REGULATORY CONTROL FOR HERBAL/TRADITIONAL MEDICINES AND HEALTH SUPPLEMENT PRODUCTS IN MALAYSIA

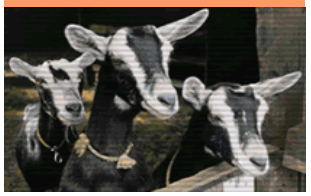
11th MARCH 2015

DATIN SHANTINI THEVENDRAN
COMPLEMENTARY SECTION, PPP, NPCB

CONTENTS

- Definition
- Product Registration Process
- Registration Criteria
- Safety, Quality, Efficacy / claimed benefits
- Statistics

Registration Phases

NEW PRODUCTS	Phase 1	Phase 2	Phase 3	Phase 4	Phase 5	Phase 6
BIOTECHNOLOGY 	Registration Aug 1985 (Prescription Drugs)	Registration 1988 (OTC)	Registration Jan 1992 (Traditional Medicine)	Registration Feb 2002 (Cosmetics)	Registration Aug 2007 (Veterinary)	Registration beginning with NCE Jan 2012 (API)**
VETERINARY MEDICINE 	Licensing May 1987	Licensing 1992	Licensing Manufacturer Importers Jan 1999	Licensing Jan 2004	Licensing 1 Jan 2012	No licensing Requirements as registration of API is linked to products
ACTIVE PHARMACEUTICAL INGREDIENTS 	Surveillance 1990	Surveillance 1995	Licensing Wholesalers July 2002 Surveillance 2000	Surveillance 2005	Surveillance (to be announced)	Surveillance (to be announced)

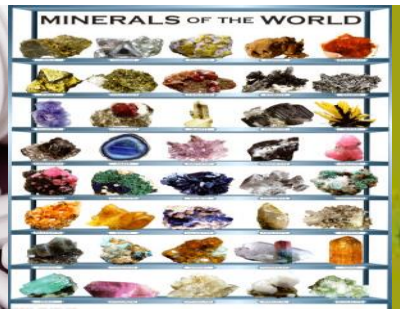
1st January 2008 – Registration of Cosmetics replaced by NOTIFICATION

** Voluntary registration of API commenced in April 2011. Registration of generic API will be announced at a later date.

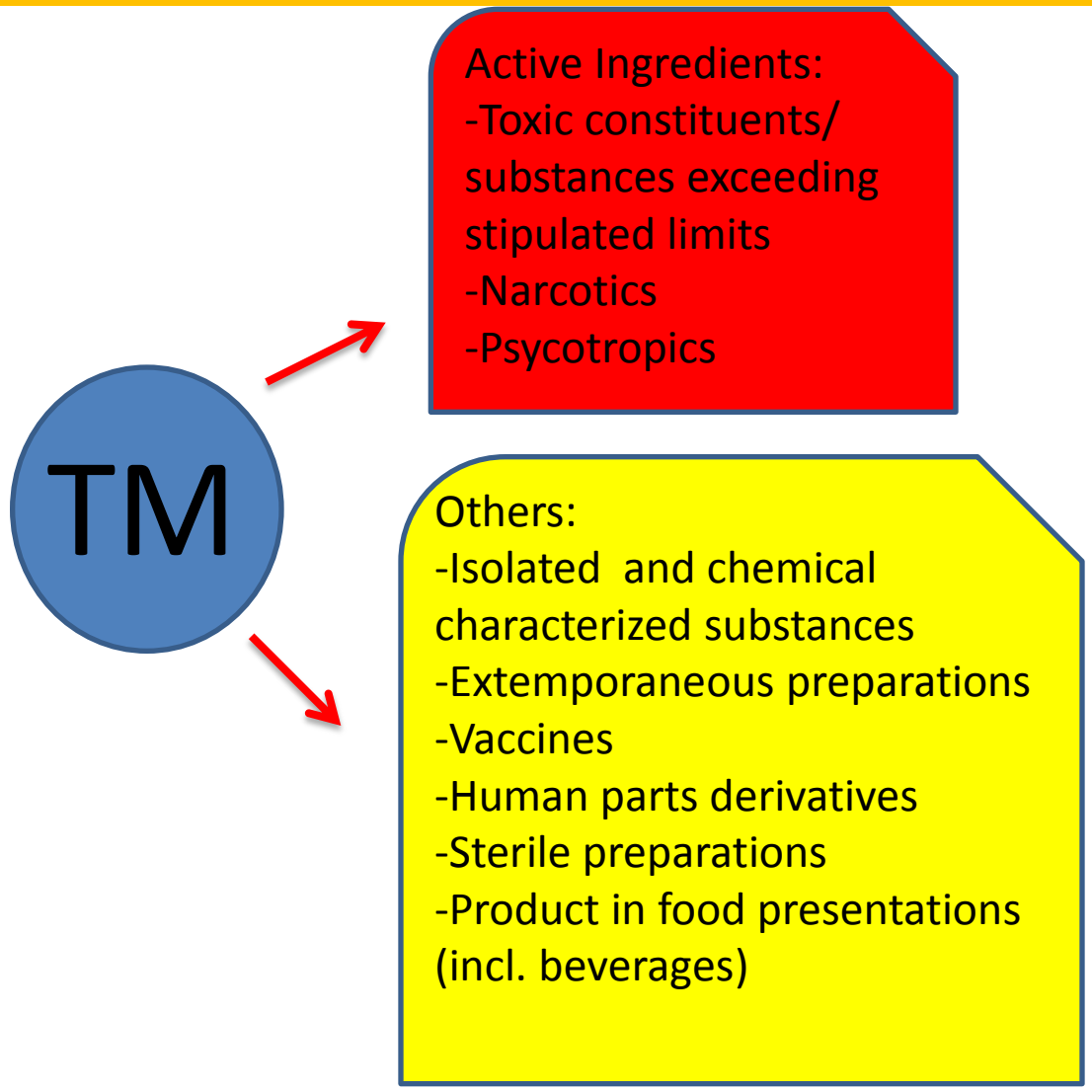
What is a Traditional Medicine?

- Traditional medicine is defined as any product used in the practice of indigenous medicine, in which the drug consists solely of one or more naturally occurring substances of a plant, animal or mineral, or parts thereof, in the unextracted or crude extract form

- Indigenous medicine is defined as a system of treatment and prevention of disease established through traditional use of naturally occurring substances


SUBSTANCE TO BE EXCLUDED



Traditional medicine claims

traditionally used . . .

- Traditional general claims
  - general health
- Traditional medium claims
  - reduction of risk of a disease/disorder
  - relief of symptoms
  - aids/assists in the management of a named symptom/ disease
  - prevents/stops/ slows down the progress of a mild/ self-limiting disease or medical condition

HERBAL PRODUCT

- **Finished herbal products:**

  herbal preparations made from one or more herbs. If more than one herb is used, the term mixture herbal product can also be used. Finished herbal products and mixture herbal products may contain excipients in addition to the active ingredients. However, finished products or mixture products to which chemically defined active substances have been added, including synthetic compounds and/or isolated constituents from herbal materials, are not considered to be herbal.

  World Health Organization (WHO) Guidelines (4th October 2010)

Herbal product claims

herbal product used . . .

- General health maintenance
- Medium claims
  - reduction of risk of a disease/disorder
  - relief of symptoms
  - aids/assists in the management of a named symptom/ disease
- High claims
  - treats/ cures/manages any disease/disorder
  - adjunct / to complement any treatment

GUIDELINES : final draft

IMPLEMENTATION : 2015

Health Supplement Definition

A Health Supplement (HS) means any product that is used to supplement a diet and to maintain, enhance and improve the health function of human body.

It is presented in small unit dosage forms (to be administered) such as capsules, tablets, powder, liquids and shall not include any sterile preparations (i.e. injectables, eye drops).

(Malaysian DRGD 2014 July)

Health supplements may contain one or more, or the following combination:

i)Vitamins, minerals, amino acids, fatty acids, enzymes, probiotics, and other bioactive substances;

ii)Substances derived from *natural sources, including animal, mineral and botanical materials in the forms of extracts, isolates, concentrates, metabolite;

iii)Synthetic sources of ingredients mentioned in (i) and (ii) may only be used where the safety of these has been proven.

Claims for Health Supplements

- General or Nutritional Claims
- Functional Claims
- Disease Risk Reduction Claims

Effective 1st March 2013

Maximum Daily Levels of Vitamins and Minerals for Adults allowed in Health Supplements

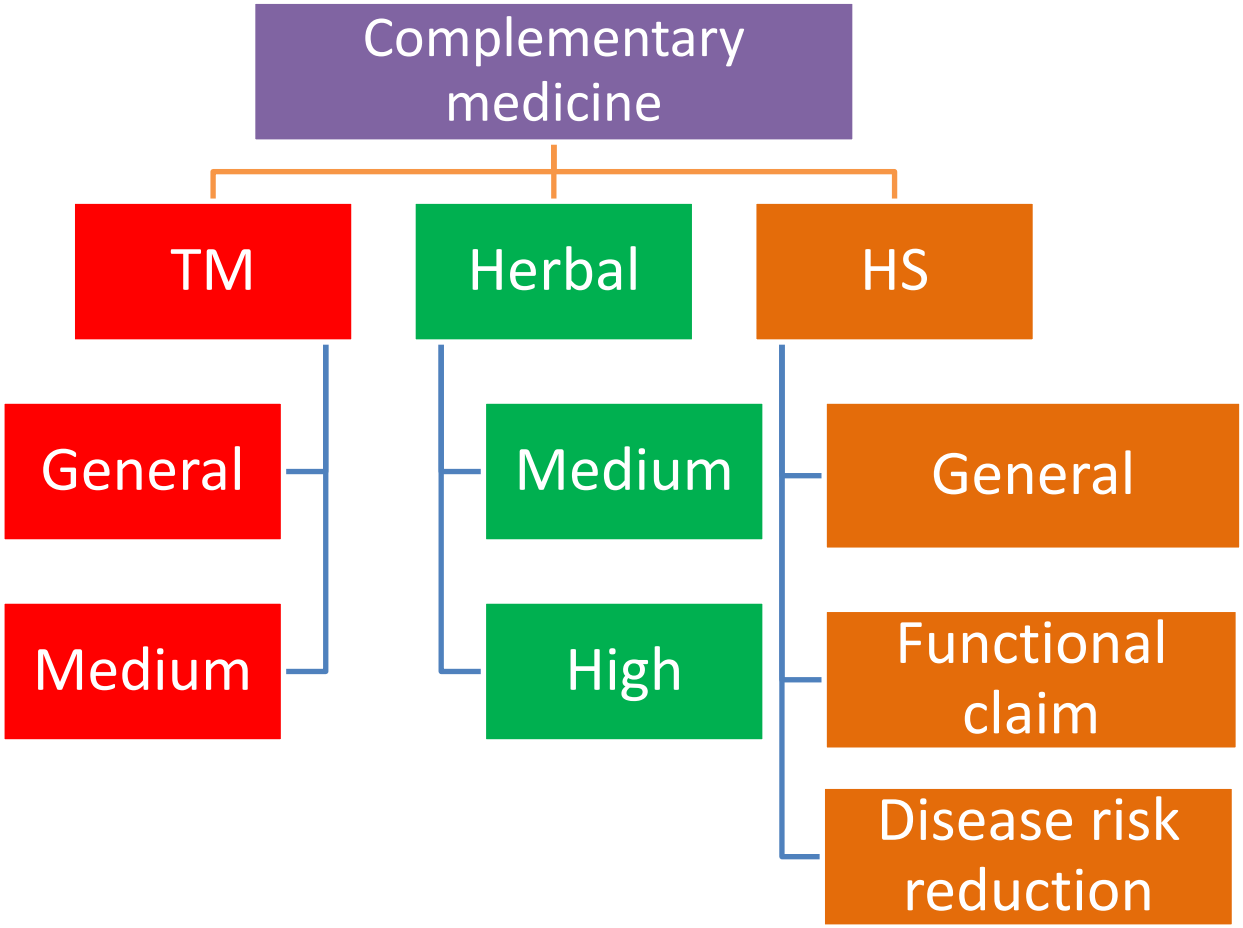
NO.	VITAMINS & MINERALS	UPPER DAILY LIMIT
1.	Vitamin A	5000 IU
2.	Vitamin D	1000 IU
3.	Vitamin E	800 IU
4.	Vitamin K (K1 and K2) [1]	0.12mg
5.	Vitamin B1 (Thiamine)	100 mg
6.	Vitamin B2 (Riboflavine)	40 mg
7.	Vitamin B5 (Panthothenic Acid)	200 mg
8.	Vitamin B6 (Pyridoxine)	100 mg
9.	Vitamin B12 (Cyanocobalamin)	0.6 mg
10.	Vitamin C (Ascorbic Acid)	1000 mg
11.	Folic Acid	0.9 mg
12.	Nicotinic Acid	15 mg
13.	Niacinamide (Nicotinamide)	450 mg
14.	Biotin	0.9 mg
15.	Boron	6.4 mg
16.	Calcium	1200 mg
17.	Chromium	0.5 mg
18.	Copper	2 mg
19.	Iodine	0.3 mg
20.	Iron [2]	20 mg
21.	Magnesium	350 mg
22.	Manganese	3.5 mg
23.	Molybdenum	0.36 mg
24.	Phosphorus	800 mg
25.	Selenium	0.2 mg
26.	Zinc	15 mg

Vitamins/ Minerals:

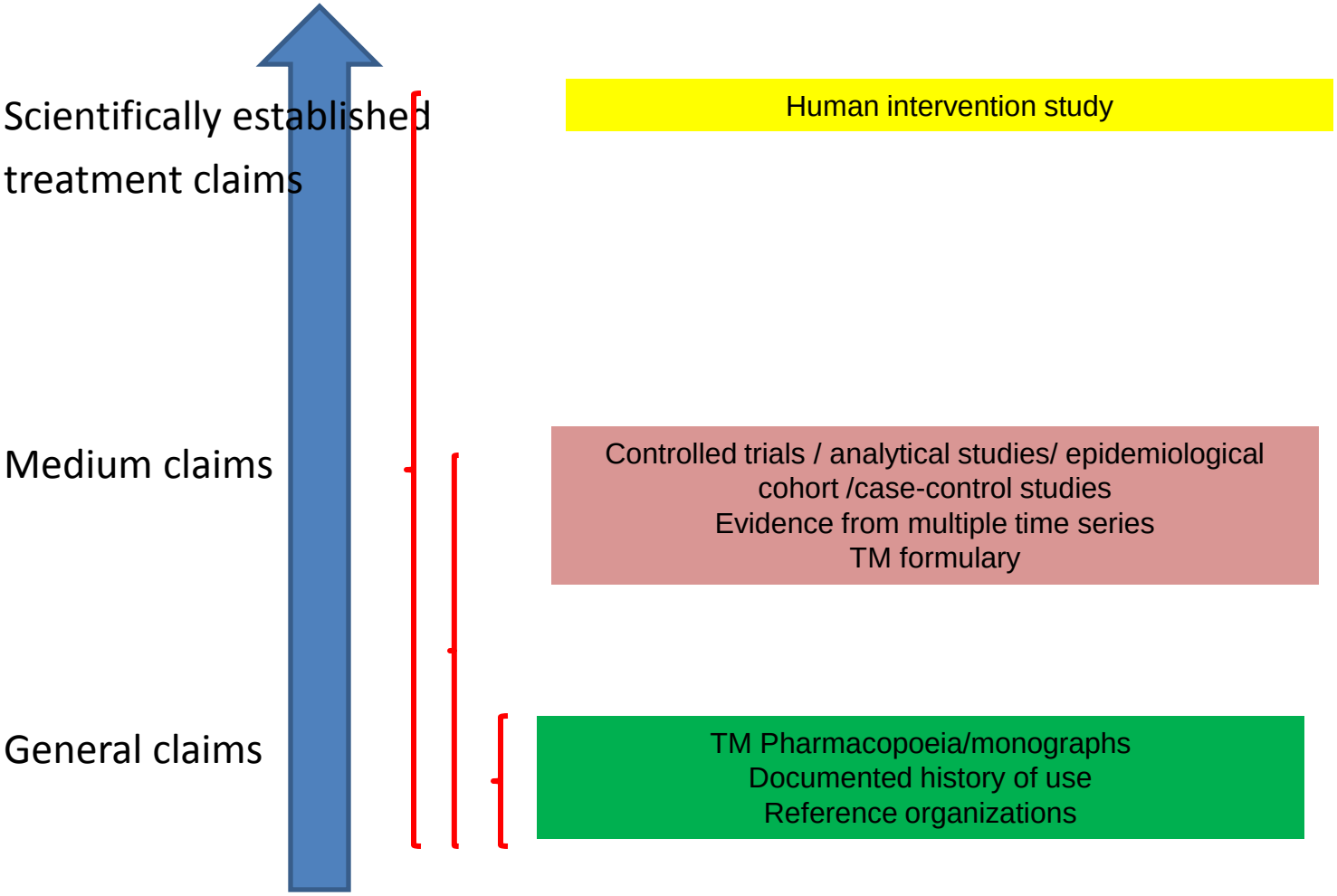
- Daily levels must not exceed maximum daily levels for adults allowed in health supplement
- For pre and antenatal use, as part of a multivitamin and mineral preparation, levels higher than the 20mg limit established for adults may be permitted at the discretion of the Authority.

Ref : ASEAN Guidelines for HS

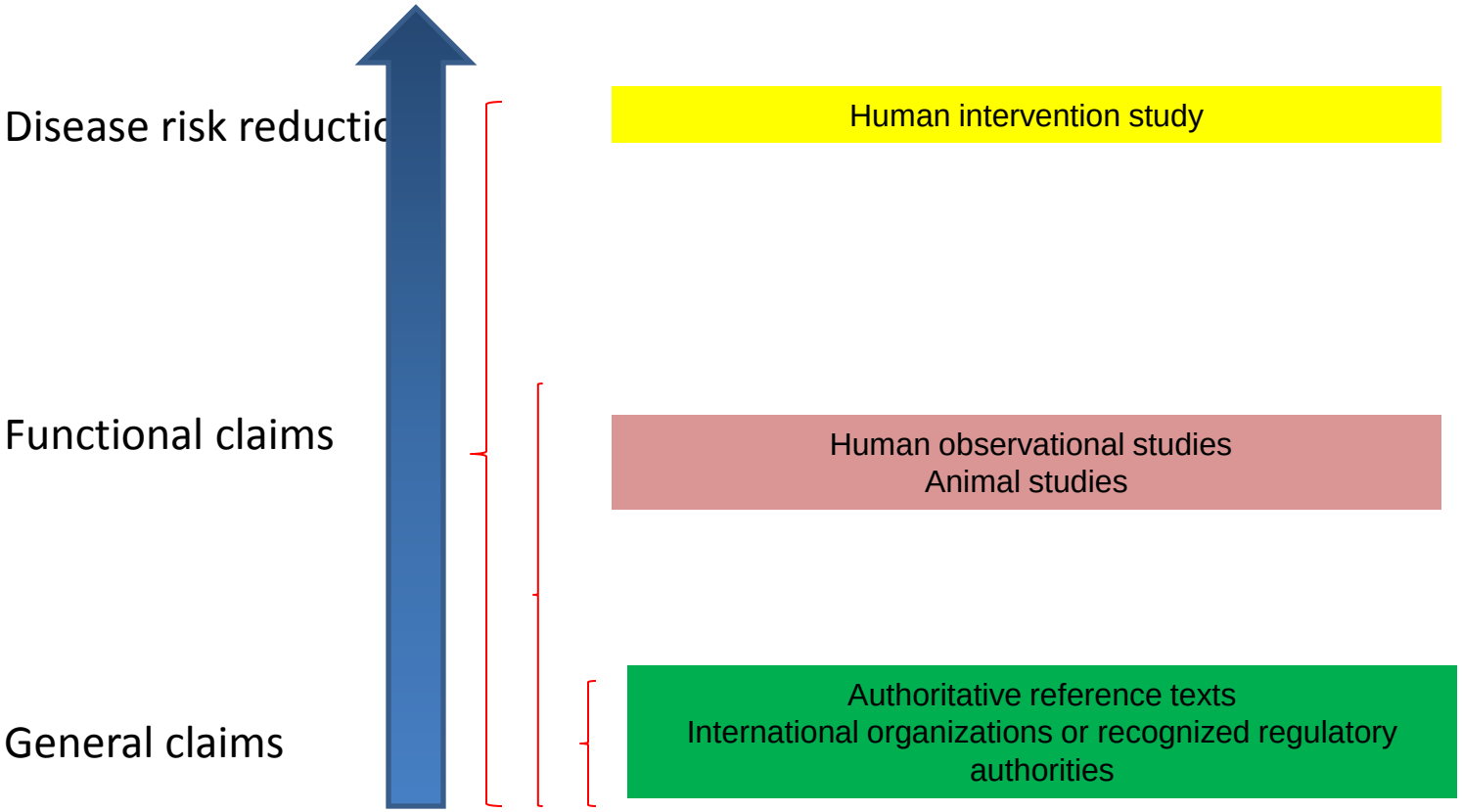
SUMMARY OF CLAIMS



Sources of evidence – TM/Herbal



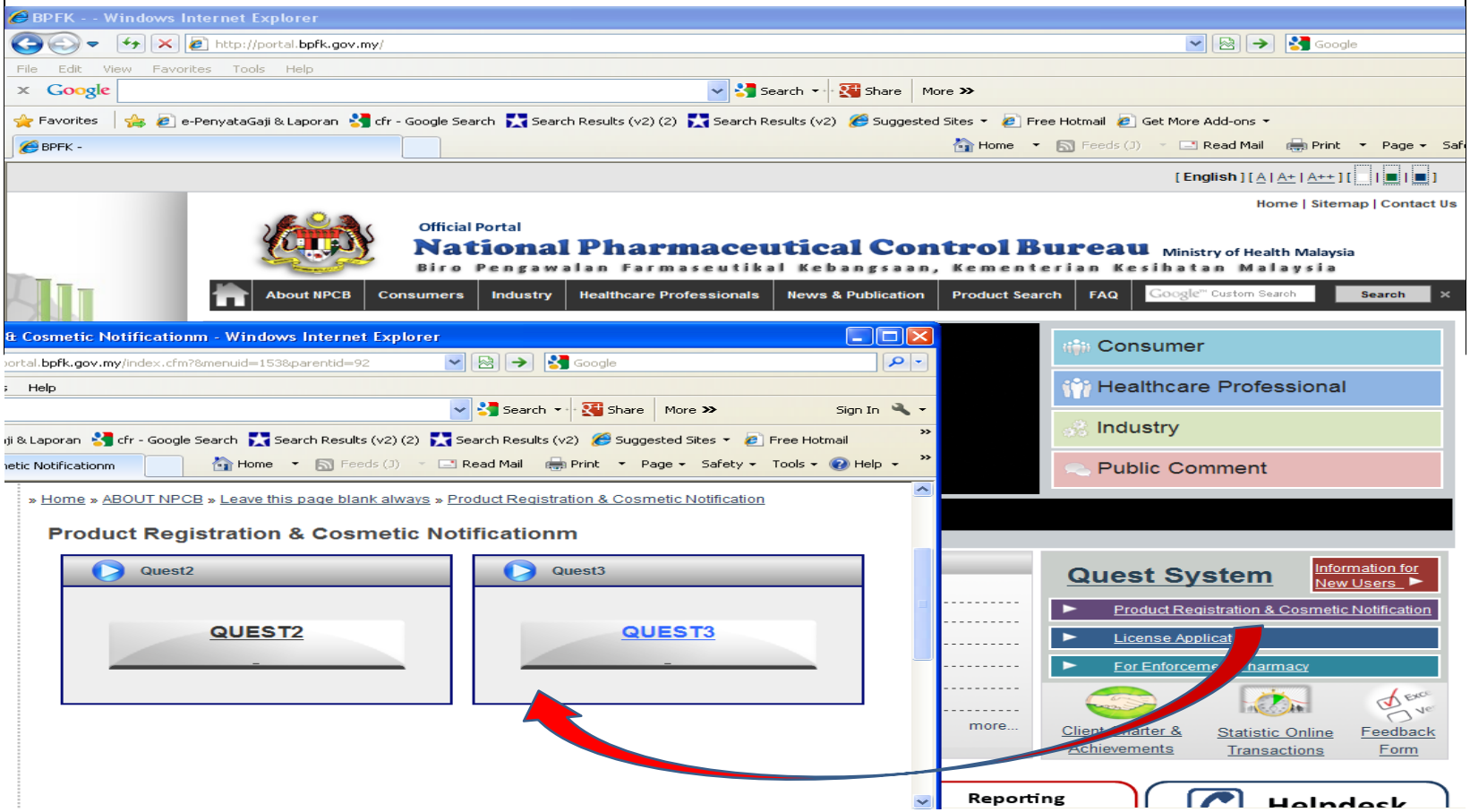
Sources of evidence - HS



ON-LINE REGISTRATION

National Pharmaceutical Control Bureau

http://www. bpfk.gov.my – Quest 3

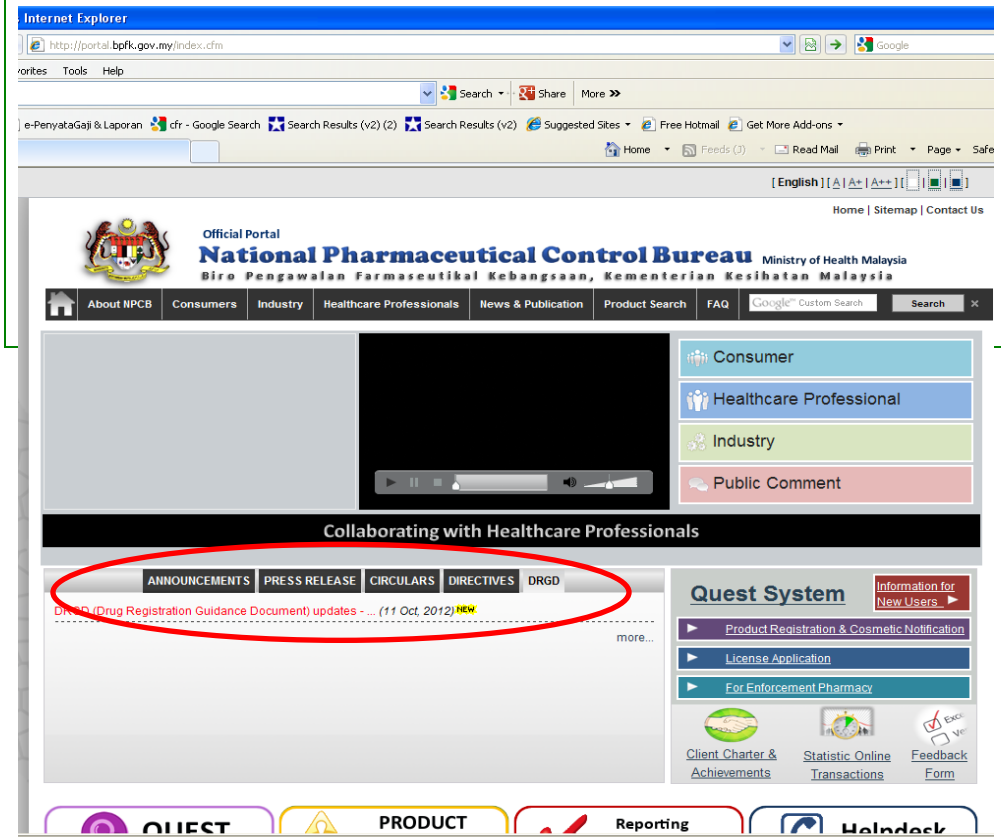


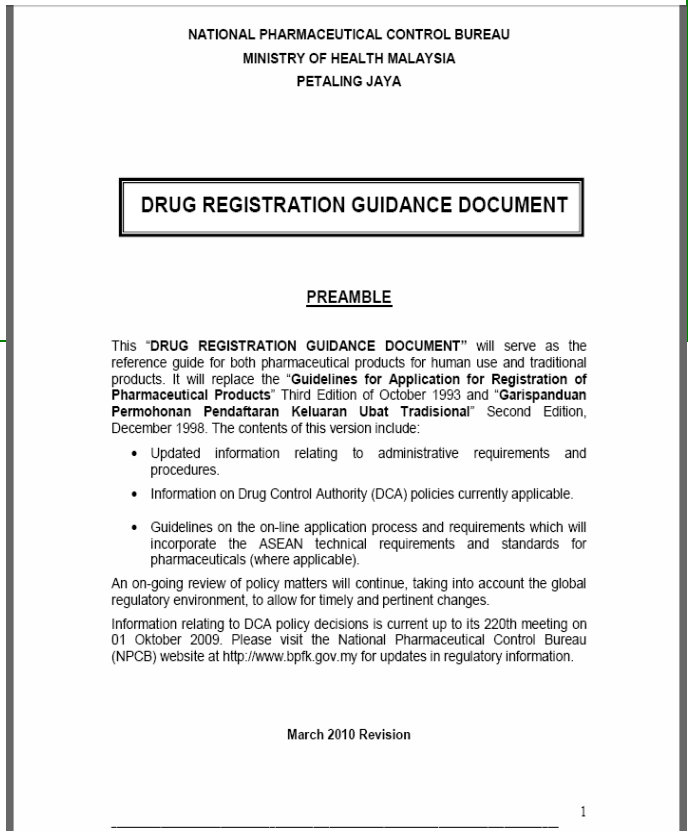
DRUG REGISTRATION GUIDANCE DOCUMENT

1) National Pharmaceutical Control Bureau :

http://www. bpfk.gov.my – Regulatory Information

2) Drug Registration Guidance Document





NATIONAL PHARMACEUTICAL CONTROL BUREAU
MINISTRY OF HEALTH MALAYSIA
PETALING JAYA

DRUG REGISTRATION GUIDANCE DOCUMENT

PREAMBLE

This "**DRUG REGISTRATION GUIDANCE DOCUMENT**" will serve as the reference guide for both pharmaceutical products for human use and traditional products. It will replace the "**Guidelines for Application for Registration of Pharmaceutical Products**" Third Edition of October 1993 and "**Garispanduan Permohonan Pendaftaran Keluaran Ubat Tradisional**" Second Edition, December 1998. The contents of this version include:

- Updated information relating to administrative requirements and procedures.
- Information on Drug Control Authority (DCA) policies currently applicable.
- Guidelines on the on-line application process and requirements which will incorporate the ASEAN technical requirements and standards for pharmaceuticals (where applicable).

An on-going review of policy matters will continue, taking into account the global regulatory environment, to allow for timely and pertinent changes.

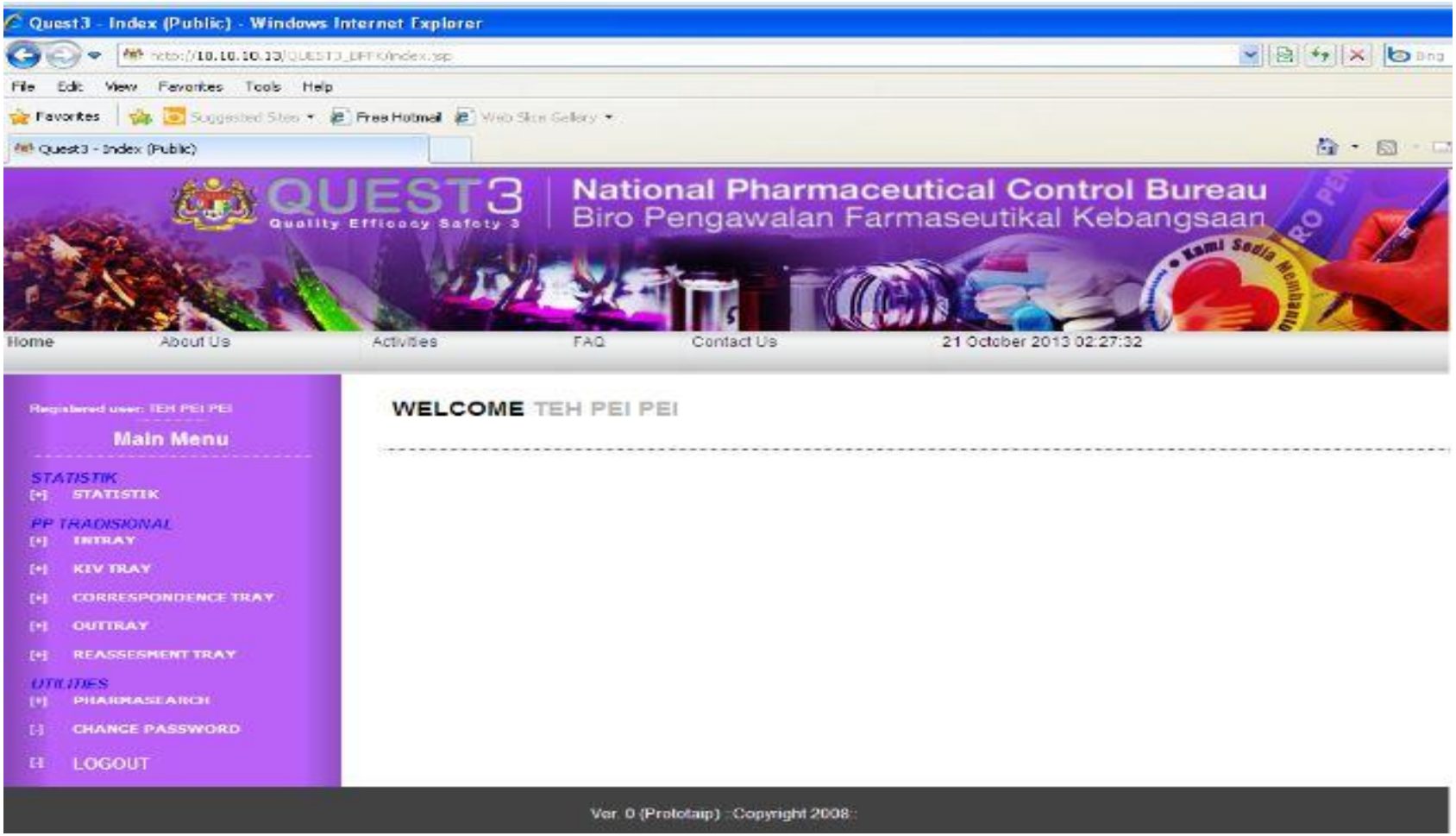
Information relating to DCA policy decisions is current up to its 220th meeting on 01 Oktober 2009. Please visit the National Pharmaceutical Control Bureau (NPCB) website at http://www.bpfk.gov.my for updates in regulatory information.

March 2010 Revision

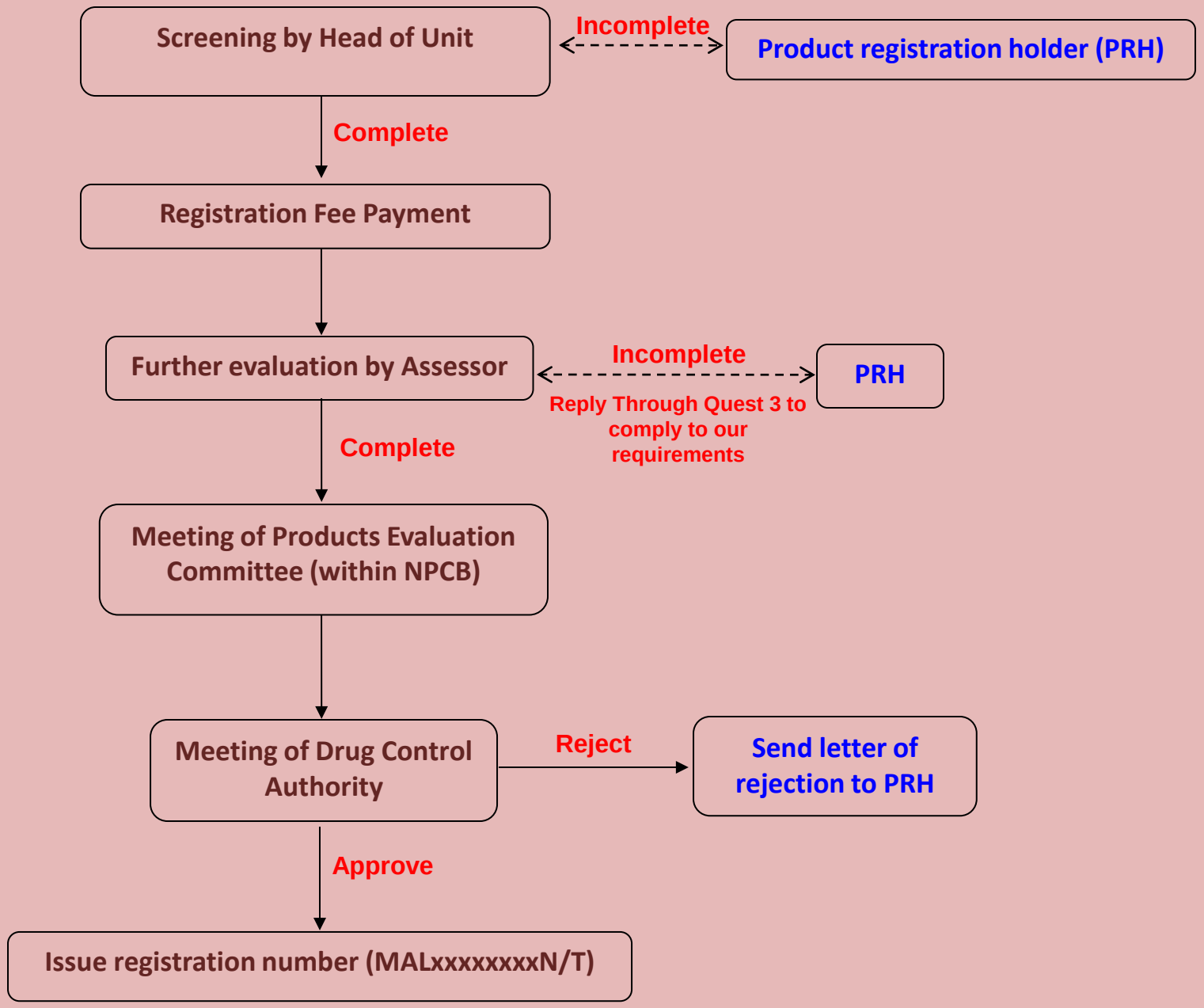
1

Product Registration Application

QUEST 3 LAYOUT



REGISTRATION PROCESS FLOW CHART



Product Registration Number

MAL2014…. "Code"

A: Scheduled Poisons
X: Non-scheduled Poisons
(over the counter products)
T: Traditional Medicines
N: Health Supplements
C: Contract Manufacturer
E: Export Only
R: Repacked
S: Second source

- Validity period of registration – 5 years
- Renewal of product registration should be done not later than 6 month prior to expiry of product registration

CLIENT'S CHARTER

NCE & Biotech	**-**	**< 245 working days**
Generics & OTC	**-**	**< 210 working days**
TM & HS (high claims)	**-**	**< 210-245 working days**
TM & HS (single ing)	**-**	**< 113 working days**
TM & HS (comb)	**-**	**< 136 working days**

On condition → *Full Compliance to Requirements*

FEES

- PROCESSING FEES
  - Pharmaceuticals RM 1000
  - Traditional RM 500
  - Cosmetics RM 50

- LABORATORY TESTING
  - Pharmaceuticals RM 1200- 2000
  - Traditional RM 700

REGULATORY REQUIREMENTS

Quality

Status of manufacturer

Safety

maximum daily limits

Heavy metals

Microorganisms

Efficacy

As claimed

Registration Criteria

Product Particulars

Product Name
Product Description
Dosage Form

Product Formula

Active ingredient
-Banned item
-Excipient

Manufacturer
Name and address
-CPP
_GMP
-CFS

Labeling Requirement

-Compulsory labeling requirement
-Additional Warning/ Precaution

Packing Particulars

-Pack size
-Type of container

SECTION A
PRODUCT PARTICULARS

Fields	Description
A1	Name of Product
A2	Product Description
A3	Dosage Form
A4	Name and Strength of Active and Excipient Substance
A5	Product Indication
A6	Dose / Usage instruction
A7	Contraindication
A8	Warning / Precaution
A9	Drug Interaction
A10	Side Effects / Adverse Reaction
A11	Signs of Overdose
A12	Storage Condition
A13	Shelf Life
A14	Therapeutic Code

SECTION B
PRODUCT FORMULA

Fields	Description
B 1.1	Batch Manufacturing Formula
B 1.2	Attachment of Batch Manufacturing
B 2.1	Manufacturing process
B 2.2	Attachment of manufacturing
B 3.0	In Process Quality Control

SECTION C
PACKING

Fields	Description
C1	Pack Size
C2	Container Type /Container Type Description e.g. : HDPE Plastic Bottle, Glass Bottle, Aluminum Blister Pack
C3	Barcode/Serial Number
C4	Recommended Distributor's Price, RM
C5	Recommended Retail Price, RM

SECTION D
LABELS & PACKAGE INSERT

Fields	Description
D 1	Label (mock up) for immediate container
D 2	Label (mock up) for outer carton
D 3	Proposed package insert

SECTION E
PARTICULARS OF THE MANUFACTURER/ IMPORTER / REPACKER/ PRODUCT OWNER/STORE ADDRESS

Fields	Description
E 1	Product Owner
E 2	Manufacturer
E 3	Repacker
E 4	Other Manufacturer(s) Involved (If Any)
E 5	Store Address
E 6	Importer

SECTION F
SUPPLEMENTARY INFORMATION

Fields	Description
F 1.0	Letter of Authorisation from Product Owner
F 2.1	Letter of Appointment of Contract manufacturer from Product Owner
F 2.2	Letter of Acceptance from Contract Manufacturer
F 3.0	Is the Active Substance(s) Patented in Malaysia
F 4.0	Certificate of Pharmaceutical Product (CPP)
F 5.0	Certificate of Free Sale (CFS)
F 6.0	Good Manufacturing Practice (GMP) Certificate
F 7.0	Summary of Product Characteristics (Product Data Sheet – if any)
F 8.0	Patient Information Leaflet (PIL)
F 9.0	Attachment of Protocol Analysis
F 10	Attachment of Certificate Analysis (Finished Product)
F 11	Attachment of Certificate of Analysis (Active Ingredient)
F 12	Other Supporting Document

SAFETY CRITERIA

- Limits for heavy metals
- Limits for microbial contamination
- Absence of steroids and other adulterants
- Indications and claims
- Prohibition of herbs/ingredients with known adverse effects
- Labeling

SCREENING FOR ADULTERANTS

Based on product indications:	
Men's health	- e.g. Sildenafil, Tadalafil and its analogues
Slimming	- e.g. Fenfluramine
Muscle and joint pains	– e.g. NSAIDs, Steroids
Cough and cold	- e.g. Anti- histamines

RED YEAST RICE…

For products containing Red Yeast Rice (*Monascus purpureus*), applicants shall provide certificates of analysis (for both raw material and finished product) showing the Monacolin-K content.

The percentage of Monacolin-K shall not exceed 1% and the Monakolin-K consumed shall not exceed 10 mg per day.

Supporting Documents for New Active Ingredients/ New Dose

Reference Countries	• United Kingdom, Sweden, France, United States of America, Australia, Canada, **Japan** and Switzerland • Must be provided from competent authorities (e.g. US FDA, TGA, Health Canada) • Examples: Registration status, established monograph
Clinical Studies / Scientific Evidences / Researches	• Full articles from the published journals • Examples : Human clinical studies, scientific reviews, animal toxicological studies etc
Established References	• Examples: Martindale, Pharmacopeias, US PDR, The Merck Index etc

QUALITY CRITERIA

HEAVY METAL SPECIFICATION

Mercury	**-**	**not more than 0.5 ppm**
Arsenic	**-**	**not more than 5.0 ppm**
Lead	**-**	**not more than 10 ppm**
Cadmium	**-**	**not more than 0.3 ppm**

QUALITY CRITERIA

12.6 QUALITY CONTROL TEST SPECIFICATIONS FOR TRADITIONAL MEDICINE PRODUCTS

1. Limit Test for Heavy Metals

Maximum limit for heavy metals:

1.1	Lead	:	NMT 10.0 mg/kg or 10.0 mg/litre (10.0ppm)
1.2	Arsenic	:	NMT 5.0 mg/kg or 5.0 mg/litre (5.0ppm)
1.3	Mercury	:	NMT 0.5 mg/kg or 0.5 mg/litre (0.5ppm)
1.4	Cadmium	:	NMT 0.3 mg/kg or 0.3 mg/litre (0.3ppm)

2. Disintegration Test (for tablets, capsules and pills)

Disintegration time

2.1	Uncoated tablets	:	NMT30 minutes
2.2	Film-coated tablets	:	NMT 30 minutes
2.3	Sugar-coated tablets	:	NMT 60 minutes
2.4	Enteric-coated tablets	:	Does not disintegrate for 120 minutes in acid solution but to disintegrate within 60 minutes in buffer solution
2.5	Capsules	:	NMT 30 minutes
2.6	Pills	:	NMT 120 minutes

3. Test for Uniformity of Weight (tablets and capsules only)

Not more than 2 capsules / tablets exceed the limit by ± 10% from the average weight AND no tablet / capsule exceed the limit by ± 20% from the average weight.

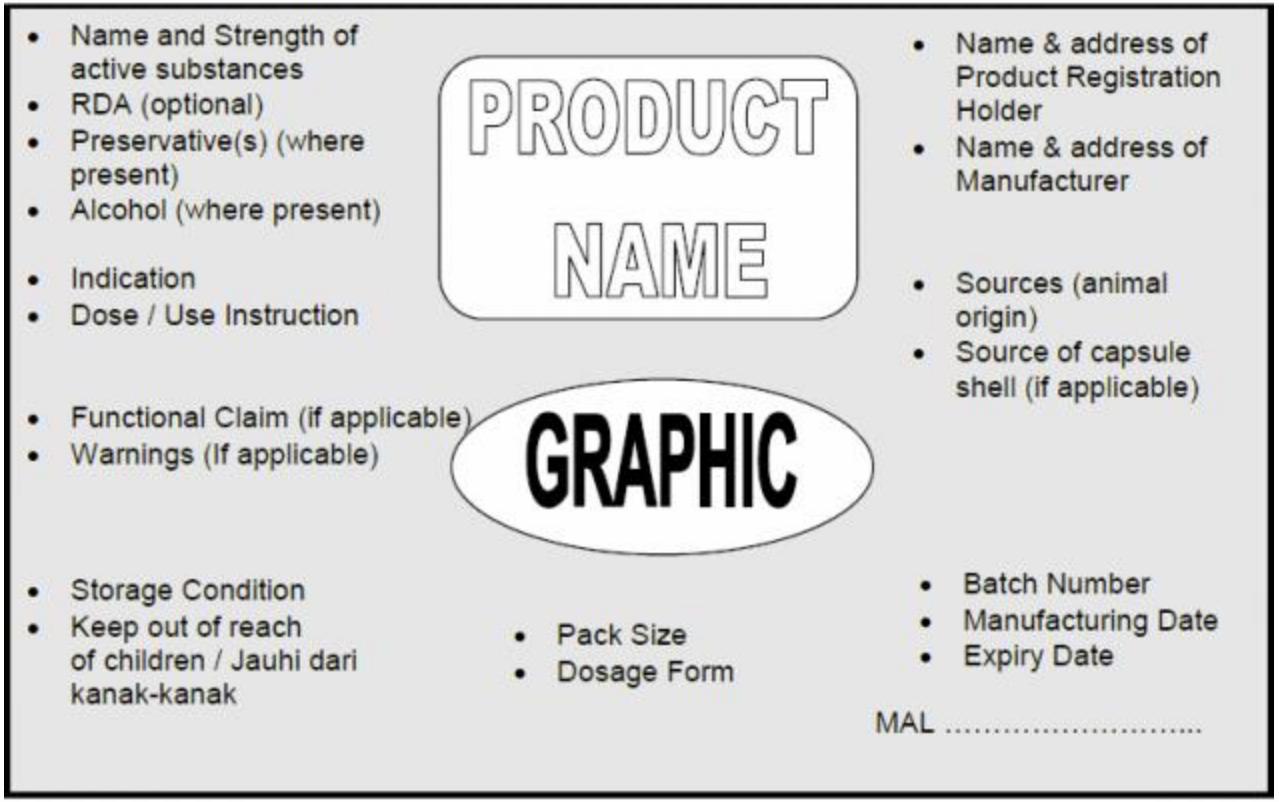
4. Test for Microbial Contamination

Route of Administration	TAMC (CFU/g or CFU/ ml)	TYMC (CFU/g or CFU/ ml)	Test for Specified Microorganisms
Rectal Use	NMT 2×10^3	NMT 2×10^2	
Oromucosal Use Gingival Use Cutaneous Use Nasal Use Auricular Use	NMT 2×10^2	NMT 2×10^1	- Absence of Staphylococcus aureus in 1g or 1ml - Absence of Pseudomonas aeruginosa in 1g or 1ml
Vaginal Use	NMT 2×10^2	NMT 2×10^1	- Absence of Staphylococcus aureus in 1g or 1ml

SUMMARY - ASSESSMENT CRITERIA

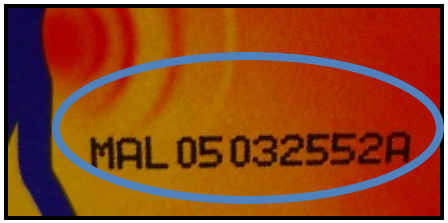
SAFETY	QUALITY	INDICATIONS & CLAIMS	LABELLING
•Absence of banned/prohibited ingredients •Pre registration testing •Heavy metals – Mercury, Arsenic, Lead, Cadmium •Microbial limit test •Adulterants •Prohibition on the use of premixes •Declaration that product is free from TSE •ADR reporting	•Compliance with Good Manufacturing Practices •Limits for disintegration time •Uniformity of weight •Stability data •Evidence of marketing authorization in exporting country	•Low level claims supported by documents/literature on traditional use •Prohibition on claims for 20 diseases as stipulated in the Medicines (Advertisement & Sale) Act •Revocation of license if found to be making false / unauthorized claims	•Full ingredient listing •Name of Marketing Authorization Holder •Name of manufacturer (and repacker, if any) •Serialized Security label (Hologram) •Warning statements •Precautions

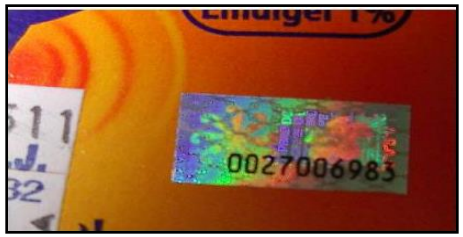
Label


Name and Strength of active substances
RDA (optional)
Preservative(s) (where present)
Alcohol (where present)
Indication
Dose / Use Instruction
Functional Claim (if applicable)
Warnings (If applicable)
Storage Condition
Keep out of reach of children / Jauhi dari kanak-kanak
PRODUCT NAME
GRAPHIC
Pack Size
Dosage Form
Name & address of Product Registration Holder
Name & address of Manufacturer
Sources (animal origin)
Source of capsule shell (if applicable)
Batch Number
Manufacturing Date
Expiry Date
MAL .....

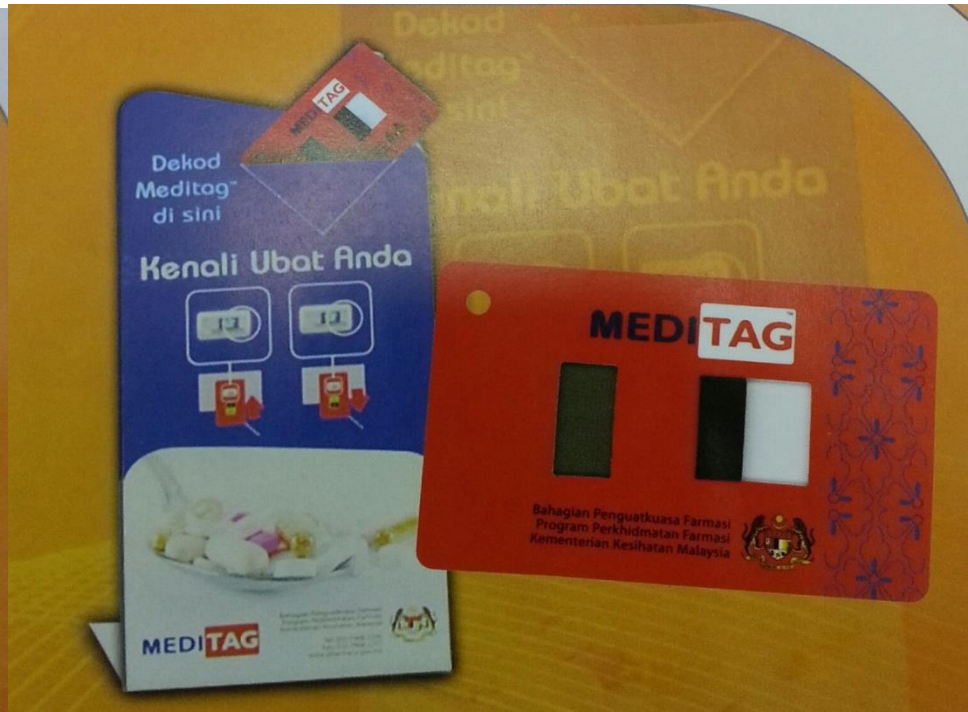
HOLOGRAM MEDITAG®

SECURITY FEATURES





- **Both overt (visible) and covert (hidden)**



Challenges

- TM and HS have differences in their functions, requiring different 'tools' for the pre market control and assesment for the risks.
- TM can not only be seen as a trade commodity but also as a comprehensive health care involving traditional practitioner.
- Doses and usage of the same ingredients may be different
- Selective publication of study results (limited research budget)
- CAM products in most countries are not required to be registered
- Ingredient or product ?

Challenges

- New active ingredients
- Products of new combinations of active ingredients
- New claims
- New technology (e.g. bilayer technology)
- New invention (e.g. new dosage form, extended release/slow release)

Challenges

- Adulteration
- Illegal Manufacturing
- Unregistered Products
- Slick marketing campaigns involving unsubstantiated gimmicky products
- Misleading Claims
- Premix

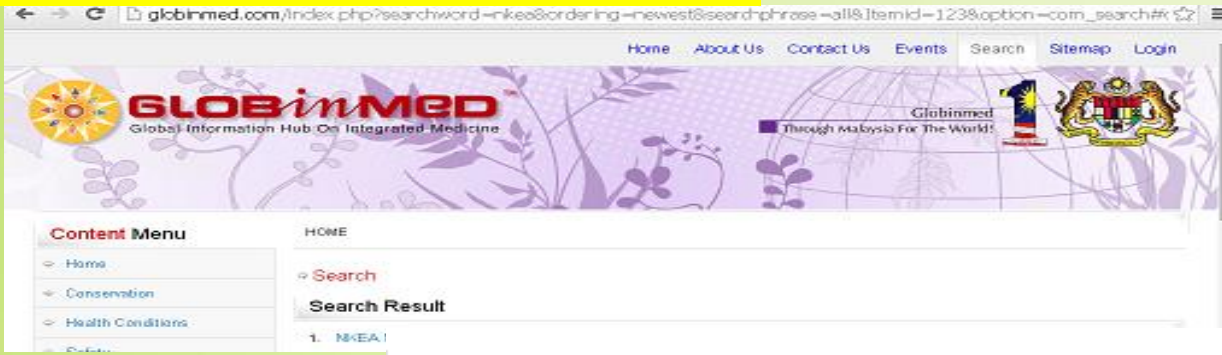
THE WAY FORWARD

- ✓ Educating the public about current CAM evidence
- ✓ More quality research
- ✓ Intellectual property protection
- ✓ CAM to be used as adjunct to modern medicine (complementary)
- ✓ CAM to be used in place off conventional therapy (alternative)
- ✓ Physicians being oriented to CAM modalities and philosophy

THE WAY FORWARD

- Official analytical methods
- Pre-cleared information -Recognized standards monographs
- Herbal reference standards
- Competent expertise
- Laboratories

MONOGRAF HERBA MALAYSIA NKEA



Search Result

1. NKEA Monograf

   Category: Uncategorised

1	Andrographis paniculata Nees
2	Centella asiatica (L.) Urban
3	Eurycoma longifolia Jack
4	Ficus deltoidea Jack
5	Hibiscus sabdariffa Linn
6	Labisia pumila
7	Morinda citrifolia Linn.
8	Orthosiphon stamineus Benth
9	Phyllanthus amarus Schum
10	Zingiber officinale Rosc

On-going research projects

- **Gamma Aminobutyric Acid (GABA) active ingredient**
  - GABA will be prohibited until data of it's safety and recommended dosage can be provided.
- **Active ingredients containing naturally occurring Theophylline and Caffeine.**
  - Assessment of the level of Theophylline and Caffeine in registered products will be done starting with the list of registered products in QUEST 2.
  - Maximum level of Theophylline/ Caffeine will be set based on safety assessment for traditional products

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- Quantification of α & β-asarone in finished traditional products

-α and β-asarone were reported to cause toxicity ad carcinogenicity in mammalians

- EMEA has set the safety level as not more than 115 µg/ day or 2 µg/ kg bw/ day)

- On-going assessment of the levels of α and β-asarone on registered finished products on the market

NEW PROPOSAL

NEW INDICATIONS FOR Traditionally used……

-To conduct a pilot study starting with the CHINESE PHILOSOPHY OF USE first, followed by the other traditional practices later

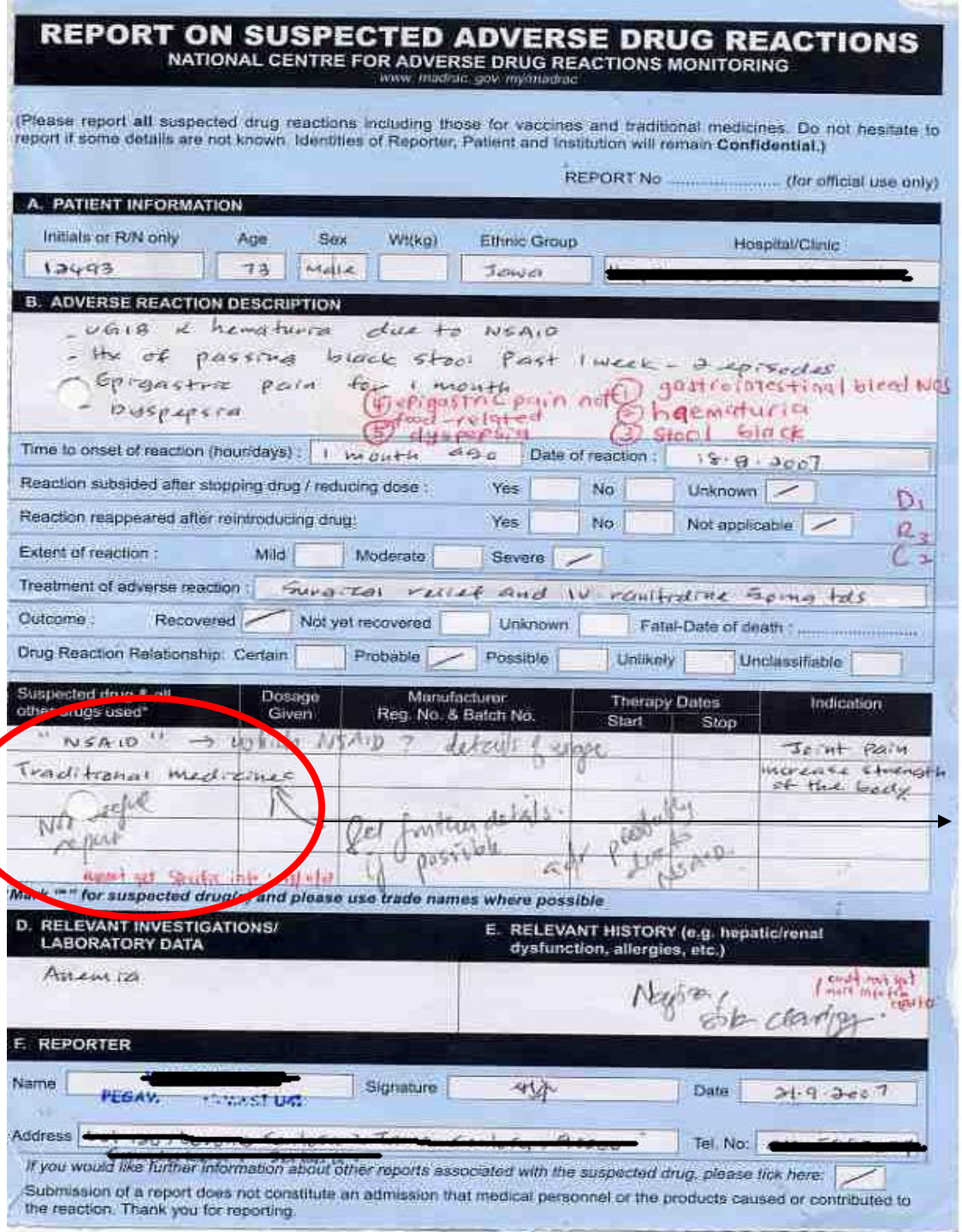
-A working group will be formed to address the issues and prepare a guideline for the convenience of the industry

-The committee may wish to list our the acceptable references

NEW INDICATIONS FOR Traditionally used.....

BASED ON PHILOSOPHY OF USE – EXAMPLES

PRODUCT NAME	INDICATION REGISTERED	INDICATION BASED ON THE PHILOSOPHY
ABC Tablet	Traditionally used for general health	Deficient and insecure exterior pattern manifested as spontaneous sweating, aversion to wind, bright pale complexion or people with weak constitution who are susceptible to wind
Dang Gui Bu Wie Tang Extract XYZ	Traditionally used for improving blood circulation	To tonify Qi and nourish blood
DEF	Traditionally used for reducing toothache	Stomach heat with yin deficiency, marked by fever, thirst, headache, toothache, nosebleed, hemoptysis, red tongue with white or dry yellow coating and rapid pulse



REPORT ON SUSPECTED ADVERSE DRUG REACTIONS

NATIONAL CENTRE FOR ADVERSE DRUG REACTIONS MONITORING

www.nadrac.gov.my/nadrac

(Please report **all** suspected drug reactions including those for vaccines and traditional medicines. Do not hesitate to report if some details are not known. Identities of Reporter, Patient and Institution will remain **Confidential.**)

REPORT No ..... (for official use only)

A. PATIENT INFORMATION

Initials or R/N only	Age	Sex	Wt(kg)	Ethnic Group	Hospital/Clinic
12493	73	Male		Jawa	[redacted]

B. ADVERSE REACTION DESCRIPTION

- UGIB & hematuria due to NSAID
- Hx of passing black stool past 1 week - 2 episodes
- Epigastric pain for 1 month
- Dyspepsia

(1) gastrointestinal bleed NOS
(2) haematuria
(3) stool black
(4) epigastric pain not food-related
(5) dyspepsia

Time to onset of reaction (hour/days) : 1 month ago Date of reaction : 18.9.2007

Reaction subsided after stopping drug / reducing dose : Yes [ ] No [ ] Unknown [/]

Reaction reappeared after reintroducing drug: Yes [ ] No [ ] Not applicable [/]

Extent of reaction : Mild [ ] Moderate [ ] Severe [/]

Treatment of adverse reaction : Symptomatic relief and IV ranitidine 5 amp tds

Outcome : Recovered [/] Not yet recovered [ ] Unknown [ ] Fatal-Date of death : .....

Drug Reaction Relationship: Certain [ ] Probable [/] Possible [ ] Unlikely [ ] Unclassifiable [ ]

Suspected drug & all other drugs used*	Dosage Given	Manufacturer Reg. No. & Batch No.	Therapy Dates Start	Therapy Dates Stop	Indication
"NSAID" → ? NSAID ? details if urgent					Joint pain
Traditional medicines					increase strength of the body
Not useful report					
Get further details if possible					

Mark "" for suspected drug(s) and please use trade names where possible*

D. RELEVANT INVESTIGATIONS/ LABORATORY DATA

Anemia

E. RELEVANT HISTORY (e.g. hepatic/renal dysfunction, allergies, etc.)

Nephro / Gb clearing.

F. REPORTER

Name [redacted] Signature [redacted] Date 21.9.2007

Address [redacted] Tel. No: [redacted]

If you would like further information about other reports associated with the suspected drug, please tick here: [/]

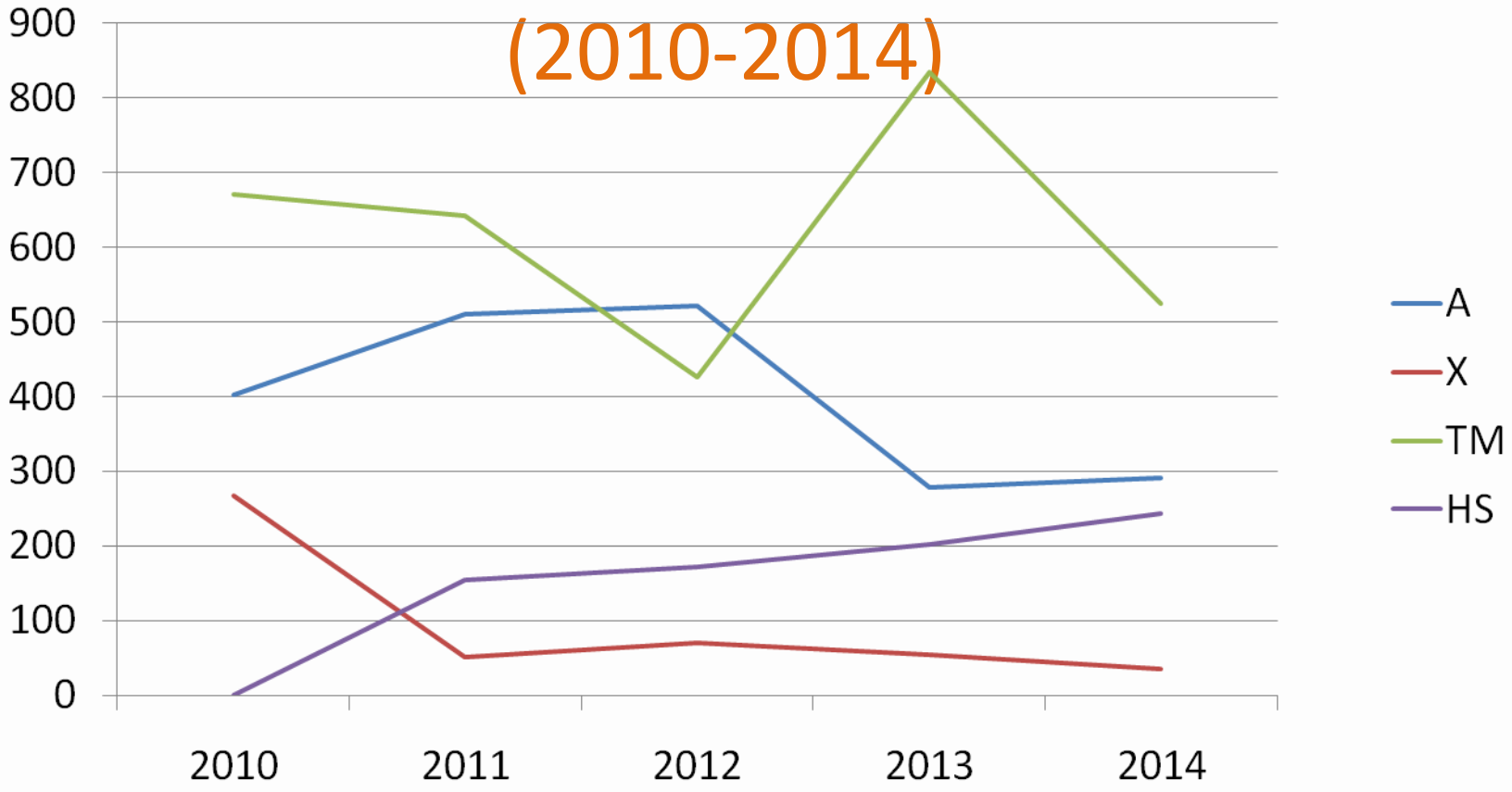
Submission of a report does not constitute an admission that medical personnel or the products caused or contributed to the reaction. Thank you for reporting.

Suspected Drug : Traditional Medicine

Local Report : Whitening Cream

- Information on product used and where it was purchased was provided
- Sample taken for testing and was found to contain 25% hydroquinone
- Actions taken:
  - GMP audit done of manufacturing premise
  - Found gross violation of GMP principles
  - Manufacturer instructed to shut down
  - Total product recall
  - Decision made not to allow use of hydroquinone in Over-The-Counter products

Number of applications (payment made) (2010-2014)




TAMAN HERBA


CEKUR MERAH


KACIP FATIMAH


NAGABUANA


DUKUNG ANAK

Malaysia

Truly Asia