal Plants for more than a decade. The organization is a recognized scientific institution of the Government of India's Department of Science and Industrial Research (DSIR) and the Indian Systems of Medicine and Homeopathy (ISM&H) of the Ministry of Health. Several formulations with herbs for a variety of diseases are systematically studied under stringent self-regulated guidelines followed by clinical trials on human subjects with the approval of an ethical committee. All trials are monitored by a team of Physicians and specialists from modern medicine and recognized degree holders from the complimentary system of medicine.

Highlights of the FDA document

The United States Document has issued these guidelines to be followed before marketing, defining clearly when a Botanical Drug may be marketed over the counter (OTC) and the FDA approvals that are required in the case of a new drug application (NDA). In addition the document provides guidance on submitting investigational new drug applications (IND). The guidance also recognizes the need for reduced documentation of pre-clinical safety and of Chemistry and manufacturing controls (CMC) to IND for initial clinical studies of botanicals that have been legally marketed in the United States as dietary supplements or cosmetics without any safety concern.

The document further recognizes the basic fact that Botanicals are unique in nature and regulatory policies to be applied to this class would have to different from those applied to synthetic, semi synthetic or highly purified or chemically modified drugs.

Our Suggestions

Nearly all cultures, both ancient and recent have used plants as a source of medicine. After a period of disregard and decline, these traditional systems of Green Medicine are once again back to the center-stage of our health care programmes. There has been a steady increase in demand for such medicine. The bane of these systems of medicine in gaining respectability among the scientific community, the world over has been due to the long-standing problem of accurate determination of drug sources through accurate scientific identification of plants, adequate quality control measures during manufacture and the lack of highly controlled clinical trials to substantiate the claims.

The sudden need for alternative medicines have come up largely due to the excess focus and obsession of the modern medicine towards curative or system-regulating medicines. This approach has been dubbed *reductive and never holistic* by practitioners of Complimentary medicine. However the second approach paves way to a lot of lackadaisical approaches, which lacks specifics. The present set of guidelines will certainly eliminate most of these non-conforming standards to bring about more uniformity.

The guidelines are elaborate and has recognized the major areas of lacunae and the strengths of using plant materials as a source of drug. We wish to comment in the following three areas, which are the most critical segments in herbal research.

- ***Foreign Marketing Data***

Several Ayurvedic, Siddha and Unani drugs have been marketed for centuries in India. The drugs are also dispensed to the patients by recognized and qualified physicians of the complimentary systems. Most of these drugs have been found to be safe. It may be worthwhile for the FDA to accord adequate weightage to the data already available in these countries in determining whether a "drug has been used under particular conditions to a material extent and for a material time" to qualify for inclusion in an OTC drug monograph. Since the FDA is proposing to make it available the facility for OTC marketing agencies in the United States, who are already marketing their products, the same exemptions can be made available to overseas marketing firms who have safely marketed their products in their respective countries.

- ***Chemistry, Manufacturing Controls (CMC) information for the botanical drug products***

Botanical drugs are derived from vegetable matter and are usually complex mixtures. The chemical constituents of such a mixture are not always defined and in most cases even the active constituent in a botanical drug is not defined nor its biological activity well characterized.

It may be worthwhile to note that some of the Siddha formulations have more than 20-30 herbs, which are mixed to together. Some of these formulations may be achieving synergy *(Synergy as defined by The Concise Oxford Dictionary 1990 - combined effect, that exceeds the sum of their individual effects, that co-operates with another or others)* or other positive effects whose mechanism are yet to be understood. Such studies could take several years to arrive at logical conclusions. As long as the pros and cons are weighed and if the beneficial effects out-weigh other considerations, the FDA should probably allow these drugs to be marketed after completing the routine requirements. On the contrary, if the FDA expects considerable data to fulfill the information requirements of an application, then such complex beneficial mixtures may never be able to enter the market in the years to come. This organization is using certain Siddha formulations for the combat of HIV (AIDS), which has around 30 herbs. While it is possible to have basic CMC information generated and followed, it would be virtually a very difficult task to provide data to the FDA similar to synthetic or modern drugs on 30 herbs.

Therefore the CMC documentation would have to be substantially liberal in comparison to that of synthetic or highly purified drugs. Simple or combination tests like spectroscopic, chromatographic, fingerprints, chemical and or biological assays can be the main reliability

criteria to understand the product. While these tests may not generate the necessary specifics that are desirable, it can atleast bring about a rational approach to Quality Control.

- ***Applicability of Combination Drug Regulations***

It would be practical not to confine the botanical drug products that are derived from a single part of a plant such as leaves, stems, roots seeds under the fixed combination drug category.

The current requirement of Botanical drugs composed of multiple parts of a single plant species under the combination requirement should also be revised and exemption accorded.

- ***Studies on bioavailability and drug interactions.***

Bioavailability and Pharmacokinetic studies are cumbersome and extremely difficult to generate in complex formulations where a number of herbs are involved. It would be desirable to have a very practical view in this area. Well-controlled clinical trials can substitute the bioavailability and Pharmacokinetic studies.

Ayurvedic and Siddha pharmacopoeia are full of formulations which have a combination of several herbs and most of them can never be launched in the next decade or two if requirements are not simplified by the FDA.

In the holistic approach, these herbs needs not always have to contribute to the alleviation of the disease directly, but could bring about healthy changes in the human being to boost his defenses in combating the disease. Thus even if attempts are made to elucidate the mechanism of each of the herbs in alleviating the disease, it is amply clear that some of them may not be contributing to cure of the disease directly. This means, that its presence in the drug formulation may never be understood. If the formulation passes the basic criteria in say animals or has been very extensively used on a population without any adverse effects, then the formulation should be considered safe and marketable if it is efficacious.

- ***Natural Vs Cultivable source of Plants.***

In a country like India where the source of raw materials for Drug preparations is predominantly from the forests (80%) a practical solution has to be found in connection with the source of the raw material for quality enforcements. When a medicinal plant is cultivated a lot of the Quality aspects are directly under the control of the grower. However, when the plant material is collected from the forests, it would be reasonable to presume that the origin of the source is from nature and variations if any would be natural. The document should highlight separate guidelines for natural and cultivable sources for manufacturers using plants from the above two sources.

Conclusions:

Stringent guidelines are necessary in this sector. However, the objective should be to minimize quality variation. It is however not possible to have an absolute procedure when it comes to using plants from natural sources.

Presently, the holistic approach is gaining tremendous support and hence it may be useful to initially allow the science to first get a food hold and flourish before enforcing the complete set of guidelines. As these guidelines get more difficult, several organizations may be discouraged in introducing tried and tested formulations at the risk of incurring enormous costs which may go into data generation.

Already there is a view prevailing that one science (Complementary Medicine) should not be judged through another (modern allopathic concepts). Even though this may be quite true as both systems namely modern medicine and complimentary medicine perpetuate radical differences in approaches, the underlying uniqueness in both the systems is the enormous efforts directed at the patient's well being and quality of life after using the drug. While purists of the modern science would like a very clear cut- definitions on quality of life with proof, the traditionalist acknowledge the role of the mind in the patient well being as well. After all if this was not the case, placebo controlled studies would have been irrelevant. It is therefore recommended that when allowing the entry of a new system of medicine, the initial attempt should be to allow the science to grow and not burden it with innumerable strictures which will make it extremely tedious cumbersome for its introduction.

References

1. Edward F. Tarabilda. 1998. Ayurveda Revolutionized: Integrating Ancient and Modern Ayurveda. Motilal Banarsidass Publishers Private Limited, Delhi.

2. Sharadini Dahanukar, Urmila Thatte. 1996. Ayurveda Unravelled: National Book Trust, New Delhi.

3. Shivarajan,V.V., Indra Balachandran. 1996. Ayurvedic drugs and their plant sources: Oxford & IBH Publishing Co. Pvt. Ltd., New Delhi.

4. The concise Oxford Dictionary. 1992. Oxford University Press, New Delhi.

5. Angela Hope-Murray, Tony Pickup. 1997. Healing with Ayurveda: Jaico Publishing House, Mumbai.

6. Judith Hoad. 1997. Healing with Herbs: Jaico Publishing House, Mumbai.

7. Mark Evans. 1994. A guide to Herbal Remedies: Orient Paperbacks, Delhi.

8. Bakhru,H.K. 1992. Herbs that heal: Natural Remedies for good Health. Orient Paperbacks, Delhi.

9. Ram Manohar, P. 1994. Nomenclature and Taxonomy in Vrkshayurveda: Lok Swasthya Parampara Swamvardhan Samithi.

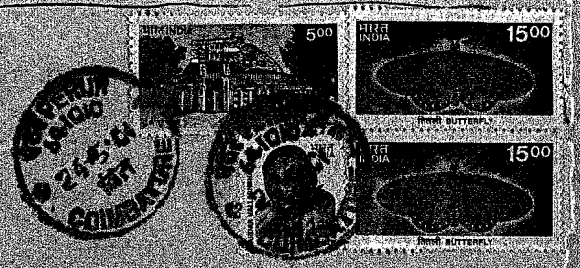
10. Vijayalakshmi, K., K. M. Shyam Sundar. 1993. Vrkshayurveda an Introduction to Indian Plant Science: Lok Swasthya Parampara Swamvardhan Samithi.

11. Abdul Kareem, M. 1997. Plants in Ayurveda: A compendium of Botanical and Sanskrit names. Foundation for Revitalisation of Local Health Traditions.

12. Ethical Guidelines for Biomedical Research on Human Subjects. 2000. Indian council of medical research, New Delhi.

BY AIR MAIL

KIND ATTN: MR. YUAN-YUAN CHIU, 301-827-5113



TO

DOCKETS MANAGEMENT BRANCH (HFA-305)
FOOD AND DRUG ADMINISTRATION
5630 FISHERS LANE, RM. 1061
ROCKVILLE, MD 20852
U.S.

DALMIA CENTER FOR RESEARCH & DEVELOPMENT
9/83-C, SIRUVANI MAIN ROAD
KALAMPALAYAM, COIMBATORE-641 010.
TEL: 0422-807987 FAX: 91-422-807688