Market Authorization of Nutraceuticals: A Global Scenario

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Seeking market expansion into North America and globally!
Why Traditional Medicines are popular worldwide?

- Unbroken tradition of practice-Efficacy established
- Immigration of population leads to cultural exchange
- Boundaries disappearing due to excellent information and communications
- Increase interest into other System of Medicines due to failure of Modern System of Medicine in certain diseases
Popularity vs. Accountability

Quality

Safety

Efficacy

Regulations to allow trade of Traditional Medicines (TM)
How to trade the TM??

- As Traditional Herbal Medicines
- As Drug
- As Supplements
Market authorization: Definitions

Market:
- The business of buying and selling a specified commodity

Authorization:
- A document giving an official instruction or command
- The act of conferring legality

Registration of the product in a country and right to market the product in that country
Market authorization: Requirement of documents

- Dossier preparation
- Format of dossier varies countries to countries
- CTD(Common Technical Document) to make things easier (Based on ICH Guidelines)
CTD-Herbal(Module 1-5)

- Module 1-Administrative data
- Module 2-CTD Summaries
- Module 3 Quality
- *Module 4-Bibliographic review of Safety
- *Module 5-Traditional use evidence

*CTD-ICH differs from CTD-HERBAL with respect to Module 4, where Pre-clinical studies are required and Module 5, where they need Clinical Studies.
Regulatory requirements Worldwide
Directive 2001/83/EC requires that applications for authorization to place a medicinal product on the market have to be accompanied by a Dossier containing particulars and documents relating in particular to the results of Physico-Chemical, Biological or microbiological tests as well as pharmacological and toxicological tests and clinical trials carried out on the products and thus proving its quality, Safety and efficacy.
EU: THMPD
Directive 2004/24/EC

The THMP’s definition: A herbal medicinal product that fulfills the conditions laid down in article 16a(1)

Herbal Medicinal product: any medicinal product, exclusively containing as active ingredients one or more herbal substances or one or more herbal preparations, or one or more substances in combination with one or more such herbal preparations;

Article 16c....1.(c) Traditional use is established at least 30 years of preceding the date of application, including 15 year within the community (Data on safety and efficacy will not be required)
EU:THMPD

......The quality aspect of the medicinal product is independent of its traditional use so that no derogation should be made with regard to the necessary physicochemical, biological and microbiological tests. Products should comply with quality standards in relevant European pharmacopoeia monographs or those in pharmacopoeia of member state.
Bottlenecks in EU:THMPD Directive 2004/24/EC

There is need to amend Article 16c
The traditional use data for the TM should be based on authorized text books and pharmacopoeias of the countries of its origin
The quality parameters to be uniform and rational
Natural Health Products Regulations

- Traditional medicines, Herbal remedies, homeopathic medicines, vitamins, minerals, probiotics, amino acids and essential fatty acids
- A product licensing system requires that all licensed products display a Product identification Number prefixed by NPN/NPN-HM
- The number is issued once a product is authorized for sale in Canada by Natural Health Product Directorate
Canada: Natural Health Products Regulations

- The site licensing has been developed, requires that all manufacturers, packagers, labelers and importers be licensed.
- The site to meet GMPs as per Natural products Regulations.
- GMPs are to be employed to ensure product safety and quality.
- For foreign sites - The certificate of the compliance by the regulatory authorities of any countries as in Appendix 3 (US/UK/ EU/ Malaysia/Singapore etc.) - inspection report no more than 3 yrs.
Those countries not in Appendix 3, have real problems, inspections from Health Canada-SAARC does not fall into it.

Traditional use of data, sometimes not available in English and copies of translation need to be certified and accepted.
United States

Regulations in US

Three categories-
- Drug
- Food
- Dietary supplement
Dietary supplements in US

- DSHEA (Dietary Supplement Health and Education act of 1994)

Definition of Dietary Supplements. Section 291 (21 U.S.C. 321)-
“(1) means a product (other than tobacco) intended to supplement the diet that bears or contains one or more of the following dietary ingredients-
(A) a vitamin;
(B) a mineral;
(C) an herb or other botanical;
(D) an Amino acid..................
(2) means a product that.......(c ) is labeled as dietary supplement”
Dietary supplements in US

Dietary supplements: Statement of Nutritional support for the purpose of the paragraph (r)(1)(B)

- ...(A) statement claims a benefit related to a classical nutrient deficiency disease and discloses the prevalence of such disease in the United States, describes the role of a nutrient or dietary ingredient intended to affect the structure and function in humans...
- (B) The manufacturer of the dietary supplement has substantiation that such statement is truthful and not misleading, and
- (c) display on label… “this statement is not evaluated by the Food and Drug Administration”

A statement under this subparagraph may not claim to diagnose, mitigate, treat, cure or prevent a certain disease or class of diseases.
Dietary supplements in US

Comments

- There is no separate category for Traditional medicines
- No treatment claims are allowed under the DSHEA
- GMP is proposed and final notification is awaited.
The Ayurvedic medicines and Traditional Chinese Medicines are classified as complementary medicines. Quality standards are same as other medicines.

TGA maintains the Australian Register of Therapeutic Goods (ARTG) - Approx. 16000 (Complementary medicines included). TM may be included on ARTG as Listed (low risk) or Registered Medicines (high risk).
Listed complementary Medicines-
- Listed medicines may be supplied following application to the TGA by the sponsor
- Self certification by sponsor
- Validation by TGA that certain Key requirements of the legislations are being met

Registered Complementary medicines
- Registration is similar to modern medicines
- The licensing and audit of manufacturers
- Pre-market assessment of the products
- Post market activities
Food and Drug Administration

- The Drug Act of B.E.2546(2003) is in the final stage of promulgation

- Types of Medicines classified into Prescription only, Pharmacy dispensing and Household remedies

- Market Authorization for 5 years; GMPs mandatory

- Subcommittee on review and approval on TM
Thailand: Food and Drug Administration
Drug control division

Pre market control
- Licensing-license to sale/manufacture/Import TM
- Drug registration-for 5 years
- Registration of General Medicines
- Registration of TM

Post market control
- Inspection of GMP
- Receiving and handling of complaints
- Safety monitoring
- Reevaluation of Products
Guidelines for Traditionally used Herbal Products

Department of Health (Bureau of Food and Drugs BFAD)
To ensure safety, good quality and claimed application of Traditionally used Herbal Products
Traditional usage more than 50 years as documented in medical, historical and ethnological literature
For products originating from other countries
Authentication of the documents – Philippine consulate

Registration Requirements

- Initial Registration - 1-5 years depends on fee
- Re-registration – valid for 5 years
Health Sciences Authority
Centre for Drug Administration

Health supplements is currently not defined in legislation

Quasi-medicinal products (includes “medicated beverages”,
Vitamins and nutritional preparations from natural sources under legislation Medicines(TM, Homeopathic medicines and other substance)

- Traditional Medicines (other than CPM, Jamu, Ayurvedics, Homeopathic) including herbal preparations under the legislation medicines(TM, Homeopathic medicines and other Substances)
- Health foods with vague and general medicinal claims

Health supplements “a product that is used to supplement a diet, with benefits beyond those of normal nutrients and/or to support or maintain healthy functions of human body
Safety and quality requirements-

- not subjected to pre market approvals and licensing for their importation, sale or manufacture in Singapore
- Shall not contain any other substance except those stated on the label
- Shall not contain any human part....
- Shall not contain substances listed in the Schedule of poisons act
- Shall not exceed the limits for microbial contamination and toxic heavy metals
- Shall not make claim to directly or indirectly refer to the list of conditions diseases and disorders

Medical advertisement control

Safety and quality specifications
Ministry of Indigenous Medicine

Board of indigenous medicines set up in 1928

Ayurvedic Drug Formulary Committee under Ministry of Indigenous Medicines is regulatory body for the Ayurvedic Drug Registration.

The particulars required to register a herbal product

- The certificate of registration for the manufacturing institute or the drug importing agent with the govt. and the provincial council
- Reports on the experimental and clinical reports
- The certificate to ensure that the drug (product) is registered by the Government of original country
- Experimental reports to ensure that the drug is free side effects
- Composition of the proposed medicine
- Procedure of preparation
- Details of preservatives in the preparation
- Details of coloring agents in the preparations
- Details of the percentage of Alcohol (to be noted when relevant)
Drug registration Guidance document

Application type

Application for product registration via the abridged procedure (certain categories of OTC products and also for traditional Medicines)

Data requirements

Administrative data (Part I)

A-Product particular- indication, dose/ use instructions, contraindications, warning and precautions, Drug interactions, Side effects / adverse Reactions, Storage conditions, Shelf life

B-Product Formula-Manufacturing process, Attachment of in process quality control, Finished product quality control, Stability data

C-Packaging
Ministry of Health

Definition of pharmaceutical Products
“products intended for human consumption for the purpose of prevention treatment relief or diagnosis of diseases or for the modification of physiological functions”

Registration must with MOH

Registration requirements

- FSC from country of origin
- GMP certificate
- Product information
- Manufacturing process
- Real time stability
- Quality specifications for Finished products and Raw Materials
- Samples with Certificate of analysis
- Packaging material
Registration of products derived from natural source: 2002

- Registration of the manufacturer of products derived from natural sources
- Registration of products derived from plant origin

- Traditional Herbal medicines (THM):- Finished products intended for self-medication that contain, as the active principles, herbal ingredients that have received relatively little attention in the world scientific literature, but for which traditional of folkloric use is well-documented in herbal references. THM may contain chemically defined or herbal-based excipients in addition to the active principles.

- Registration of products derived from animal source
Observations and suggestions

The spirit of Traditional Medicines need to carried in regulations.

Quality:

- Need for Uniform GMPs regulations for export of TM
- Need for Uniform limits for heavy metals, pesticides etc.

Efficacy

- Traditional usage to be certified by regulatory authorities of exporting countries—which will ensure the evidence from authoritative text books /Pharmacoepias or other data for traditional usage
- Claims of efficacy be allowed

- Registration processes to be made uniform & easy
Useful Links:

http://www.emea.eu.int
http://www.hc-sc.gc.ca
http://www.fda.gov/opacom/laws/dshea.html
http://www.tga.gov.au
http://www.fda.moph.go.th
http://www.doh.gov.ph
http://www.hsa.gov.sg
http://www.ayurveda.gov.lk
http://www.bpfk.gov.my
http://www.pom.go.id
http://www.moh.gov.vn
http://www.moh.gov.ae

We should find new ways to move forward by reducing the scope for conflict between our regulatory approaches and by forging closer cooperation.

Peter Mandelson
Canada: Natural Health Products Regulations

The regulations are in force since Jan.1,2004
Transition period-2 years for Site Licensing
Transition period-6 years for Products with Drug identification Numbers(DIN)
Product Authorization requires either-

- Reference to a Natural product monograph (Published by NHPD)
- Or Submission of other evidence of safety and health claims (NHPD is working on standards of evidence framework)
Philippines:
Guidelines for Traditionally used Herbal Products

Registration Documents required

- Notarized application form 8
- Certificate of brand name clearance (if applicable)
- Certificate of agreement between manufacturer, trader, importer and/or distributor
- Raw material authentication
- FPS-finished product specification COA-certificate of Analysis
- Free sale certificate
- Quality control procedures
- Stability studies
- Labels Claims. “traditional/folklorically used to relieve…”
- Display on label in box. ‘The traditional application/use of this product has not been evaluated by the Bureau of Food and Drug”