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Comparative Study of Nutraceutical Products Authorization Requirements in Singapore, Malaysia & Cambodia

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ABSTRACT: The **high cost of branded name pharmaceuticals in the nutraceuticals sector is a problem in Asian countries such as Singapore, Malaysia, and Cambodia. Generic medications, which are less expensive and more competitive than branded drugs, play an important role in boosting drug access and lowering drug costs. The pharmaceutical market in Southeast Asia is rapidly expanding. There are ten countries in the Asian region. All countries have a comparable regulatory environment. However, the registration requirements and procedures differ from country to country throughout the Asian region. Despite the fact that ACTD is harmonized for all ten nations, various local criteria, such as administrative, technical, clinical, and non-clinical papers, GMP, and ICH standards vary by country. This review article will provide an overview of the drug registration regulations of nutraceuticals in three key player ASEAN member states such as Singapore, Malaysia & Cambodia.**

***Indexed Term*: ACTD, ICH, ASEAN, GMP (keywords)**

I. INTRODUCTION

Nutraceutical is a combination of the word's "nutrition" and "pharmaceutical." Nutraceuticals are foods or parts of foods that alter and sustain normal physiological function, hence assisting in the maintenance of human health by offering medical or health benefits in the prevention and/or treatment of disease. [1]

Natural sources (procured from plants, animals, minerals, or microbiological sources) are used to categorize nutraceutical items.[2]

Nutraceutical dietary sources include:
- Dietary Fiber
- Probiotics
- Prebiotics
- Polyunsaturated fatty acids
- Antioxidant vitamins
- Polyphenols
- Spices

Nutraceuticals have the potential to deliver significant health advantages, particularly in the prevention and treatment of acute and chronic human disorders. However, its advancement is contingent on its quality, safety, long-term adverse effects, and toxicity, as well as supplementation research and human clinical trials. Nutraceuticals such as enzymes, probiotics, and fortified foods are used to try to avert genetic problems. To have a positive impact on an individual's health, commercial nutraceuticals must satisfy severe regulatory restrictions.

A dietary supplement that provides benefits beyond those of ordinary nutrition and/or supports or maintains the human body's healthy functions. One or more of the following components, or a combination of them, can be found in health supplements [3]:

a) vitamins, minerals, and amino acids (natural and synthetic); b) compounds produced from natural sources, such as animal and botanical material in the form of extracts, isolates, and concentrates; and delivered in capsules, tablets, soft gel, liquid forms, and any other dosage forms allowed by the regulatory body to be supplied in small unit quantities.

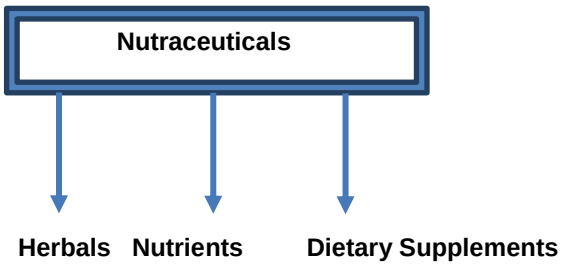

Fig. 1: Categories of Nutraceuticals

Nutrients:

Nutrients are naturally occurring components in our diets that meet nutritional standards such as minerals, vitamins, fatty acids, and polysaccharides. Many natural foods, such as fruits, dairy products, vegetables, and poultry meat, contain all of the nutrients we need. As a result, these nutrients are utilized to treat and prevent a variety of disorders, including cardiovascular diseases, lowering cholesterol, Diabetes Mellitus, for many diseases related to sleep apnea as well as osteoarthritis.[3]

Herbals:

Herbals are goods obtained by separating them from a variety of plant sources. These herbal preparations were once used as a medication to treat and prevent a variety of biological problems. Information about herbal goods can be found in ancient history and has proven to be highly useful in improving one's quality of life [3]. With the help of herbs, nutraceuticals play a vital role in promoting health and preventing chronic diseases.[4]

Dietary Supplement:
Dietary supplements are compounds that are created by combining certain necessary ingredients in our diet.

These dietary supplements are consumed along with food. Dietary supplements are substances that include some necessary elements, as defined by the Dietary Supplement Health and Education Act of 1994.

Due to the low level of selenium in the serum, supplementing our diet with selenium can lessen the risk of cancer. Zinc is a vital component of enzymes that are utilized in metabolism, wound healing, and digestion. Arginine is a crucial amino acid in the production of nitric oxide. Arginine additions can help people suffering from angina exercise more effectively. There are numerous nutrients having health benefits [5].

Natural food sources used as Nutraceuticals:

Different natural foods are employed as nutraceuticals, and they are classified into several groups based on their mechanism of action and constituent nature. Dietary fibers, probiotics, prebiotics, polyunsaturated fatty acids, vitamins, antioxidants, and spices are examples of food sources employed as nutraceuticals.

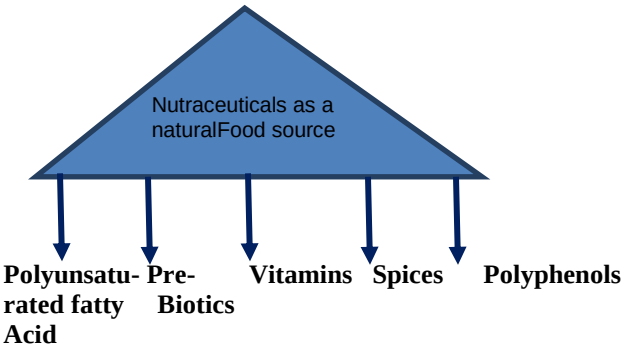

Fig. 2: Natural food source of Nutraceuticals

Dietary fibers are further divided into two categories: Soluble Dietary Fibers & Insoluble dietary fiber

Soluble Dietary fiber is easily dissolved in water, While Insoluble dietary fiber is poorly water-soluble Due to this Feces become bulky, therefore insoluble dietary fibers are useful in symptoms like constipation, colon related disorder. Soluble dietary fiber can control blood sugar and cholesterol levels in the body. [6-7]

Region of ASEAN countries:
ASEAN is a regional organization made up of 10 member countries: Brunei Darussalam, Cambodia, Indonesia, Laos, Malaysia, Myanmar, Philippines, Singapore, Thailand, and Vietnam.

The governments of five countries—Indonesia, Malaysia, the Philippines, Singapore, and Thailand—formed ASEAN in 1967. Brunei Darussalam joined the Association in 1984, along with its neighbors. These early participants are collectively known as the ASEAN 6. Since 1995, Vietnam has been a member, followed by Laos and Myanmar in 1997, and Cambodia in 1999. The CLMV group is the name given to these four new members. Although there are lots of products of nutraceuticals available in the market, numerous research groups and companies are still working to make it bigger scale. [8]

Fig. 3: Member countries with the ASEAN region

ASEAN members collaborate in a variety of sectors, including economics, social issues, security, and culture. Over time, the members evolved what is now known as the "ASEAN way" of collaborating and reaching group consensus through consensus-building. The evolution has also resulted in a strong tradition of all members participating in all initiatives that fall under the cover of allAsian countries. [9]

Dossier requirements

The ASEAN countries' dossier requirements are, in general, fairly comparable to the ICH countries' criteria. [8]

The ASEAN Common Technical Dossier (ACTD) is a standard application format for submitting pharmaceutical products for human use to ASEAN regulatory authorities.

Despite the fact that certain ASEAN countries have their owndrug registration formats, the ACTD is accepted by all ASEAN countries. The ASEAN countries adopted the ACTD as their submission format.[11-12]

Countries that require LOA, Quality, and safety data are Cambodia, Malaysia Thailand

a. Southeast Asia, with its rapidly rising population and large uninsured population, represents a huge opportunity for generic pharmaceuticals. [10]

b. While the generic market is still tiny, greater access to

medications in the region has resulted in rapid growth, with a value of US$3.9 billion in 2016.

c. This is likely to increase competition while also attracting international pharmaceutical companies to the area.

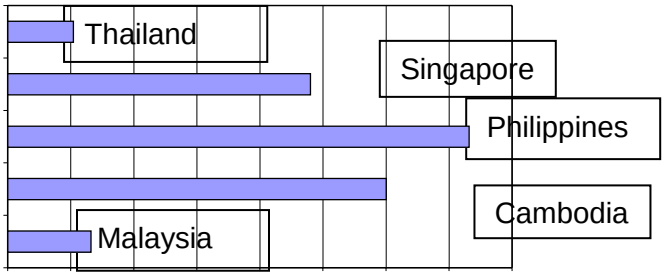

Fig 4. New Drug Registration in Asian competitive Market

Problem Faced by Exporter:

Asian Consumer have different price Demand with related to their buyer, so they directly deal with local dealers.

Therefore, such consumers also required their exporter to directly deal with their local partner for specific products.

For an instance some Asian countries demands that the product should contain ≥ 80% of Nutrient value mentioned on their label.

However, Countries like Singapore demand 100% Label claim on each of the product related to nutraceuticals.

Some countries also demand Safety and efficacy data.

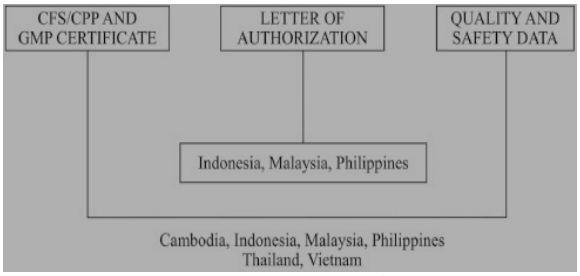

Fig. 5: General documentation of ASEAN Region

For Singapore Registration requirements are stringent. Also, technical data are more as compare to other Asian countries. [13]

1}FSC
2}COPP
3}LOA
4}GMP

These are the four documents which are legal and require in each of the Asian country.

Evaluation of the documents are also done by the ASEAN member state as per the registered committee.

However, payment method is different in each of the member state.

Payment and submission of sample are different and changed as per the new or generic submission.

Those guidelines are mentioned in their MOH or FDA website with detail.

Issuance of certification of product registration is mandatory and received once product is finalized and registration is completed.

Though renewal process is done by applicant on timely manner.[14]

ACTD comprises with four different parts

Part I- Country specific Admin data Introduction, TOC, Application Form,

Labelling

Part II- Quality Documents, TOC, Summary, Body of Data

Part III- Non clinical, TOC, Overview,Summary, Study Reports

Part IV- Clinical, Overview, Summary Tabulated Listing of studies & study reports

Table 1: Organization & difference between ACTD& CTD

Document Type		DOCUMENTS
ASEAN Common Technical Dossier (ACTD)	Common Technical Dossier (CTD)- ICH	
Part I	Module 1	Administrative Documents and Product Information
Incorporated in Parts II, III	Module 2	Common Technical Document Overview and Summaries Quality documents
Part II	Module 3	Quality documents
Part III	Module 4	Non-clinical documents
Part IV	Module 5	Clinical documents

Asian countries have maximum 5 years of limit to sale, distribute and import of pharmaceutical products. [15]

The administrative documents which are mandatory to submit are described as below:

- Letter of authorization

- Certificate of Pharmaceutical product
- GMP
- Manufacturing License.
- Plant Inspection Copy
- Site Master file
- Stability Data
  a) Real Time
  b) Accelerated

Table 2: Validity for ACTD

S NO	FORMAT TO SUBMIT	COUNTRY	MAXIMUM LIMIT
1	ACTD	Singapore	5 yrs
2	ACTD	Malaysia	5 yrs
3	ACTD	Thailand	5 yrs
4	Country specific & ACTD	Philippines	
5	ACTD	Indonesia	5 yrs
6	ACTD	Vietnam	5 yrs
7	ACTD	Brunei Darussalam	5 yrs
8	Country specific & ACTD	Myanmar	5 yrs
9	ACTD	Cambodia	5 yrs
10	Country specific & ACTD	Laos	5 yrs

Documents requirements for the Asian market are easy andeasily acceptable.

The amount of acceptance ratio and avail drug registration copy from regulatory agencies is comparatively less time-consuming and easily adaptable.

However, Labelling and sample requirements are stringent and have to be fulfilled in the application form with sample requirements on the stipulated time for ease and to achieve a high acceptance ratio.

The main goal of registration is to ensure that users receive only safe, effective, and high-quality pharmaceuticals. Permission is granted by the relevant state authority to use and distribute a specific drug. [16]

In Asia, the process of acquiring registration permission for drug items can be lengthy and difficult. Each Asian country's regulatory bodies have their own set of rules and regulations that must be followed, and any errors oromissions in your first application dossier can cause considerable delays in the registration process. [17]

The process for approving drugs varies from country to country. In certain countries, a single authority regulates the drug and is responsible for all regulatory work, making it difficult for pharmaceutical companies to produce a single dossier that can be submitted for approval in many countries at the same time.

The regulatory environment is similar in all nations, although the registration requirements differ.[5]

Tiny countries with small markets and hence less price-negotiation power have a well-known issue in cost-effective procurement. The problem of "small markets" can also apply to entire product groupings that only require tiny quantities.

Antidotes are an example of "orphan pharmaceuticals," which are difficult to obtain due to global shortages or the small quantities required at any given moment.[6]

For more better understanding the data in Table 3, demonstrates those countries, who only follow ACTD format for registration and in Table 4 explain the documents and technical support. [7]

As per the table administrative documents for countries like Singapore, Cambodia and Malaysia is mentioned.

From the study it is clearly mentioned that free sale certificate in such countries isusually not required. As those countries are only accept Certificate of Pharmaceutical products. While Labelling requirements are well mentioned in the dossier and in the Part -I of the dossier.[18]

Summary of Product characteristics are mandatory in every Asian country, as this document contains the major part of the drug formulation such as drug master formula, list of excipients, Strength, Dosage form, Side Effect, Posology and clinical information of the drug.

Good manufacturing practice or GMP certificate is mandatory for getting registration done in Asian Countries.

Next part of the dossier is for technical documents which are already mentioned in table 3.

Table 3: Evaluationof country specific PART-I Administrative documents in Singapore, Malaysia, Cambodia.

Sr No.	Part-I Administrative Documents	Singapore	Malaysia	Cambodia
1	Application Form	✓	✓	✓
2	Copy of valid certificate of brand Name clearance	✓	✓	✓
3	Certificate of Pharmaceutical product	✓	✓	✓
4	Free Sale Certificate	✗	✗	✗
5	Good Manufacture Practice	✓	✓	✓
6	License for pharmaceutical Manufacture	✓	✗	✓
7	Site Master File	✗	✗	✓
8	Permission for manufacturing & Marketing in country of origin	✗	✗	✗
9	Letter of Authorization	✓	✓	✓
10	Labeling Documents	✓	✓	✓
11	Patent Information	✓	✗	✓
12	Summary Product Characteristics	✓	✓	✓
13	Patient Information Leaflet	✓	✓	✗
14	Product Information Already Approved In Any State/Country	✓	✓	✗

Part II Registration process, Singapore registration related to drug description and composition is not required. On the other hand, Cambodia and in Malaysia such

documents related information are most prior for Submission.

Secondly, Drug substance part such as DMF is not that much necessary for submission in Cambodia and, Malaysia. But in Singapore DMF or Drug master file is must to submit. [18]

Table 4: Part -II Technical/ Quality documents of Asian countriesin Singapore, Malaysia, Cambodia.

Sr. No.	Quality DOCUMENTS	Singapore	Malaysia	Cambodia
1	Drug Substance	✗	✗	✗
2	Quality overall summary	✗	✓	✓
3	General information	✗	✓	✓
4	Manufacture of Drug substance	✗	✓	✓
5	Characterization	✗	✓	✓
6	Quality control of drug substance	✓	✓	✓
7	Reference standards	✗	✓	✓
8	Container closure system	✗	✓	✓
9	Stability	✓	✓	✓
10	CEP (Certificate of European Pharmacopeia)	✓	✗	✗
11	Drug Master File	✓	✗	✗
12	Drug Product	✓	✓	✓
13	Description &Composition	✗	✓	✓
14	Pharmaceutical Development	✓	✓	✗
15	Manufacture	✓	✓	✓
16	Quality Control of Excipients	✗	✓	✓
17	Quality Control of Finished Product	✓	✓	✓
18	Reference Standard	✓	✓	✓
19	Container Closure System / Packing	✓	✓	✓
20	Product Stability	✓	✓	✓
21	Product Interchangeability	✓	✓	✓

Also, in Singapore quality control related to Excipients part is also not required, while in other country it is required and compulsory to submit.

Part III of non-Clinical Documents are such as toxicological data and animal studies are included in it. But most Asian marketsubmission happen only for existing molecule, which are well versatile and already have good amount of non-clinical studies. Therefore, for such molecules not any non-clinical studies are required.

Table 5: Part III Non clinical documents Evaluation of Singapore, Malaysia, Cambodia.

Sr. No.	Part-III Non Clinical Document	Singapore	Malaysia	Cambodia
1	Non clinical Overview	✗	✓	✓
2	Non clinical written & Tabulated summary	✗	✗	✗
3	Non clinical study Reports	✗	✗	✗
4	Literature references	✗	✗	✓

As per the table it is clearly stated that nonclinical requirements for Singapore is very less, And in Malaysia Agency only demand non clinical overview, or in Cambodia MOH required Literature references along with non-clinical overview of desired product, which applicant need to register.

Table 6: Part IV Clinical documents Evaluation of Singapore, Malaysia, Cambodia.

Sr. No.	Part-IV Clinical Document	Singapore	Malaysia	Cambodia
1	Clinical Overview	✗	✗	✓
2	Clinical Summary	✗	✗	✗
3	Tabular Listing of All Clinical Studies	✗	✗	✗
4	Clinical Study Reports	✗	✗	Only BE
5	List of Key Literature	✗	✗	✓

With respect to the Part IV Clinical Documents, there are not any stringent requirements to submit documents in Singapore and in Malaysia. In Cambodian Study Guidelines, it is clearly stated that registration process documents for part IV Clinical documents, required a Clinical Overview of the product. In the diction of the Clinical study report Some molecule or if it exists in the newer chemical entity in Cambodia, required BE Study as well. [12-16]

As per the ACTD format, till now it is clearlyunderstood that requirements for clinical, quality and technical documents are different and may vary from country to country in Singapore, Malaysia & in Cambodia.[19]

The Medicines Act mandates the Centre for Drug Administration (CDA), which is the responsible body under the Health Sciences Authority, to license all medicinal items supplied in Singapore and manufactured locally for export (HSA). The CDA is in charge of enforcing laws, developing drug regulatory policies and guidelines, assessing medicinal product applications, and issuing final regulatory judgments and product licenses.

The Drug Registration Branch (DRB) and the

Innovative Therapeutics Group (ITG) of the Product Evaluation and Registration (PER) Division of the CDA are in charge of medication registration and ongoing reviews of approved medicinal products.[19]

There are four categories of applications for pharmaceutical product registration: New Drug Application (NDA), Generic Drug Application (GDA), Major Variation (MAV), and Minor Variation (MV) (MIV).

In Malaysia, The Drug Control Authority (DCA) is in charge of pharmaceutical regulation, with the National Pharmaceutical Control Bureau (NPCB) serving as its secretariat. Importation, manufacture, compounding, storage, distribution, and transportation of medications, including poisons and narcotics, are all covered by regulatory restrictions in the pharmaceutical industry. It also covers pharmaceutical advertising, sales, record-keeping, and use. [20]

Laws require facilities that make, import, or distribute drugs to be licensed. GMP compliance is now a requirement for both western and traditional medicine manufacturing licences. An import permission is necessary for each consignment of registered products, as well as for experimental products.

Cambodia produces only 5 to 10% of the medications required by the entire population. Except for a few basic indigenous natural raw materials for traditional remedies, all pharmaceutical input raw materials—active and inactive compounds, as well as packaging materials—are imported at a cost of about $12 million per year. It has one government pharmaceutical production plant that is a joint venture with China, as well as six commercial pharmaceutical businesses that manufacture oral dosage forms. None of these businesses are GMP-compliant.[21]

The drug registration system was established in 1994. The Ministry of Health's Department of Pharmaceuticals and Food (DDF) is in charge of ensuring the safety, efficacy, and quality of drugs and devices, as well as the safety and quality of food and cosmetics. Only DDF-registered items are allowed to be imported, manufactured, sold, displayed, and dispensed in retail pharmacies.[22-24]

All products, both imported and made locally, as well as those from the private and public sectors, must be registered. The National Quality Control Laboratory examines pharmaceuticals submitted to the Ministry of Health for registration from all sources. [25-29]

Pharmaceutical products must be licensed before they can be manufactured, imported, exported, or distributed, according to the legislation. Despite pharmaceutical laws and regulations, unlicensed drug outlets exist, and counterfeit and inferior pharmaceuticals are in circulation. Due to a number of complicated conditions, including a lack of funding to perform regular inspections, the rules enacted are rarely enforced.
[30-36]

Brunei, Cambodia, Indonesia, Laos, Malaysia, Myanmar, the Philippines, Singapore, Thailand, and Vietnam make up the Association of Southeast Asian Nations (ASEAN). It was founded in twenty years by these five nations (Indonesia, Malaysia, Thailand, Singapore, and the Philippines) in order to promote regional economic growth, cultural development, and social frameworks. Another five countries have since joined them. [37-38]

II. CONCLUSION

The study's goal is to analyses generic medicine registration and regulations in Malaysia, Singapore, and Cambodia, as well as to identify disparities in recommendations. Because of their high population rates, largest proportion of the ASEAN pharmaceutical market, and low wealth, nations like Indonesia and Thailand are being targeted. However, because of some restrictions imposed by the governments of these countries on foreign players, they are rated after Vietnam and the Philippines. Singapore and Malaysia are the only ASEAN countries with well-established pharmaceutical rules that are more stringent on drug quality and safety. These governments value innovation and provide it with complete protection. As a result, small and medium-sized generic enterprises may not have many prospects in these nations unless their production techniques are compliant with regulatory requirements.

ABBREVIATIONS

ICH International Council for Harmonization
ACTDASEAN Common Technical Dossier
CTDCommon Technical Document
LOA Letter of Authorization
CDAConfidential Disclosure Agreements
HSA Health Sciences Authority
TOC Table of content
GMP Good Manufacturing Practice
FSC Free Sale Certificate
COPP Certificate of Pharmaceutical Products

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