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GENERAL OVERVIEW OF DRUG REGISTRATION REQUIREMENTS FOR MALAYSIA

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ABSTRACT

Regulatory requirements are different from country to country mainly the administrative content of the dossier. Some of the regulated market country (US, EU, MCC, TGA) guideline are very stringent compared to Semi Regulated Market countries (India, Singapore, Malaysia, Thailand, Russia). Regulatory Affairs in malaysia is bit compound process need to cognize the current regulations in emerging markets and one step forward towards standardization vs. localization. Since localization is critical to access and develop individual regulatory strategies for doing business are the most common reasons of failure of MNCs in the emerging markets to uptake the markets. Regulatory environment define the market dynamics and healthcare system. Patient has been evolved as center point of health care system and policies around the globe. Therefore the article outlines the awareness of drug regulation in Malaysia and how changes are evolving and what implications of these changed dimensions are necessary.

KEYWORDS: Drug, Malaysia, Procedure, Registration, Timeline.

INTRODUCTION

A registered drug is a drug that is approved by the Drug Control Authority (DCA) for sale/use in Malaysia.[1] Every registered drug has given a registration number, which must be printed on its label or package. These numbers start with MAL. Example of a registration number: MAL19976399X. Type of drug products registration includes,

a. Pharmaceutical products containing scheduled poisons.
b. Pharmaceutical products containing non-scheduled poisons (OTC) Includes

+ Medicated plaster with medicines
+ Antiseptic/ Disinfectants for use on the human body
+ Diagnostic agents for human use (in vivo)
+ Dietary supplement e.g. Probiotics, Chitosan

c. Traditional products includes

+ Homeopathic medicines
+ Ayurveda medicines
+ Medicated plaster
+ Herbal teas
+ Dietary supplements eg. Spirulina, Chlorella, Royal Jelly, Bee Pollen, Aloe Vera juice, Noni juice, Extract of chicken with herbs

d. Veterinary products includes

+ Oral solution, oral suspension, emulsion
+ Granules
+ Water soluble powder
+ Injectable
+ Powder for injection
+ Oral powders
+ Capsule, tablet

Procedure for Registration

Currently, only on-line submission is accepted for product's registration. This could be done by through NPCB's website www.bpfk.gov.my. An applicant must buy a membership for Quest before the applicant can proceed with registration. There are several packages available to choose to become a member of Quest. Any assistance/advice shall be forwarded to Digicert Customer Service Department: 03-89928888. Once the applicant has received the user and password from BPFK (via email), he/she will be able to enter the registration site and proceed with online submission. This online registration system is also applicable for NCE and biotech products, traditional registration, re-registration of products and licensing as given in Table 1.

Table 1: Summary of the online registration procedure for products.

Summary of the online registration procedure for products are as follows:
1) Go to NPCB website (www.bpfk.gov.my)
2) Become Quest member (as First-time User) * Requirements
a. Company Registration Form - Company Authorization Letter
b. Photocopy of I/C
3) After making payment to Digicert, within 7 working days, with login name and password, enter Quest, go under registration, and register the Product on-line. All forms are available in the form tray.
4) Submit data requested
5) Correspondences with NPCB officer if additional data is needed
6) Products tabled to DCA meeting

Registration Fees

Processing fee every application for registration shall be accompanied with a processing fee, as follows (effective January, 2007) as shown in **Table 2**. Applications without the correct fees will not be accepted.

Table 2: Product registration Processing fee.

S. No.	Product Classification	Processing Fees (RM)	Analysis Fees (RM)	Total Fees
1	New Chemical Entity	1,000.00	Single active ingredient : 3,000.00	4,000.00
			Two or more active ingredients : 4,000.00	5,000.00
2	Pharmaceutical	1,000.00	Single active ingredient : 1,200.00	2,200.00
			Two or more active ingredients: 2,000.00	3,000.00
3	Traditional	500.00	700.00	1,200.00

Time Frame for Registration: The duration for each product to be registered is calculated from the date of final and complete submission. Table 3, gives the timeline for product of each category.

Table 3: Timeline for product registration.

Category of product	Timeline
1.Full Evaluation To evaluate application for registration of Prescription drugs Non- prescription drugs New drugs and biologicals	 210 working days * 210 working days * 245 working days *
2. Abridged Evaluation To evaluate the application for registration of health supplements and traditional products containing: Single active ingredient 2 or more active ingredients	116 working days * 136 working days *

Criteria for Registration

A product will be registered only if it satisfies ALL the requirements of the DCA, especially with respect to safety, efficacy and quality of the products. Other criteria taken into consideration are:

i. Whether that product is needed or not. Aspects like potential of abuse, number of registered products, different dosage forms, etc. are considered.
ii. Therapeutic effect.

The implementation phases for product registration are given in **Figure 1.**

Figure 1: Phases of implementation for product registration are as shown in [1&2]

Registration process includes quality control, inspection & licensing as well as post-registration process of medicinal products is illustrated in **Figure 2.**

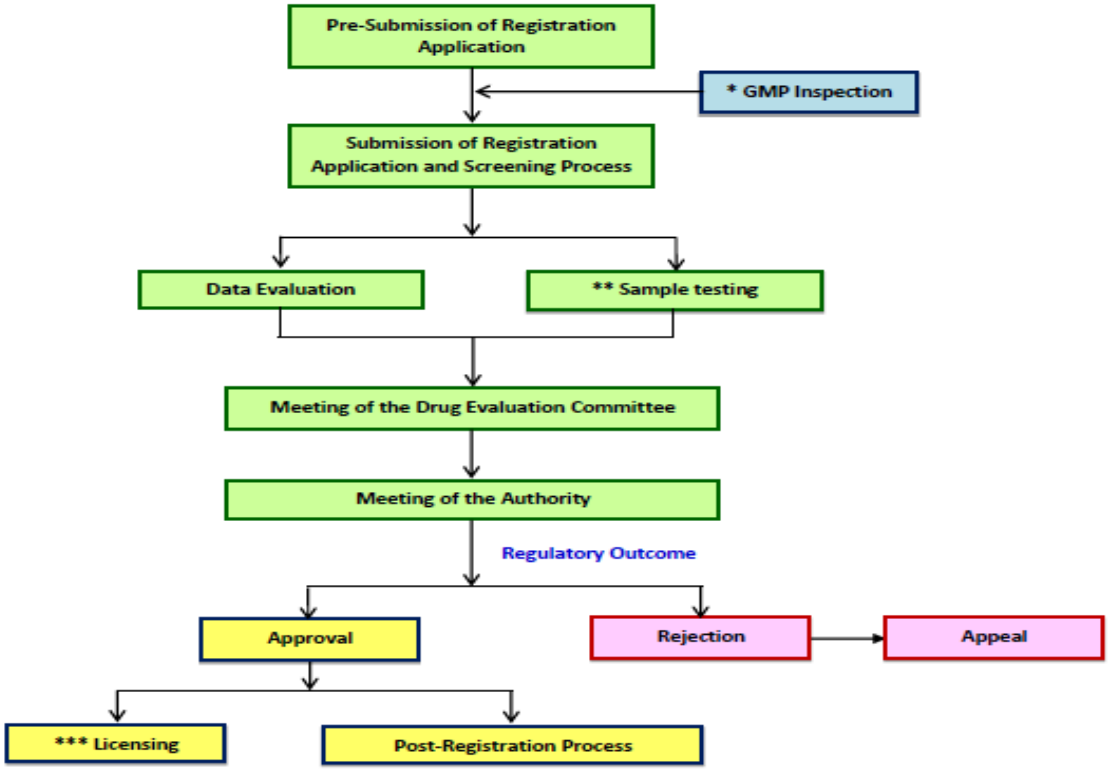

Figure 2: Schematic representation of registration process for drug products.

Registrable Products

Any product shall be registered with the CDAC authority. The products include, but not limited to the following:

a) Pharmaceutical products containing scheduled poisons

b) Pharmaceutical products containing non-scheduled poisons

c) Natural products Includes herbal and traditional products

Non-Registrable Products

1. Diagnostic agents and test kits for laboratory/ in-vitro use. Diagnostic agents/ test kits for laboratory use must be labeled 'FOR LABORATORY USE ONLY'.
2. **Medical devices**[3]
3. **Food** For more information, please refer Food Safety & Quality Division, Ministry of Health Malaysia.
4. **Sports Nutrition**.[4]
5. **Insecticides/Pesticides**[5]

Generics[6]

1. Scheduled Poison (Known as Controlled Medicine/ Controlled Poison): Products containing poisons as listed in the First Schedule under Poisons Act 1952.

2. Non-scheduled Poison (Known as Non-Poison or "Over-the-Counter", OTC): Products containing active ingredients which are not listed in the First Schedule under Poisons Act 1952; and is excluding active ingredient which is categorized under health supplements or natural products or cosmetics. For information pertaining to Register of Data Exclusivity Granted in Malaysia, please refer: Register of Data Exclusivity Granted in Malaysia (New Drug) and Register of Data Exclusivity Granted in Malaysia (Second Indication).[7] Therefore, the review article provides brief information for manufacturers, applicants, healthcare professionals and the general public on legal arrangements in Malaysia for the registration of CGTPs. The implementation of the guideline will be compulsory on 1 January 2021 as stated in the DirectiveNo. 6 Year 2017.[8]

How to Apply

An application for Data Exclusivity (DE) can be made via a Letter of Intent (LOI) in conjunction with the:

a. Application for registration of a new drug product containing a New Chemical Entity.

b. Application for a Second Indication of a registered drug product.

The LOI shall be addressed and submitted manually to the Director of NPRA. The application must comply with all terms and conditions stated in the directive *Arahan Bagi Melaksanakan Data Eksklusiviti Di Malaysia, Bilangan 2 Year 2011.* The following details are extracted from the Directive on Data Exclusivity (DE)

issued by the Director of Pharmaceutical Services under Regulation 29, Control of Drugs and Cosmetics Regulations 1984, Bil (11) dlm BPFK/PPP/01/03 Jld 1, 28 February 2011.[9]

Applicability and date of coming into force

The directive is applicable to:

a. New drug product containing a new chemical entity; and
b. Second indication of a registered drug product.

Grant of Data Exclusivity[10]

Any person may apply for Data Exclusivity. Such application shall be made upon submission of documents to the Director of Pharmaceutical Services for the:

a) Registration of a new drug product containing a new chemical entity; or
b) Approval for second indication of a registered drug product.

An application for Data Exclusivity shall only be considered if the application in Malaysia for:

a) New drug product containing a new chemical entity is made within eighteen (18) months from the date the product is first registered or granted marketing authorization; AND
b) Granted Data Exclusivity/ Test Data Protection in the country of origin or in any country, recognized and deem appropriate by the Director of Pharmaceutical Services.
c) Second indication of a registered drug product is made within twelve (12) months from the date the second indication is approved; and

Granted Data Exclusivity/ Test Data Protection in the country of origin or in any country, recognized and deemed appropriate by the Director of Pharmaceutical Services. Before the Data Exclusivity is granted

a) The applicant of a new drug product containing a new chemical entity shall provide to the Director of Pharmaceutical Services the undisclosed, unpublished and non-public domain pharmaceutical test data, the origination, of which involves a considerable effort; OR
b) The applicant for a second indication of a registered drug product shall provide to the Director of Pharmaceutical Services, the reports of new clinical investigations other than bioavailability studies, conducted in relation to the second indication and the origination of which has involved considerable effort.

The Director of Pharmaceutical Services shall decide on whether the application will be granted the Data Exclusivity. The period of the Data Exclusivity granted shall be made on a case to case basis. The period of the Data Exclusivity shall not be more than

a) Five (5) years for a new drug product containing a new chemical entity; and
b) Three (3) years for a second indication of a registered drug product. The period of Data Exclusivity is for the data concerning the second indication only.

Consideration of Other Applications upon the Grant of Data Exclusivity

For a registered new drug product containing a new chemical entity, registration of any other drug product where the active moiety is in all respect the same as the active moiety in the registered drug product which has been granted Data Exclusivity in Malaysia can be considered if

a. The applicant provides undisclosed, unpublished and non-public domain pharmaceutical test data, the origination of which involves a considerable effort to demonstrate the quality, safety and efficacy if the drug product submitted for registration; OR
b. The applicant has obtained consent in writing for right of reference or use of the test data from a person authorized by the owner of the registered new drug product containing a new chemical entity.

Non-Application of Data Exclusivity

Nothing in the Data Exclusivity shall

a) Apply to situations where compulsory licenses have been issued or the implementation of any other measures consistent with the need to protect public health and ensure access to medicines for all; or
b) Prevent the Government from taking any necessary action to protect public health, national security, non-commercial public use, national emergency, public health crisis or other extremely urgent circumstances declared by the Government.

Appealling Procedures

Any person aggrieved by the decisions of the Director of Pharmaceutical Services may make a written appeal to the Minister within fourteen (14) days from the date the decision is made known to him and any decision of the Minister made on an appeal shall be final.

A person making an appeal may submit any supporting data or documents to the Director of Pharmaceutical Services not later than:

a) 120 days for application of new drug products containing any new chemical entity; or
b) 90 days for the application for second indication of a registered drug product.

Application Formalities

Who can apply for product registration

The applicant for product registration shall be known as the Product Registration Holder (PRH) and must be a locally incorporated company, corporate or legal entity, with permanent address and registered with Companies Commission of Malaysia (with the scope of business related to the health/ pharmaceutical product).

The name of the PRH, including product manufacturer shall not reflect the following

a) Name of a government agency;

b) Name of a research/ institute of higher education;
c) A name that reflects the quality of pharmaceutical product e.g. "*AmalanPerkilanganBaik (APB)*", Good Manufacturing Practice (GMP);
d) Name of a disease;
e) Name of an organ.

e.g. Heart, Brain, Kidney etc.
The PRH (if the company is not the product owner) should be authorized in writing by the product owner to be holder of the product registration and be responsible for all matters pertaining to quality, safety and efficacy of the product. This shall include updating any information relevant to the product/ application.

How to apply
For registration of products, only web-based online submissions via QUEST.[11]To conduct transactions via QUEST system, the applicant must first register a membership for QUEST system with NPRA and purchase a USB Token that contains a User Digital Certificate, from MSC Trustgate.com Sdn. Bhd., which shall be installed to the applicant's computer. For details, please refer to Frequently Asked Questions on QUEST System.[12]For charges regarding QUEST USB token, please refer to section 4.1.The applicant shall be responsible for any act of fraudulence or misuse pertaining to its authorized QUEST USB token(s). The NPRA reserves the rights to approve or reject any application for the QUEST membership.

Mode of payment
The processing fee and any other charges shall be paid in the form of bank draft/ banker's cheque/ money order/ postal order made payable to "Biro Pengawalan Farmaseutikal Kebangsaan". A separate bank draft/ banker's cheque/ money order/ postal order are required for each application.

Types of Applications
Registration of combination pack (combo pack)
a) Where a combination pack consists of registered and unregistered products, the unregistered product needs to be registered first, prior to submission of the application;
b) Where a combination pack consists of registered products from different product owners/ PRH, letters of authorization which Include product name and product registration number from each product owner shall be submitted.

A product which is packed together with diluent(s)/ adjuvant(s) is NOT considered as a combination pack. Labelling requirement specifically for combination pack is shown in below Table 4

Table 4: Labelling requirement for combination pack.

S. No.	Outer Label	Immediate Label
1.	Name of combination pack	Individual name for each products OR name of combination pack
2.	Registration number for the combination pack	Individual registration number for each products OR registration number for combination pack
3.	Name and address of manufacturer and product registration holder	Name and address of manufacturer and product registration holder
4.	Batch number of the combination pack product	Individual batch number for each products
5.	Expiry date (according to the shortest expiry date from the individual products)	Individual expiry date for each products

Registration of starter pack/ patient initiation pack
a. Combination of products with different strengths which are packed together in one packaging such as blister or calendar pack.
b. Combination of more than one pre-filled pen containing different strengths of preparation in one packaging.
c. Must be registered under the same product owner and PRH.Labelling requirement specifically for combination pack is shown in below **Table 5.**

Table 5: Labelling requirement for *starter pack.*

S. No.	Outer Label	Immediate Label
1.	Statement of starter pack/patient initiation pack. Individual name for each products	Individual name for each products
2.	Individual registration number for each products	Individual registration number for each products
3.	Name and address of manufacturer and product registration holder	Name and address of manufacturer and product registration holder
4.	Individual batch number for each	Individual batch number for each products

	products	
5.	Manufacturing date	Manufacturing date
	(according to the earliest manufacturing date from the individual products)	(according to the earliest manufacturing date from the individual products)
6.	Expiry date (according to the shortest expiry date from the individual products)	Expiry date (according to the shortest expiry date from the individual products)

Amendments To Particulars of A Registered Product

Variation

Variation refers to change of particulars of a registered product.

- For pharmaceutical products, there are three (3) types of variation, which are Major Variation (MaV), Minor Variation Prior Approval (MiV-PA) and Minor Variation Notification (MiV-N). For details, please refer Malaysian Variation Guideline (MVG). [13]
- For health supplement and natural product, there are three (3) types of variation, which are Major Variation (MaV), Minor Variation Prior Approval (MiV-PA) and Minor Variation Notification (MiV-N). For details, please refer Malaysian Variation Guideline (MVG) For Natural (Traditional Medicine & Homeopathy) And Health Supplement Products (Abridged Evaluation). [14]For biologic products, please refer to the Malaysia Variation Guidelines for Biologics (MVGB) and Section E: 16.1.3 Variation Application for Biologic Products.[15]

Renewal of Product Registration

The registration shall be valid for five (5) years or such a period as specified in the Authority database (unless sooner suspended or cancelled by the Authority); The renewal of product registration should be submitted within six (6) months prior to the expiryof the validity period of a product registration, together with the appropriate fee.

Certificates

Certificate of pharmaceutical product (cpp)

A CPP which follows the format recommended by WHO shall be issued to locally manufactured products that are to be exported. For application of CPP, applicant shall fill in form BPFK 412.2: PermohonanPerakuanKeluaran Farmaseutikal.[16.] A fee, as stated in section 4.2: Fees, is payable on the issue of such certification. Upon receipt of complete application, the certificate shall be issued within fifteen (15) working days.

Good manufacturing practice (gmp) certificate

Upon complete application, a GMP certificate will be issued and a fee, as stated in section 4.2: Fees, is payable on the issue of such certification. If a manufacturer who wishes to build a new manufacturing premise, the manufacturer may submit a proposed premise layout plan to the Centre for Compliance and Licensing, NPRA for evaluation. (Only between OTC products with Abridge Evaluation category)

Licenses: For more information pertaining application of appropriate licences, please refer to NPRA website.

General Conditions for Registration Of Drug Products Under The Control Of Drugs And Cosmetics Regulations 1984

Registration code/ number

The product registered with the Registration Number as stated in the Authority database shall have the name, composition, characteristics, specifications and origin as specified in the registration documents and Authority database.

Registration number appears as MALYYMM$$$$@##, e.g. MAL11070001ACERSY:

- MAL refers to "Malaysia"
- YYMM refers respectively to year and month of registration by the Authority (e.g. 1107: July 2011);
- $$$$ refers to a serial number for a product being registered (e.g. 0001);
- @ refers to category of product being registered i.e. A/ X/ N/ T/ H; and
- ## refers to administrative code used by NPRA i.e. C/ E/ R/ S/ Y.

The symbols @ and ## refer to:

a) A= Scheduled Poison
b) X= Non-scheduled Poisons
c) N= Health Supplements
d) T= Natural Products/ Traditional Medicines
e) H= Veterinary Products
f) C= Contract Manufactured (the product is manufactured by a GMP certified contract manufacturer)
g) E= For Export Only (FEO) (the product is to be sold for export only and not for sale in the local market)
h) R= Packed and/or repacked (the product is packed and/or repacked by an approved GMP certified packer and/or repacker)
i) S= Second source (the product is from a second source/ approved second manufacturer)
j) Y= Orphan products
k) Z= Products gazetted as zero-rated under the Goods and Services Tax Act 2014, Goods and Services Tax (Zero-Rated Supplies) Order 2014.

Product Authentication

The registered product shall be affixed with the security device approved by the Authority. The said security device (hologram), which is serialized, shall be used to authenticate and verify that the product is registered with the Authority, and will be affixed to each unit pack of the product, whether locally manufactured or imported. The security device shall be affixed onto the outer packaging

of the product, (or, where there is no outer packaging, on the immediate packaging), on the front panel of the product label. None of the product particulars on the label shall be covered over by the security device.
Please refer to:

a. Labelling Requirements where the security device/ label may be affixed on the product label
b. FAQ no. 20 on hologram; and
c. Circulars and directives pertaining to security label (hologram)[17]

Withdrawal from registration

The holder of the registered product shall notify the Authority with regards to any decision to withdraw registration of a product and shall state reasons for the decision.
The holder shall also notify the Authority when he is no longer authorized to be the holder of the registered product

Cancellation, suspension, amendment by the authority

The Authority may, at any time and without assigning any reason suspend or cancel the registration of any product, and may amend the conditions of registration.

CONCLUSION

The ASEAN region does not have a centralised or harmonised procedure for drug registration. There are critical differences between countries in the region. As quality requirements and the cost of compliance continue to increase globally, Malaysia and other emerging markets will continue to be in focus. Manufacturers continue to seek ways to decrease costs and capitalize on these rapidly growing markets, leading to greater partnership opportunities as governments strive to increase their local capabilities as a means of decreasing healthcare expenditures. Specialized manufacturing necessary for biologics, high potency, and cytotoxic medications will also drive continued deal-making and regional investment in ASEAN region and countries like Malaysia/Singapore. Foreign market players looking to expand their footprint and established players in ASEAN Countries will benefit from emerging companies seeking to further develop their manufacturing and expertise in this growing region.

Abbreviations

ASEAN - Association of Southeast Asian Nations
EU- European Union
TGA- Therapeutic Goods Administration
MCC- Medicines Control Council
DCA- Drug and Control Authority
OTC- Over-the-counter
NCE- New Chemical Entity
DCA- Drug Control Authority
CDAC- Chinese Development Assistance Council
LOI- Letter of Intent
PRH- Product Registration Holder
NPRA- National Pharmaceutical Registration Agency
CPP- Certificate of Pharmaceutical Product
GMP- Good Manufacturing Process
CTX- Clinical Trail Exemption
CTIL- Clinical Trail Import License
AND- Abbreviated New Drug

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