CHAPTER 9 REGULATORY AND SAFETY CRITERIA FOR FUNCTIONAL FOODS AND DIETARY SUPPLEMENTS AND PHARMACEUTICAL MEDICINES; THE ROLE FOR MEDICINAL MUSHROOMS

Synopsis

The regulatory and safety aspects of dietary supplements in general are reviewed with reference to European, USA and Japanese laws. Herbal extracts are given special consideration and consumer product information should give special mention of active ingredients, dosage, mode of administration etc.
Dietary supplements from medicinal mushrooms are analysed in detail and current approaches to safety are examined. A central feature of the purported medicinal or chemo-preventive role of mushroom extracts must be the undoubted synergistic interaction of the many constituents.

For time immemorial mankind has used traditional medicines for human healthcare with terrestrial plants occupying a significant therapeutic role (Pezzuto, 1997). Recently, the World Health Organisation has estimated that approximately 80% of the world's inhabitants still depend on traditional (mostly herbal but also including fungal) medicines for primary health purposes (Cragg and Newman, 2001), while plant-derived pharmaceutical products play an important role with the remaining 20% of the world's population in developed countries. At least 120 important drugs are obtained from plants (Farnsworth, 1988).

Many of the now clinically useful anticancer drugs are either natural plant products or derivatives of natural products, e.g. paclitaxel (Taxol®) from *Taxus brevifolia* L. and vincristine (Oncovin®) from *Cantharanthus roseus* G.Don. (Pezzuto, 1997). Plants continue to offer a wide range of compounds with diverse structures and activities which will continue to occupy an important role in modern cancer therapy, especially within the sphere of chemotherapy.

In a previous Chapter, the role of certain complex polysaccharides derived from various mushroom species has been examined with respect to their anticancer activities. Their mode of action is likely to be through stimulating the human immune system to attack the cancer cells, though there is some evidence that they can, in some cases, also act directly on the cancer cells. In contrast to the above-mentioned plant-derived anticancer compounds the mushroom compounds are extremely complex structurally and will seldom be completely chemically pure.

While the mushroom-derived polysaccharide anticancer compounds will be used at various levels of purity in clinical applications as adjuncts to existing chemotherapeutic compounds, yet another important role could be as functional foods either consumed whole, or as concentrated extracts, as dietary supplements. In this way they may have a role in disease prevention or cancer chemoprevention. As previously noted, certain Japanese growers of medicinal mushrooms who have been regular consumers of their produce, show a lower cancer incidence when compared with the national incidence of cancer. As stated by Pezzuto (1997) “In general terms, cancer chemoprevention may be considered as the prevention of cancer in human populations by ingestion of chemical agents that prevent carcinogenesis. It is important to differentiate the concept of cancer chemoprevention from primary cancer prevention, such as the cessation of cigarette smoking and cancer chemotherapy, the therapy used after the diagnosis of cancer”.

In most Western countries, cancer incidence increases gradually after the age of 30 and is greatest for the age group between 70 and 80. It is now well-recognised that the occurrence of cancer is strongly associated with ageing or the elongated lifespan of humans, and that a preneoplastic condition could often have already started in the cells many years earlier. Consequently, an important strategy for

preventing certain cancers could be to inhibit the development of the first clonal expansions and delay the clinical onset of tumour development (Muto *et al*., 1989).

Evidence is accumulating from human epidemiological studies and animal studies that dietary factors may reduce the incidence of some cancers, possibly by, as yet unknown, chemopreventive mechanisms (Hirayama, 1979; Boone *et al*., 1990; Havas *et al*., 1994; Zhang *et al*., 1994). There is an increasing number of compounds that may be viewed as chemopreventive and have been categorised as intentional food additives, non-nutrient food molecules, micronutrients, industrial reagents, hormones and antihormones, and pharmaceutical agents (Costa *et al*., 1990).

Before concentrating on the regulatory and safety aspects of putative chemopreventive mushroom products some important guidelines on herbal products and dietary supplements, in general, will be examined (Kingston, 2001, Wasser *et al*., 2000a,b).

Regulatory Environment for Dietary Supplements

While pharmaceutical products must have undergone clinical trials to demonstrate safety and efficacy prior to marketing, no such requirements are demanded of herbal products. This situation can be traced back to the 16th Century when Henry VIII passed laws controlling the possession of poisons but giving exemption to herbalists and their suppliers. Section 12 of the Medicines Act 1968 excludes herbal medicines from the normal regulatory process if not processed (other than crushing and/or drying), are not sold under a brand name, and no specific disease reduction or claims are made on their behalf. In this way these products do not require expensive clinical trials and since unprocessed herbal

products cannot be patented there can be little financial attraction for manufacturers to run their products through the medicine registration process.

WHO (1991) published a seminal report “Guidelines for the Assessment of Herbal Medicines” which set out “to define basic criteria for the evaluation of quality, safety and efficacy” of all herbal (including mushrooms) medicines. “As a general rule in this assessment, traditional experience means that long-term use as well as the medical, historical and ethnological background of those products shall be taken into account.” Depending on each country’s situation, “the definition of long-term use may vary, but would be at least several decades … Prolonged and apparently uneventful use of a substance usually offers testimony of its safety”. The Guidelines call for various assessments of quality, efficacy and the intended use, and reference should be made to pharmacopoeia monographs where they exist. If none exist, then the manufacturer should be required to produce a similar statement. Procedures should all correspond to Good Manufacturing Practices and include stability testing of the final product as packaged. With regard to safety “A guiding principle should be that if the product has been traditionally used without demonstrated harm, no specific restrictive regulatory action should be undertaken unless new evidence demands a revised risk-benefit assessment” (Alkerele, 1992). It is recommended that consumer product information should include a quantitative list of active ingredients, dosage, dosage form, indications, mode of administration, duration of use, any major adverse effects, contraindications, warnings, etc. (Wasser *et al*., 2000a).

The European Situation

On a European level EC Directive 65/65/EEC defines “any substance or combination of substances presented for treating or preventing disease … or which

may be administered with a view to making a medical diagnosis or to restoring, correcting or modifying physiological function" as a medical product requiring a license or marketing authorisation. Notwithstanding, in the case of herbal products, the distinction between medicine and non-medical products such as foods and cosmetics, is increasingly blurred with concomitant confusion across the EU.

Current EU regulations make few provisions for dietary supplements (DS), and are more concerned with the protection of consumers from unsafe products. DS that seek acceptance under current dietetic regulations must produce evidence to inspecting authorities that supports the statements claiming those special properties of the food that guarantee it to fulfil the purpose which, on the basis of the claim, the purchases will expect to fulfil. Medical claims, both explicit or implied, are subject to additional regulations and these products must hold a medical license (Ehrnreich, 2000).

The EU Novel Food Regulations will bring even more complexity as novel foods include food types or ingredients that have not been previously used for human consumption. Furthermore, for the near future, new functional food products must be submitted to each member state for consideration. However, it is anticipated that a new food authority will be set up with greater harmonisation potential, but for the present time, the overall thrust with novel foods is towards safety (Smith and Rowan, 2000).

The Working Party of the Pharmaceutical Committee of the European Commission has proposed a draft Directive on the regulation of herbal "medicines". These proposals would permit herbal medicines to be granted a license if the product, or a product with the same ingredient, dosage and oral route of administration, has been in "traditional use" over a period of 30 years for a particular

indication. Manufacturers would also be required to provide a bibliographic review of safety data and an expert report on those data. A significant aspect of this document would be to improve the current inadequate quality control in herbal products. Currently, herbal products are immensely variable in composition and the user has no reliable means of knowing exactly what they are consuming. Such products could well be contaminated with other organics (possibly toxic) as well as microbial presence and toxic metals (Kingston, 2001). Dosages are also problematic with identical remedies and may actually contain very different amounts of active ingredients. Furthermore, most often the amount of the active ingredient is not shown on the label. Indeed, it is often the case that the pharmacological active substance or substances have not been properly identified. The benefit from the herbal product may well rely on synergism between several ingredients.

As a consequence of the current lack of regulatory requirements reliable safety and efficacy data on herbal medicines is not easily available. Attempts at clinical trials for several plant-derived products have mostly been badly designed or the results poorly interpreted. Products were mainly not standardised, with different methods of preparation and administration which could lead to variation in the amounts of active principles reaching the patient (Kingston, 2001). Professor Ernst, the holder of the only Chair of Complementary Medicine in the UK at Exeter University, is planning to conduct objective evidence-based research to provide reliable data involving randomised controlled trials (RCTs). In these trials the herbal product is compared either with a placebo or an alternative drug on patients who do not know what treatment they are receiving. He has completed a number of these “meta-analyses” on several herbal remedies with some showing little or no efficacy but others showing some considerable promise (for references, see Kingston, 2001).

While there is some very supportive evidence of medical benefits with St John's wort preparations, patients currently taking other drugs should exert caution since complications can occur. This product has been shown to stimulate cytochrome P_{450} enzymes in the liver of some patients causing breakdown of other drugs.

The House of Lords Report on Complimentary and Alternative Medicine (2000) examined many aspects and issues including: evidence of efficacy; information available for both patients and doctors; training of CAM practitioners; regulations and risks; and possible provision of CAM on the National Health Service. With the aim of generating reliable data for regulation, it is planned "to attempt to build up an evidence base with the same rigor as is required of conventional medicine" by means of RCTs. Three central questions must be answered:

1. Does the treatment offer therapeutic benefits over placebos?
2. Is it safe?
3. How does it compare in terms of medical outcome and cost-effectiveness with other treatments.

Of the many areas of consultation by the Committee the views expressed by the group, Patient Concern, were thought-provoking, viz. that treatment with unproven therapies is not wrong if the patient is happy with the treatment, knows that it is unproven and has not been led to believe that it will definitely work! However, the report does stress that such products could be dangerous if they were relied upon to treat life-threatening diseases at the expense of other drugs.

Germany is by far the leading country in Europe for the consumption of herbal products. The German Commission E is an independent division of the German Federal Health Agency (Bundesgesund Leitsamt) which collects information on herbal medicines and evaluates them in relation to safety and efficacy.

Subsequently, they are published as brief monographs approving or disapproving the over-the-counter sale or use (Blumental, 1999). These monographs are believed to represent the most accurate information available worldwide on the safety and efficacy of herbs and phytomedicines (Tyler, 1998). These evaluations on efficacy are based on a doctrine of reasonable certainty which contrasts with the American FDA's insistence on a "doctrine of absolute proof". The FDA relies on information passively submitted to it from drug manufacturers!

The German Commission involves physicians, pharmacists, pharmacologists, toxicologists, representatives from the pharmaceutical industry and lawyers. Surely it is time for the UK government to emulate this creative initiative. It is planned that these monographs will all eventually be translated into English. It is anticipated that in the future mushroom-derived DSs will be subjected to this level of research on estimation of safety and efficacy (Wasser *et al*., 2000a,b).

The Japanese Situation

In Japan where consumers demand an increasing emphasis on safety and health, functional foods with proven clinical efficacy (now officially termed Foods for Specific Health Use (FOSHU)) are distinguished by their beneficial physiological effects. Such foods are designed to be consumed as a constituent part of a regular daily diet and to help promote and maintan health by regulating bodily functions and to protect against a range of conditions and diseases, including cancer, heart disease, diabetes, osteoporosis and hypertension. FOSHU status tends to carry claims that have the nuance of preserving or promoting health rather than to make specific claims.

In many ways the FOSHU regulatory system is possibly the most advanced in the world and is primarily designed to allow established and accepted ingredients to be used in food rather than to encourage development of new ingredients. The following requirements must be met to achieve a full FOSHU license: the product must contribute to the improvement of dietary habits and enhance health; the health benefits of the food or ingredient should have a clear medical basis; the food/ingredient must have definable levels of appropriate consumption based on medical knowledge; the food/ingredient should be safe as judged from experience; relevant information should be defined in terms of physiochemical properties; nutritional composition of the product should not differ greatly from that of ordinary foods; the product must be consumed regularly rather than occasionally; and the product must be in the form of ordinary food rather than pills or capsules. FOSHU approval differs from pharmaceutical approval in that FOSHU is for ordinary food with a "specific health benefit" that is already considered safe from prior experience (Ehrnreich, 2000).

The United States Situation

An important dilemma with respect to the regulation of functional foods is that they exist at the interface between foods and drugs (Kottke, 1998). In existing US food regulations there is no provision for foods consumed with the intention of preventing disease. The Federal Food Drug and Cosmetic Act (1938) considered such foods as drugs "articles intended for the diagnosis, cure, integration, treatment or prevention of disease" thus severely limiting labelling referring to disease-prevention or risk-reduction.

However, the Dietary Supplement Health and Education Act (DSHEA) (1994) allows many functional foods to be considered as dietary supplements which are

exempt from regulation as drugs. The Nutritional Labelling and Education Act (1990) permits health and disease prevention claims on a food label. A health claim is defined as “any substance that expressly or by implication characterises the relationships of any substance to a disease or health-related condition, e.g. fruits and vegetables and cancer prevention”.

With respect to DSHEA, Congress considered that there could well be a positive relationship between sound dietary practice and good health and that there could well be a connection between dietary supplement use, reduced healthcare expenses and disease prevention.

At present when DS manufacturers plan to market a new ingredient (ie. not marketed in US before 1974) information must be submitted 75 days in advance to the FDA that concludes that the new ingredient can be considered to be safe. Safe means that the new ingredient does not cause a significant or unreasonable risk of illness or injury under conditions of use recommended in the products labelling. This information will be in the public domain 90 days after receipt by the FDA (Wasser *et al*., 2000a). Having complied with DSHEA requirements, once a DS is marketed the FDA has the responsibility for showing that a DS is unsafe before it can take action to restrict the product’s use. The manufacturer is responsible for ensuring that the ingredient list is accurate and that the ingredients are safe. The content must match the amount declared on the label.

The DSHEA has created an Office of Dietary Supplements (ODS) at the National Institute of Health (NIH) to promote the scientific study of the benefits of DS for promoting health and preventing disease. The FDA has made major efforts to improve the labelling of DS products. All ingredients must be listed and for extracts

additional information may be provided including the solvent used and the concentration of the extract.

The FDA have recently issued the final regulations on structure/function (SF) claims for DSs under the DSHEA of 1994. There is a significant move in relation to SF claims for over-the-counter drugs, including DSs. In association with the American Herbal Products Association (AHPA) the FDA has expanded the range of SF claims by agreeing that some claims are not disease claims. Some are, instead, claims that deal with the structure or function of the body. In this way a DS can make claims as antacid, digestive aid, short-term laxative and many other uses previously not allowed for DSs.

Previously, the definition of disease was “any deviation from, impairment of, or interruption of the normal structure or function …”. Now the FDA will use the definition “damage to an organ, structure or system”. This change in definition will automatically reduce the range or number of health claims for DSs.

Dietary supplements from medicinal mushrooms

There are presently several types of DS derived from medicinal mushrooms being marketed (Wasser *et al*., 2000b).

1. Dried and pulverised naturally growing mushroom fruit-bodies in the form of capsules or tablets.
2. Artificially cultivated fruit-body powders, hot water or alcohol extracts from them, or the same extracts concentrated and their mixtures.
3. Dried and pulverised preparations of the combined substrate, mycelium and mushroom primordia following inoculation of edible semi-solid medium (usually grains).

4. Biomass or extracts of mycelium or the broth harvested from submerged liquid culture grown in bioreactors.

It has been estimated that worldwide sales of DSs from medicinal mushrooms is US$ 5-6 billion per year with the market value for Reishi DSs in 1995 estimated at US $ 1.628 billion (Chang and Buswell, 1999) (http://vm-cfson.fda.gw) . Shiitake products also have a very high profile. However, there is currently no standard protocols for guaranteeing medicinal mushroom DSs for product quality and efficacy.

Any compounds that will influence body functions such as blood pressure, immune response etc. are classified as pharmacological agents, and as such will invariably demonstrate toxicity at high dosage levels. Thus, a completely safe pharmacological agent would not have any biological activity (Huxtable, 1999).

In the case of the medicinal mushrooms they have been used for traditional medical purposes for long periods of time, in some cases for thousands of years. There are few documented examples of adverse effects to man and as such they can be considered as safe. However, from a pharmacological point of view, safety is a relative concept and it is clear that the safety of all mushroom-derived DSs cannot be guaranteed simply because they have mostly many centuries of usage.

Recently, Wasser *et al*. (2000a) have carefully examined this concept and have set out reasons for adopting a more cautionary approach but at the same time indicating the way forward to ensure adequate safety and efficacy for mushroom dietary supplements.

1. Considering the historic perspective "safety" in traditional terms is very different from that in modern times. Firstly, mortality patterns of developed societies today are very different from those of traditional ones … Secondly, traditional users rarely had the means to evaluate long-term or chronic toxicity

of agents; but we do have cautionary instances of plants and the mushroom *Paxillus involutus* that have been used medicinally for centuries and recently proved to carry delayed toxic effects (Huxtable, 1992; Schmidt *et al*., 1971).

2. Many supposedly traditional mushroom products are now marketed in ways markedly different from those in the past. Today larger amounts may typically be taken, the material is used more frequently, it is consumed in the form of enriched extracts and it may be taken simultaneously with synthetic drugs. The user of shiitake (*L.* edodes) in old China, for instance, could not ingest as much active polysaccharide (Lentinan) as a modern user taking it in pure form extracted from shiitake as a DS. Notably, 200 kg of fresh mushrooms are needed for extraction of 31 g of lentinan. This heightens the possibility of ill effects from traditionally “safe” mushrooms.
3. Also, many mushrooms or mushroom preparations traditionally taken as treatments for specific conditions are now often marketed for use as prophylactic agents. The idea of DSs themselves in many cases implies that they are taken in the absence of any indicated conditions to prevent disturbances of health.
4. Finally, reliance on traditional use as an indication of safety involves a danger, namely the poor information available to us from antiquity. Huxtable (1999) recently carried out an analysis of historical sources for different herbal medications and he clearly showed that the literary sources of such information are in many cases contradictory and vague.

Thus, it is clear that safety criteria for medicinal mushroom preparations should be based solely on modern scientific evidence and not to rely heavily on inadequate historical evidence. However, it is reassuring that when compared with

herbal preparations, mushroom preparations show little evidence of overt toxicity. The main advantage of using mushroom-based DSs with respect to safety (as opposed to herbal preparations) are the following as stated by Wasser *et al*. (2000a).

1. "The overwhelming majority of mushrooms used for production of DSs are cultivated commercially (and not gathered in the wild). This guarantees proper identification and pure and unadulterated products. In many cases it also means genetic uniformity. (However, it should be noted that the most highly prized and desired *Ganoderma lucidum* mushrooms are still collected from the wild).
2. Mushrooms are easily propagated vegetatively and thus keep to one clone. The mycelium can be stored for a long time and the genetic and biochemical consistency may be regularly checked.
3. Yet another important advantage … is the fact that many mushrooms are capable of growing in the form of mycelial biomass in submerged fermenter cultures."

The task of converting the very biodiverse raw materials of mushrooms into a consistent product will reflect industrial practices and standards and on methods of assessing efficacy. Mushrooms are complex structures both morphologically and physiologically with undoubted variations in chemical composition from batch to batch. The composition of a mushroom fruiting body will reflect substrate composition and ingredients which can vary considerably since the basic raw materials are normally of agricultural or forestry origin. Also the degree and uniformity of maturation can be critical, e.g. lovastatin levels in *Pleurotus* are highly dependent on the size and age of the fruiting body (Gunde-Cimerman, 1999). The cultivation for fruiting body production can be a long-term process taking from one to

several months for full production. Use of the complete mushroom fruiting body does imply that the standardisation of the DSs from medicinal mushrooms is in a rather poor state. Perhaps it is time that the mushroom DS manufacturing companies followed the recent example of the herbal industry who formed the Institute for Nutraceutical Advancement (INA) and within it the Methods Validation Program (MVP – the first organised effort to develop and validate botanics (www.nutraceuticalinstitute.com). The methods were also submitted to the US Pharmacopoeia (USP) and the American Organisation of Associated Chemists (AOAC) for possible publication (Lange, 1998).

The important way ahead for mushroom DSs and pharmaceuticals could be a greater use of pure culture mycelial cultivation in liquid or solid substrate fermenters. Such an approach offers several advantages:

1. Speed of growth with reduction in production time.
2. Optimisation of culture medium composition.
3. Optimisation of physico-chemical conditions to allow regulation of mushroom metabolism.
4. Improved yield of specific products.
5. Possible designed variation in product types.

Increasingly, industrial producers of DSs and pharmaceutical grade compounds such as Lentinan, LEM, Grifron, PSK, PSP and, more recently, glucuronoxylomannan from *Tremella* (Reshetnikov *et* al. 2001) are moving or have already moved over to fermenter produced products. Clearly, this may be the way ahead and it is only a matter of time before many of the main medical products from medicinal mushrooms are produced in this way.

The logical progression of medicinal mushrooms is the step across to pharmaceutical application as seen with the purified polysaccharides such as Lentinan, PSK etc. In the US, pharmaceutical companies are examining their ability to compete in the future FDA-approved herbal pharmaceutical market. Botanicals, which should include mushroom nutriceuticals, are complex mixtures that contain many chemical constituents and are marketed as dietary supplements with no regulatory control. When specific therapeutic claims are made then, as previously discussed, they become subject to standard national regulatory approval. The pharmaceutical development of such herbals or nutriceuticals creates major difficulties for the FDA which was originally set up to assess drugs that typically contain only one active ingredient (Glasser, 1999). The FDA has currently several investigational new drug (IND) applications for botanical products and may soon allow Phase II clinical trials. It is anticipated that there will be three levels of control: control of the raw materials (the plant or the mushroom); control of the manufacturing process which must be a validated and responsible process; and control of the final product which could include fingerprinting and biological assays to evaluate the active components and/or relevant chemical markers of clinical efficacy, when activities are not identified. Furthermore, there must be assurance of batch-to-batch consistency. It is believed that over 60% of the herbal products presently being marketed would fail any analytical tests for quality, identity of material or amount of active components when known!

Most of the mushroom DSs presently in the market place are highly diverse and there are currently few standard protocols to ensure product quality. There must be thorough analysis, improved quality and legal control which will, in turn, increase

and maintain consumer confidence and achieve the current and future standards set by national regulatory authorities.

A central feature of the purported medicinal or chemo-preventive role of crude herbal and mushroom extracts must be a synergistic interaction of the many constituents. In such synergistic systems it can be considered that activity results from the presence of multiple active principles which must be together to create the desirable response (Pezzuto, 1997). When such complex mixtures are submitted to fractionation the active ingredients are separated and consequently activity may be lost. The undoubted difficulties of studying this form of synergism suggests why this effect seen in herbal and related products remains a relatively unstudied aspect. Should modern medicine continue to be driven by the necessity to rely predominantly on pharmaceutically pure medicines?

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