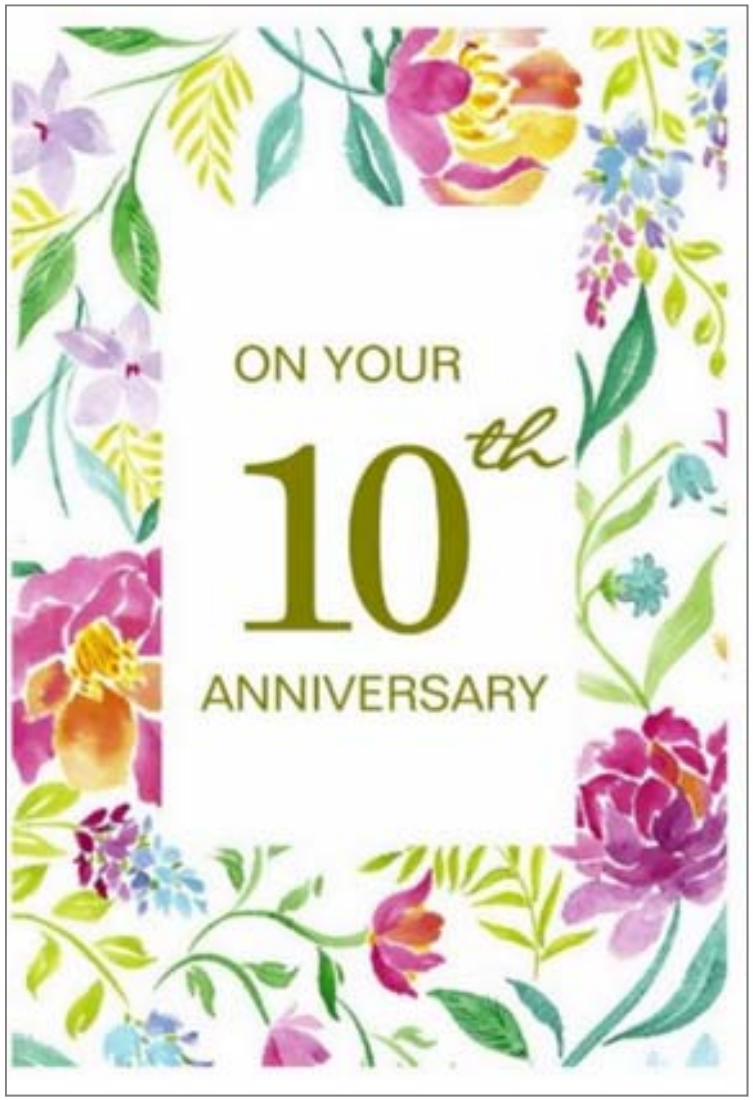
Managing Changing Regulatory Paradigms

Assoc Prof John Lim
Chief Executive Officer
Health Sciences Authority, Singapore

8 Feb 2014

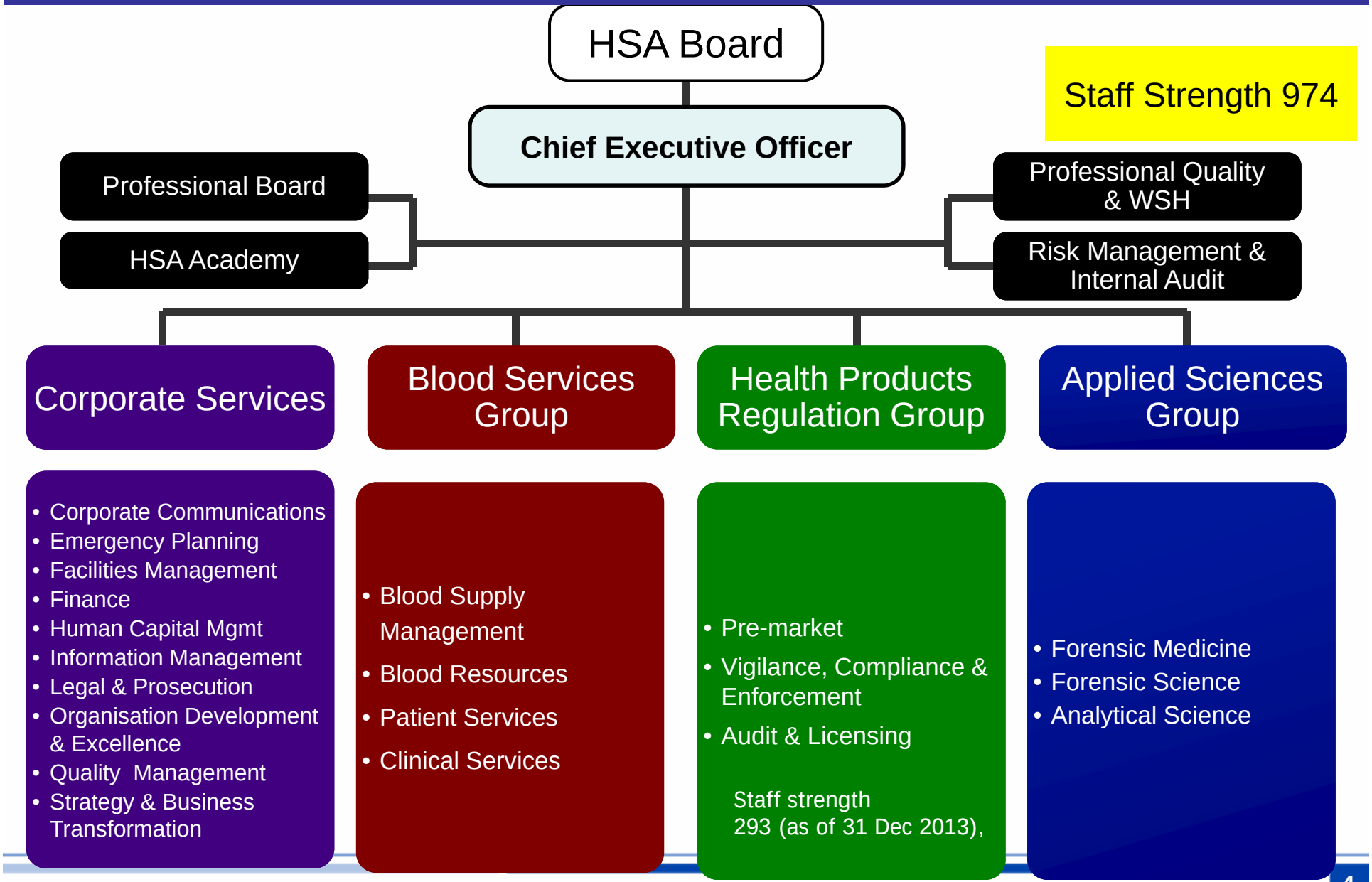
Congratulations to PMDA!



Scope

- Overview of HSA
- Responses to Changing Regulatory Trends

HSA Organisational Chart



HSA
Health Sciences Authority

Vision

To be the **LEADING**
INNOVATIVE AUTHORITY
protecting and advancing **NATIONAL HEALTH** and **SAFETY**

Mission

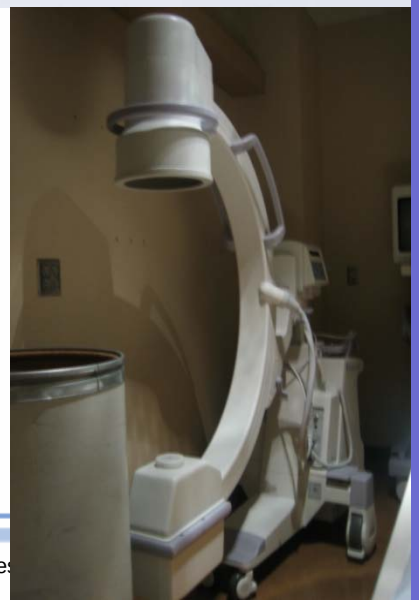
- To **wisely regulate** health products
- To **serve** the administration of justice
- To **secure** the nation's blood supply
- To **safeguard** public health

Corporate Headquarters • Health Products Regulation Group • Blood Services Group • Applied Sciences Group

A Statutory Board of the Ministry of Health | The Singapore Public Service : Integrity • Service • Excellence

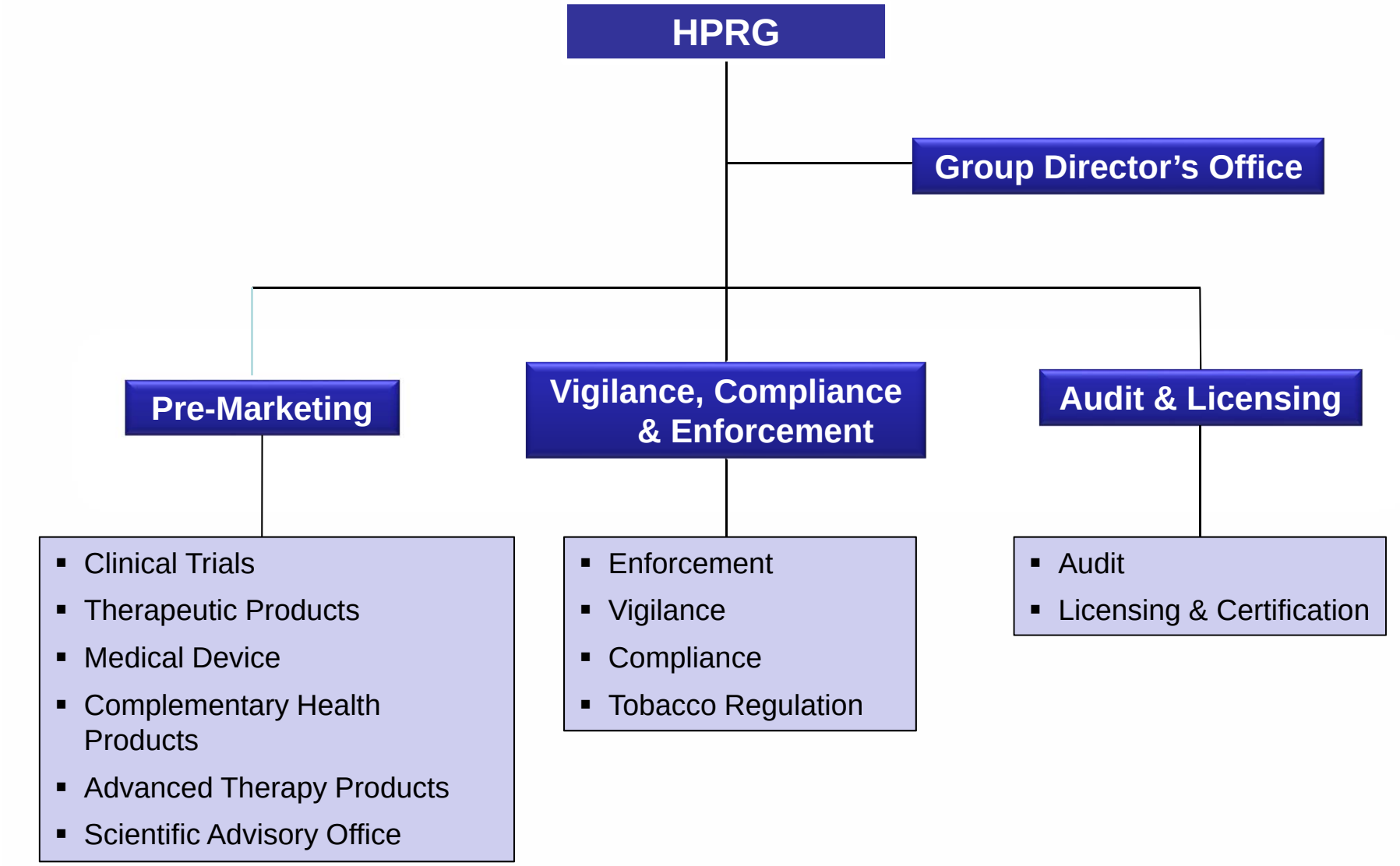
Health Products Regulation Group

Pre-marketing Div : Vigilance, Compliance & Enforcement Div : Audit & Licensing Div

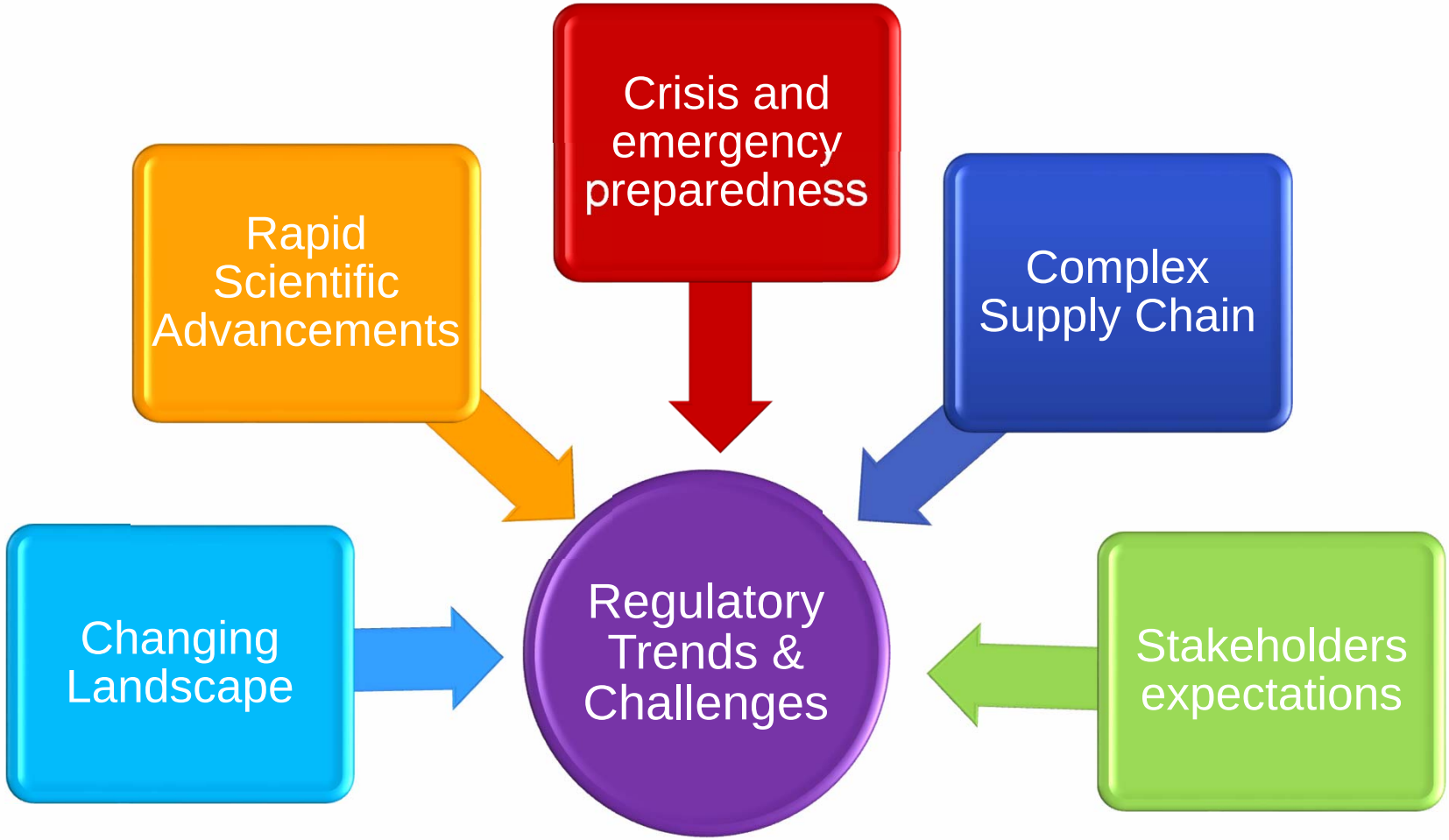


Ensures that drugs, innovative therapeutics, medical devices and health-related products in Singapore are wisely regulated to meet appropriate standards of safety, quality and efficacy

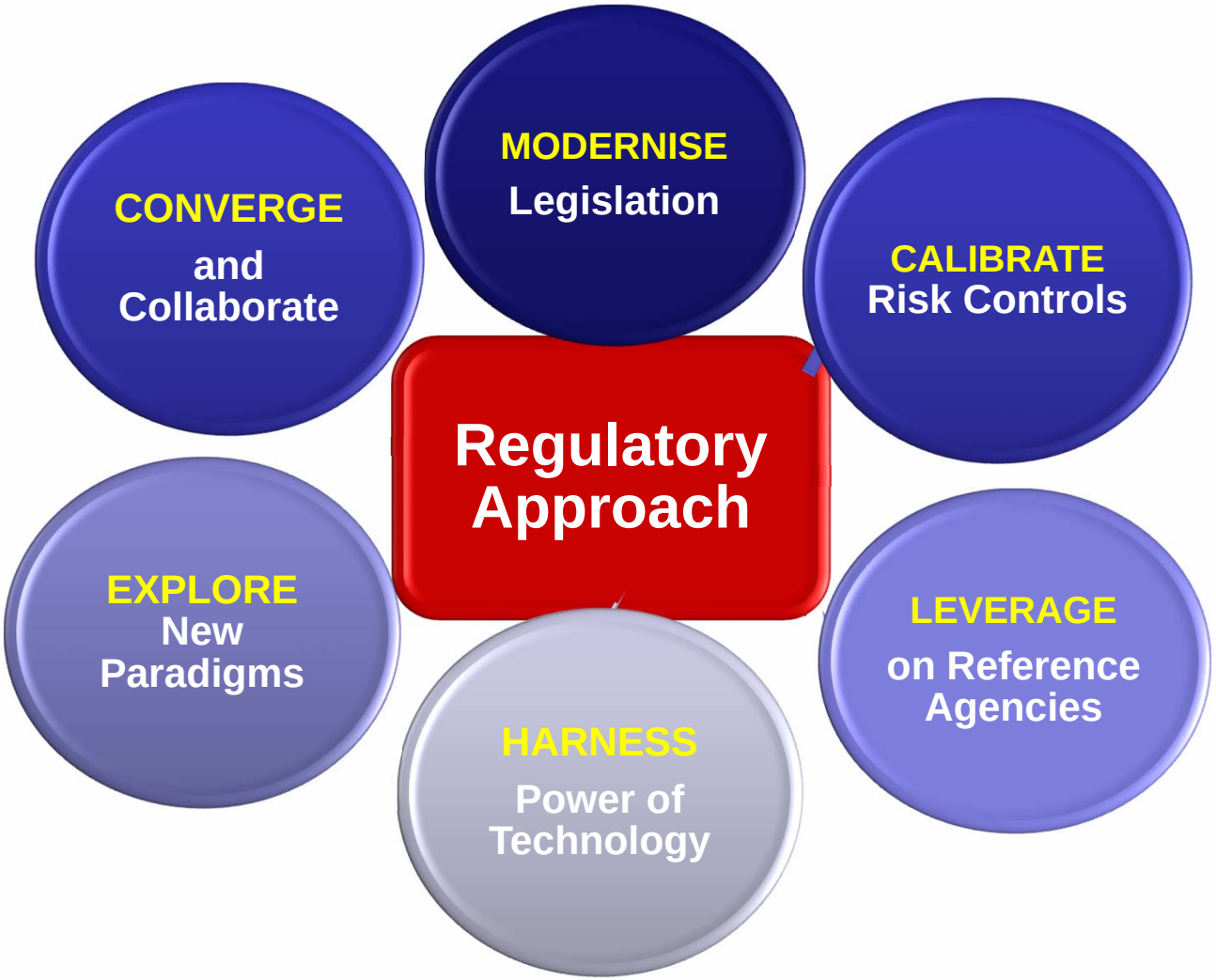
HPRG's Key Functional Areas



Regulatory Trends and Challenges



Defining the Regulatory Approach

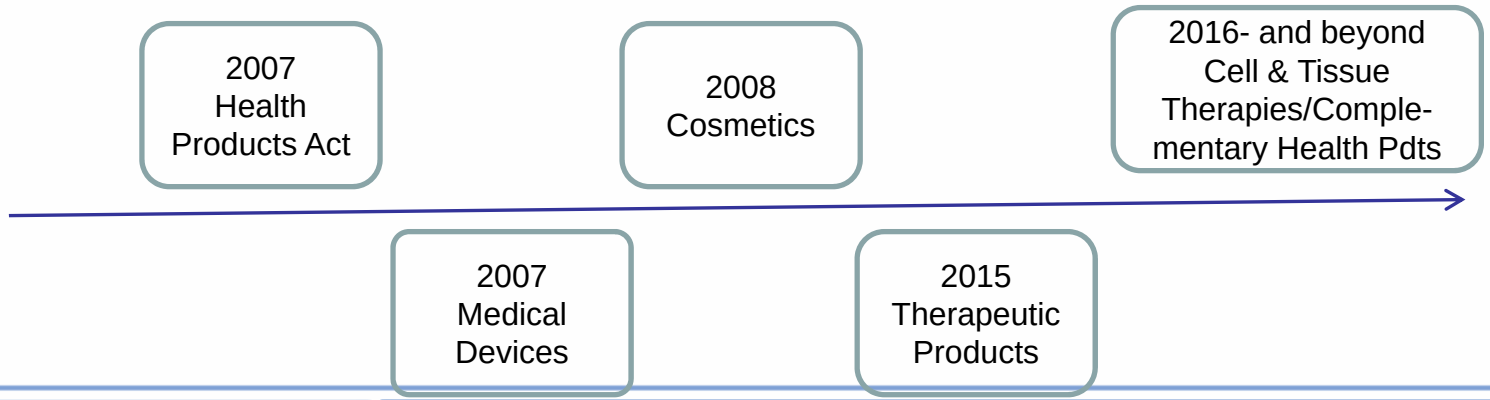


Modernise Legislation

Legislative Restructuring

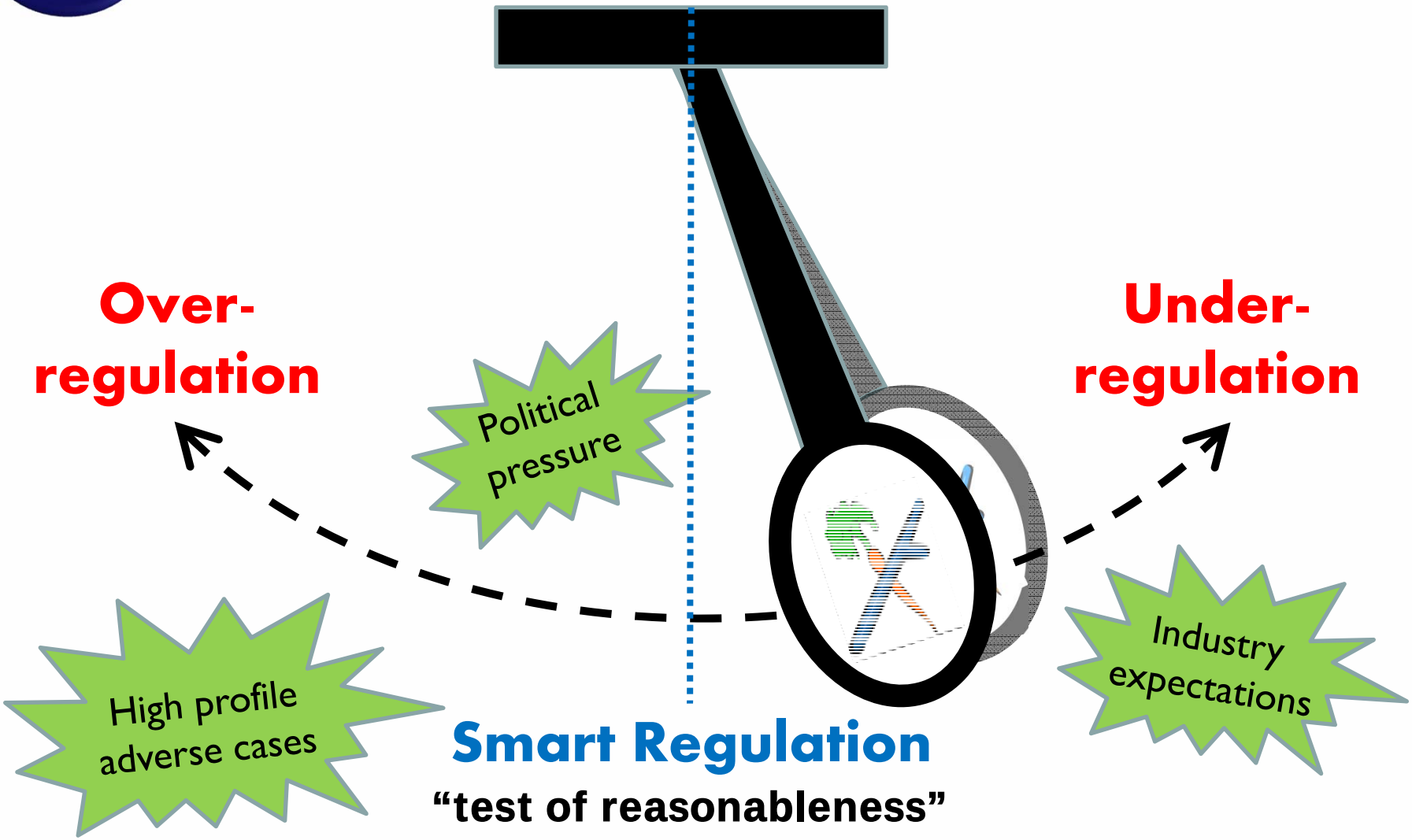
Health Products Act (2007)

- To consolidate medicines control laws
- Modular approach – more responsive & flexible to deal with different degrees of risk
- Covers regulation of health products, dealers' obligations and more appropriate penalties
- Proactive stakeholder consultations



Calibrate Risk Controls

The Regulatory Pendulum



Calibrate Risk Controls

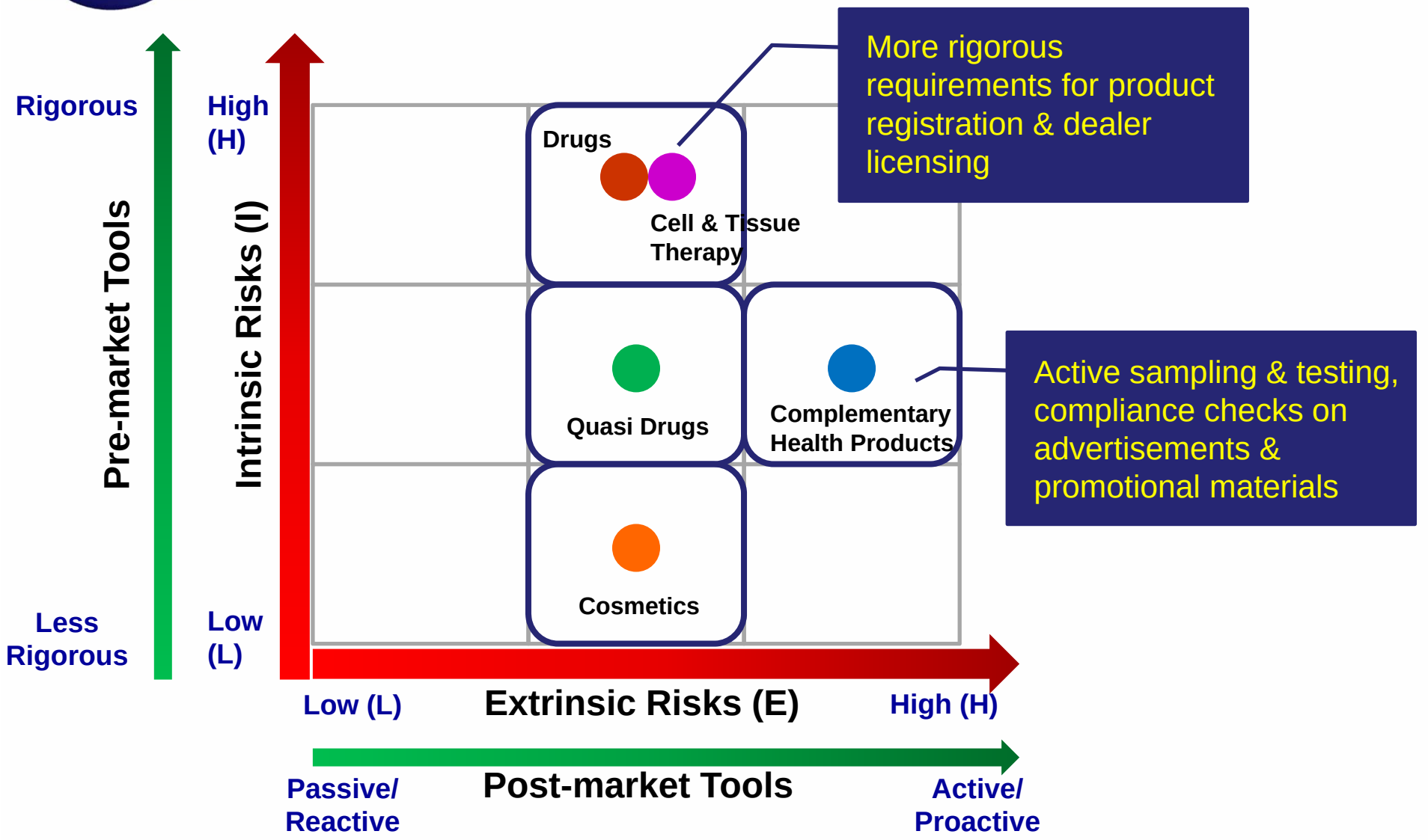
Intrinsic & Extrinsic Risks

- Intrinsic risks
  - Inherent risks of the product based on declared composition & intended use, e.g. ingredients, mode of administration, adverse effects
  - Known from disclosure by applicants or on current scientific knowledge, although uncertainties still exist
  - **Pre-market control & post-approval conditions**

- Extrinsic risks
  - Risks not attributable to declared composition & intended use, e.g. adulteration, contamination, unsubstantiated claims
  - Usually unknown but may be predicted from trends/experience or minimised through process controls
  - **Post-approval surveillance, audit, vigilance & enforcement**

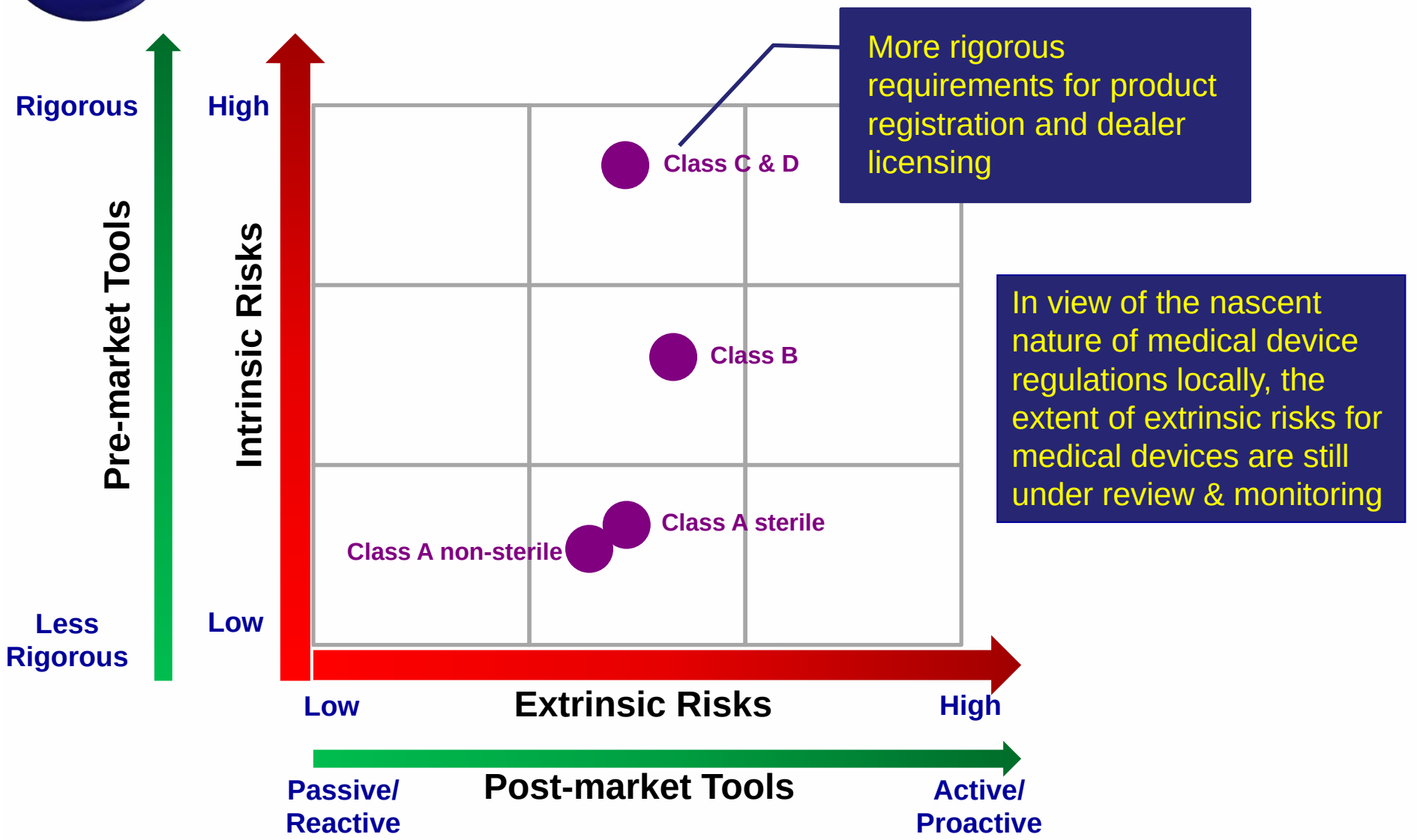
Calibrate Risk Controls

Risk Matrix for Medicines



Calibrate Risk Controls

Risk Matrix for Devices



Leverage on Ref Agencies

Confidence Based Pathways (Drugs)

3 confidence-based pathways allow companies to opt for route potentially offering shortest time to market for medicines

Full (from 1998)	No prior approval by any drug regulatory agency	Full quality, non-clinical, & clinical	Total: 270 working days
Abridged (from 1987)	Approved by one drug regulatory agency	Quality, clinical & abridged early phase clinical studies and non-clinical	Total: 180 working days
Verification (from 2003)	Approved by two reference agencies*	Reference agency assessment report	Total: 60 working days

Reference agencies : TGA, FDA, EMA, Health Canada, MHRA

Leverage on Ref Agencies

Confidence Based Pathways (Devices)

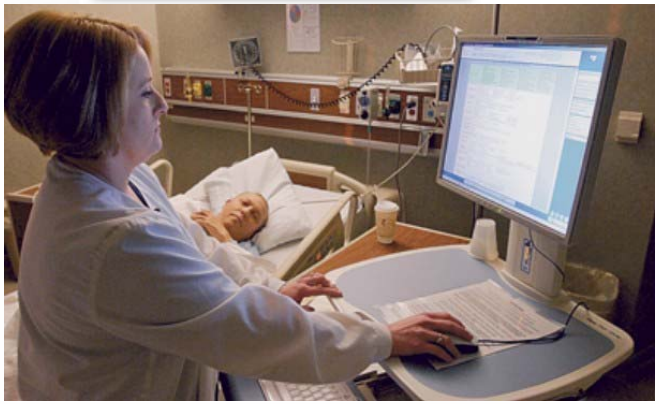
Reference agencies * European Union, Health Canada, Japan MHLW, US FDA, Australia TGA

Full Evaluation	No prior approval by any of medical device reference agencies*	Full quality, pre-clinical & clinical document	Total: 160 to 310 working days depending on risk class of medical devices
Abridged Evaluation	Approval by at least one medical device reference agency*	Quality, pre-clinical & clinical summary reports	Total: 100 to 220 working days depending on risk class of medical devices
Expedited Registration (For Class B)	Review of label claims, quality and pre-clinical summary documents	Total: 60 working days	
Immediate Registration (For Class B)	Verification of certificates/documents	Immediate registration upon successful submission	

Harness Power of Technology

Electronic AE Reporting

Fax
Post
Email
Tel



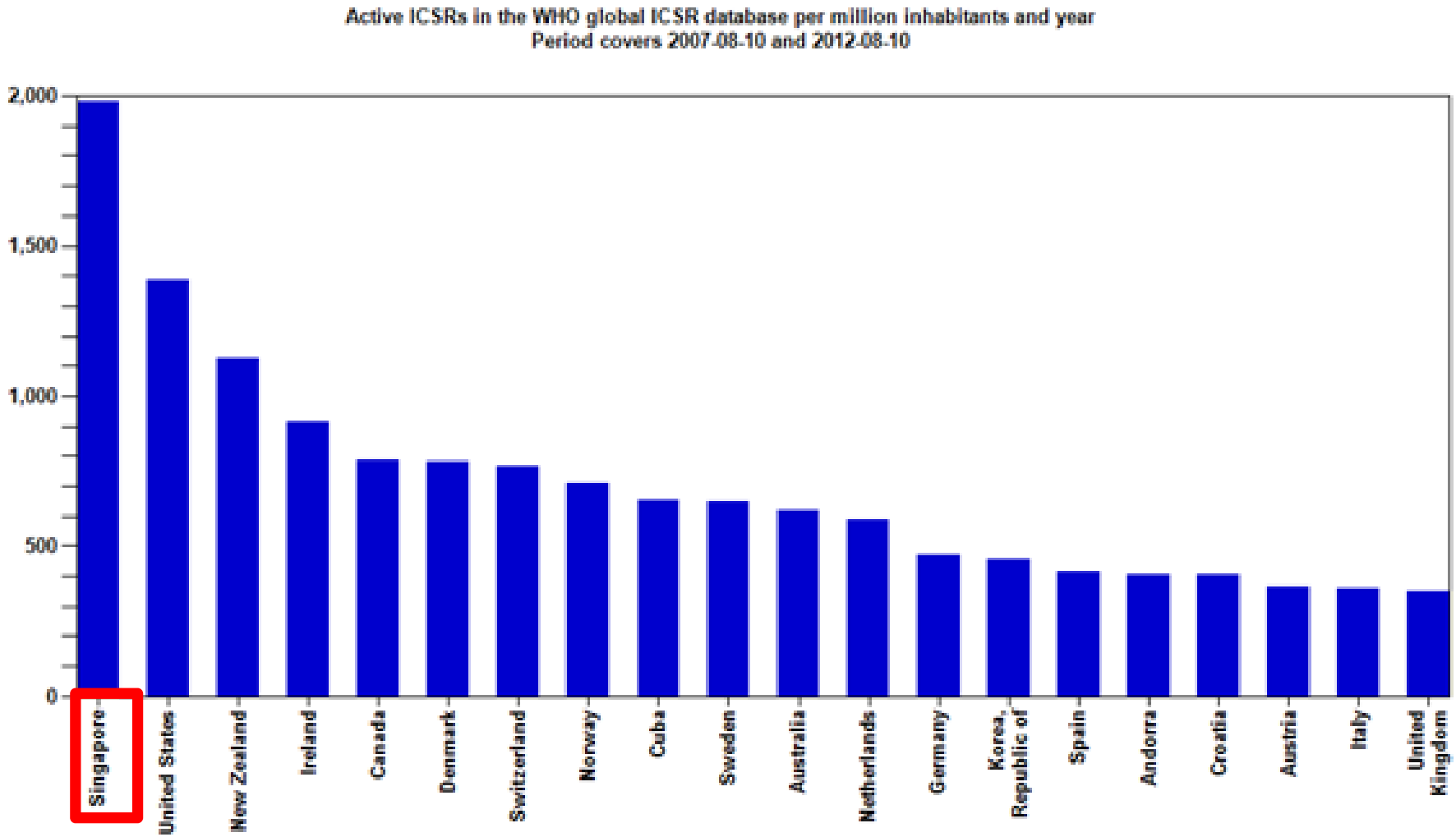
Online AE reporting 2004

2006

AE reports from hospital EMRx (Critical Medical Information Store)

Harness Power of Technology

Global AE Report Ranking



Harness Power of Technology

Electronic Health Records

- Maximizing IT tools & electronic health records for signal detection, data mining & communication
  - Exploring e-reporting of adverse events from private practitioners & community hospitals
  - Leveraging on current projects for compulsory online notification of infectious diseases: CLEO (private practitioners) & CHIC (community hospitals)
- Secondary data analysis of EHR for active surveillance

Explore New Paradigms

Pharmacogenomic Studies

Association between HLA-B*1502 and Carbamazepine-induced Steven-Johnson Syndrome & Toxic Epidermal Necrolysis

Explore New Paradigms

New Standard of Care

B4 | HOME TUESDAY, JULY 16, 2013 THE STRAITS TIMES

Epilepsy patients should take genetic test: HSA

Screening detects predisposition to possibly fatal skin reactions to drug

By POON CHIAN HUI

LOCAL epilepsy patients are now being told to take a genetic test which may save their lives.

The test detects whether a patient has a genetic predisposition to possibly fatal skin reactions after taking carbamazepine, a drug commonly given to epileptics.

This is the first time here that genetic screening is being "highly recommended" for a drug, after the health authorities investigated the problem among the local population. It may pave the way for more personalised care in other diseases, said Ms Dorothy Toh, director of the Health Sciences Authority's (HSA) vigilance branch.

About one in 100 people has epilepsy, a nerve disorder marked by sudden seizures. To control the incurable disease, carbamazepine – available here since 1988 and also used to treat other nerve-related ailments like bipolar disorder – is the drug of choice.

But the drug has also caused two life-threatening skin reactions, Stevens-Johnson syndrome and toxic epidermal necrolysis, among patients here over the past decade. These involve burn-like rashes and painful ulcers.

Last year, about 80 cases of the two conditions were reported, after a high of 110 in 2010.

In 2009, HSA, three public hospitals and other agencies began investigating. They found the reactions were linked to the presence of the HLA-B*1502 genetic variation in local patients. Singapore Immunology Network data also showed the HLA-B*1502 allele is most common among Malays here, a fifth of whom carry it.

On April 30, HSA urged doctors to send new patients for a test to detect the allele. A letter issued with the Health Ministry states that genotype testing before prescribing carbamazepine is now the new standard of care.

The test costs about $190 but may be subsidised to about $50. It takes about two to four days for a result. Those testing positive can then be given alternative drugs.

Patients on the drug for more than three months without problems do not have to be tested.

A 44-year-old who had Stevens-Johnson syndrome in 2003 after taking carbamazepine for a nerve injury, feels the genetic test will help. He was in a brief coma within days of falling ill, his skin blackened and sores developed.

"Doctors asked my mother to prepare for the worst," he recalled. "All doctors prescribing carbamazepine should ask their patients to do this test."

One in 20 people who get Stevens-Johnson syndrome dies.

So far, no adverse skin reactions linked to carbamazepine have been reported since the new standards kicked in, said Ms Toh. "Moving forward, this will change the way doctors prescribe medicine to their patients."

But she said establishing a link between genes and drug safety is a long and complicated process. Multiple genes can influence the way a person responds to a drug.

Professor Edmund Lee, from the National University of Singapore's pharmacology department, was involved in the HSA investigation and said this is a good first step towards personalised health care. But there is still a long way to go, especially to find links between genes and drugs.

"For the genetic platform to show its true colours, it requires a lot of validation," he said.

chpoon@sph.com.sg

LENGTHY PROCESS INVOLVED

For the genetic platform to show its true colours, it requires a lot of validation.

– Professor Edmund Lee, from the National University of Singapore's pharmacology department, on finding links between genes and drugs

Explore New Paradigms

Adaptive Licensing

Adaptive licensing (AL) approaches are based on *stepwise learning* under conditions of *acknowledged uncertainty*, with *iterative* phases of *data gathering* and *regulatory evaluation*.

Adaptive Licensing: Taking the Next Step in the Evolution of Drug Approval

H-G Eichler[1,2], K Oye[2,3,4], LG Baird[2], E Abadie[5], J Brown[6], CL Drum[2], J Ferguson[7], S Garner[8,9], P Honig[10], M Hukkelhoven[11], JCW Lim[12], R Lim[13], MM Lumpkin[14], G Neil[15], B O'Rourke[16], E Pezalla[17], D Shoda[18], V Seyfert-Margolis[14], EV Sigal[19], J Sobotka[20], D Tan[12], TF Unger[18] and G Hirsch[2]

Traditional binary regulatory decisions

Accelerated Approval/Conditional Market Authorization

Future state: flexible patient-centered, continuous learning, controlled rollout, & use optimization

Adaptive approaches to development, market access, utilization and monitoring

Converge and collaborate

Growing need for collaboration

- **With globalisation and rapid advancements in technology and novel products**
  - Growing need to ensure that regulatory expertise is at the cutting edge
  - Growing realization that no single regulatory authority has a monopoly on good science or can function in isolation
  - Growing importance to foster closer regulatory cooperation with local and international partners to support long term efficient global approach to authorization and supervision of health products

International Partnerships

Converge and collaborate

Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Netherlands Forensic Institute
Ministry of Security and Justice

Beijing Red Cross Blood Center

Ministry of Health, Labour and Welfare

MINISTRY OF HEALTH MALAYSIA

IRISH MEDICINES BOARD

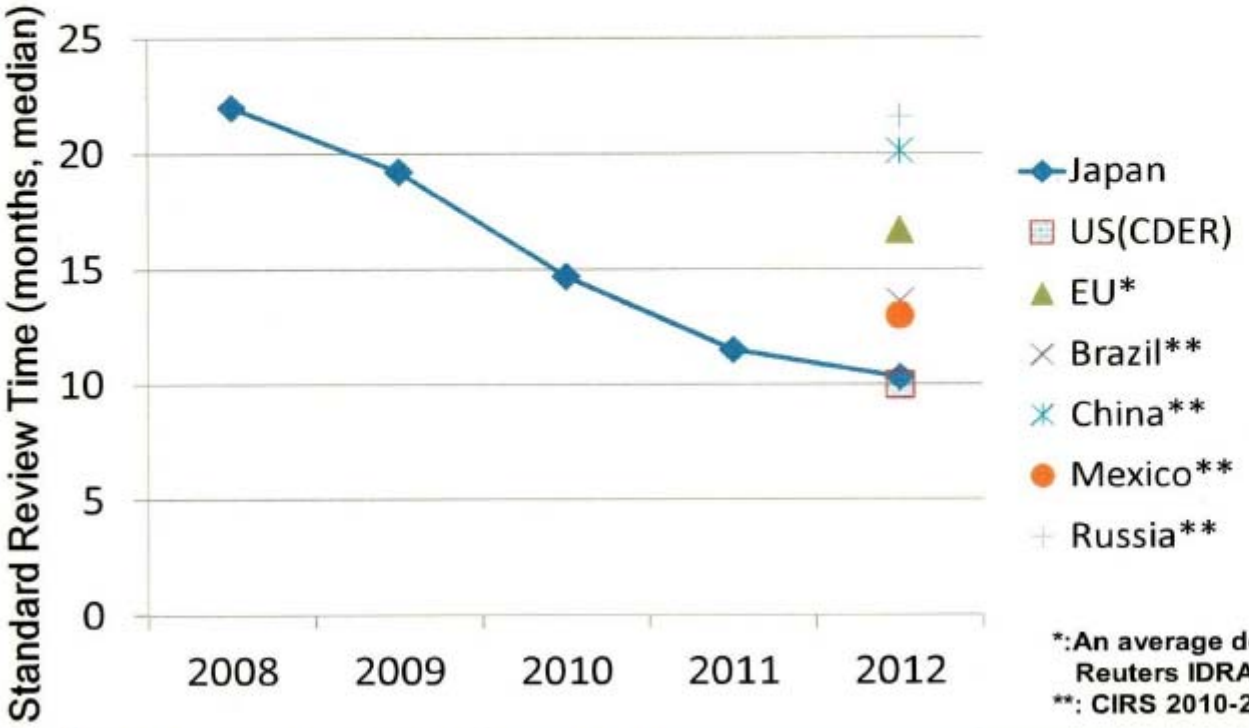
Health Canada

Health Care Inspectorate
Ministry of Health, Welfare and Sport

Netherlands Medicines Evaluation Board

Japan's performance on NDA review

Japan authority have achieved the target on review, 12 months for standard review and 9 months for priority review as median, in the mid-term plan of PMDA for 2009-2013. Now it has the world's highest performance.



*:An average derived from Thompson Reuters IDRAC database
**: CIRS 2010-2011 benchmark

5