

Risk Assessment through the Life Cycle of Medicinal Products

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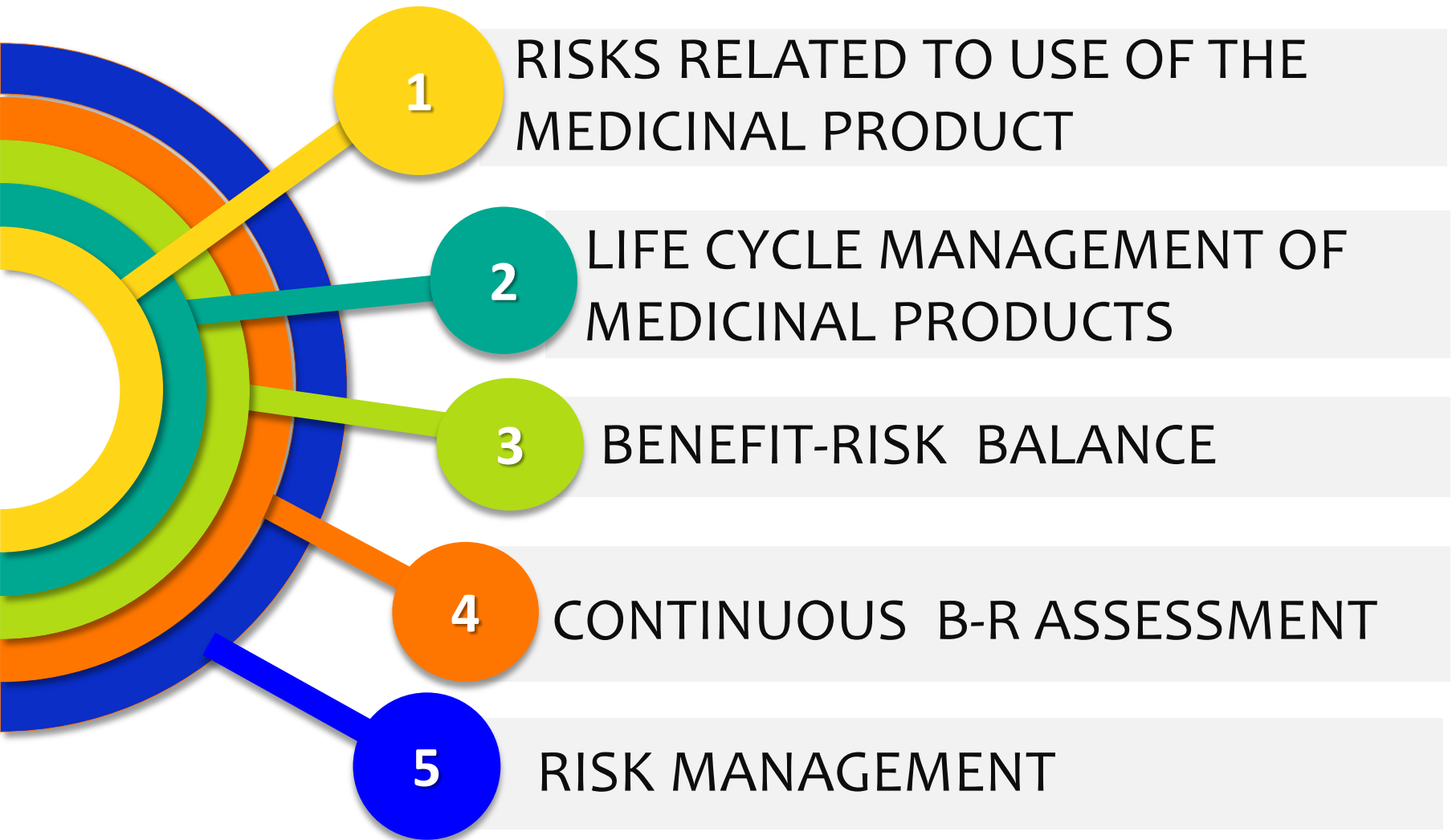
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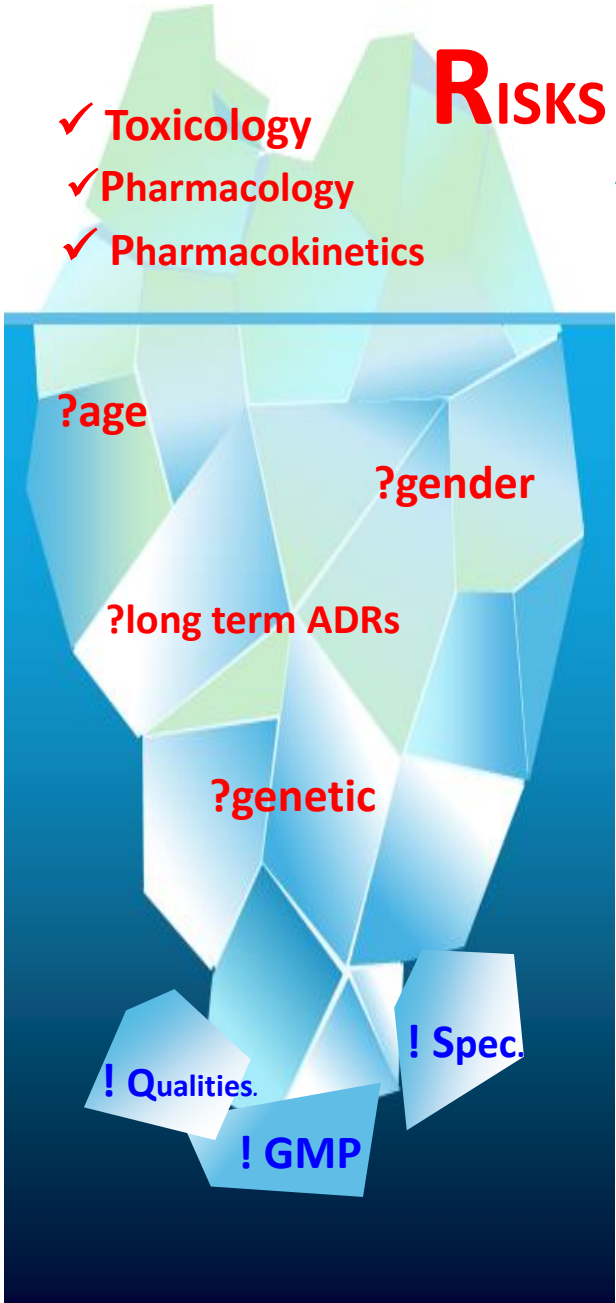
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OUTLINE



- 
- The diagram shows an iceberg floating in water. Above the waterline, three red checkmarks are listed: '✓ Toxicology', '✓ Pharmacology', and '✓ Pharmacokinetics'. Below the waterline, several blue and white geometric shapes (polygons) are scattered, each containing a red question mark followed by a label: '?age', '?gender', '?long term ADRs', and '?genetic'. At the very bottom of the iceberg, three blue shapes contain exclamation marks followed by labels: '! Qualities.', '! GMP', and '! Spec.'.
- ✓ Toxicology
 - ✓ Pharmacology
 - ✓ Pharmacokinetics

RISKS RELATED TO USE OF THE MEDICINAL PRODUCT

Any risk relating to the **Quality, Safety or Efficacy** of the Medicinal Product as regard patient's health or public health.

Safety and Efficacy (intrinsic)

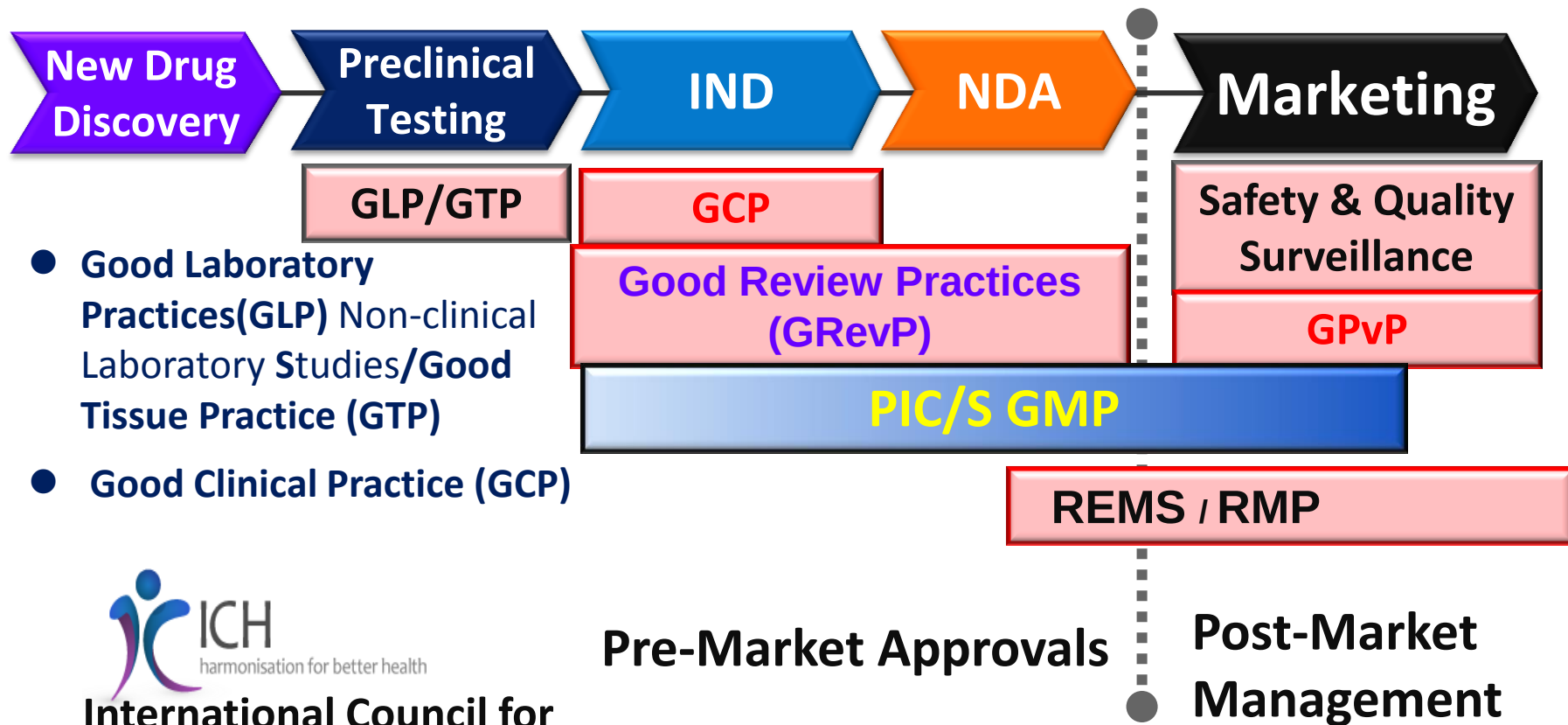
- *Safety* : side effects which may occur in some patients
- *Efficacy* : extent to work as intended effect

Benefit-Risk balance should be assessed for each candidate.

Risk to Quality (extrinsic) ; deviations from GMP, failure to meet drug specifications, may affect the **B-R balance** and put patients at risk, should also be identified and controlled .

LIFE CYCLE MANAGEMENT OF MEDICINAL PRODUCTS

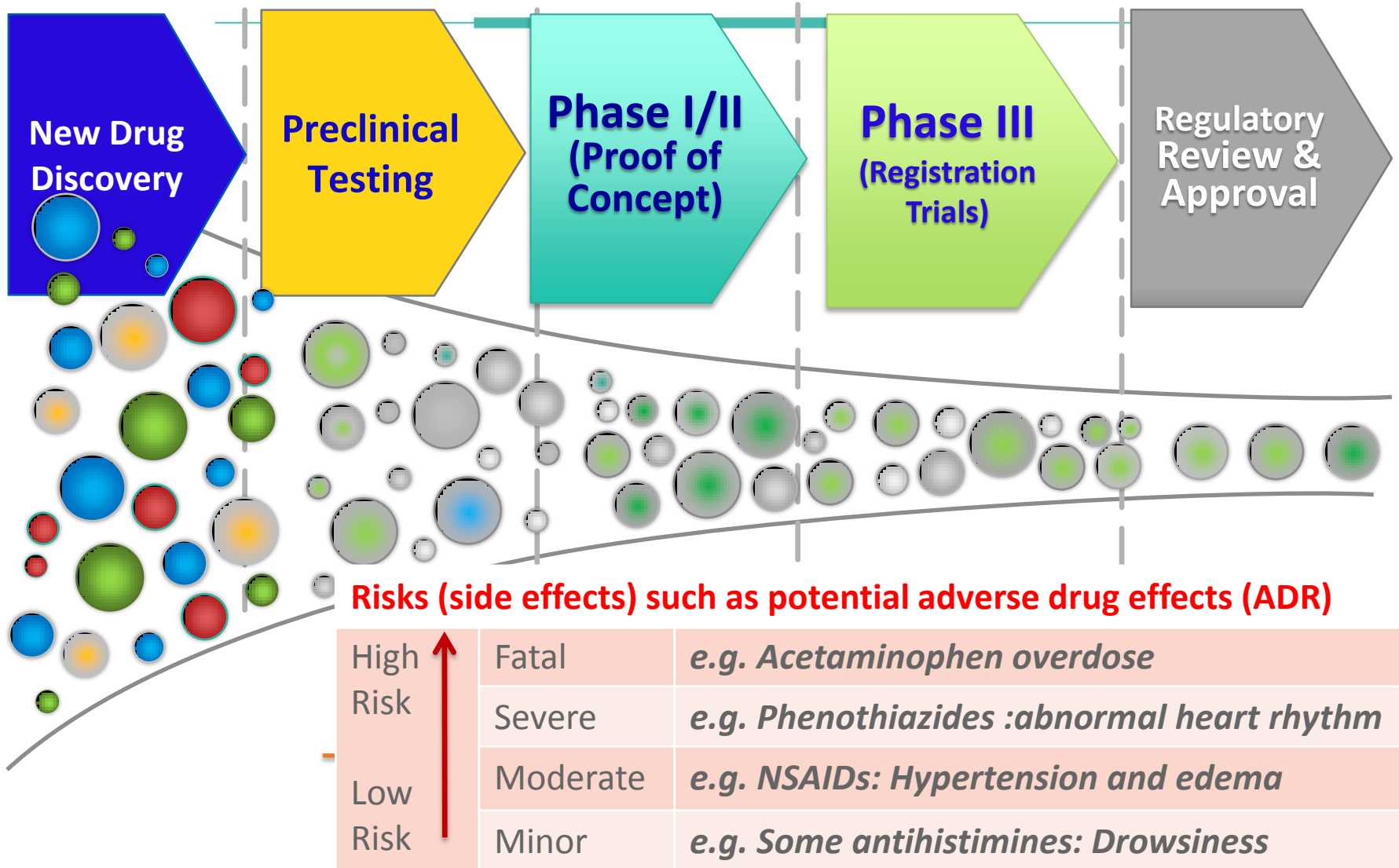
ICH –Based Regulations




ICH
harmonisation for better health
International Council for
Harmonisation (ICH)



Pre-Market Approvals

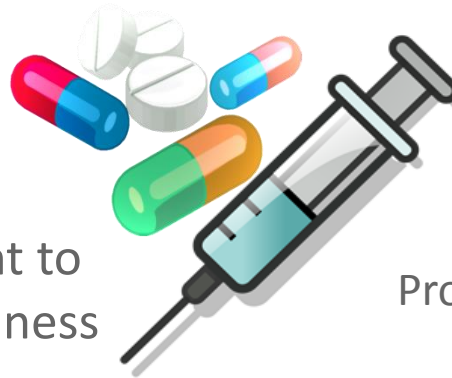


Benefit-Risk Balance

Do the benefits outweigh the risks?

Benefit

Ability to work as intent to protect patients from illness



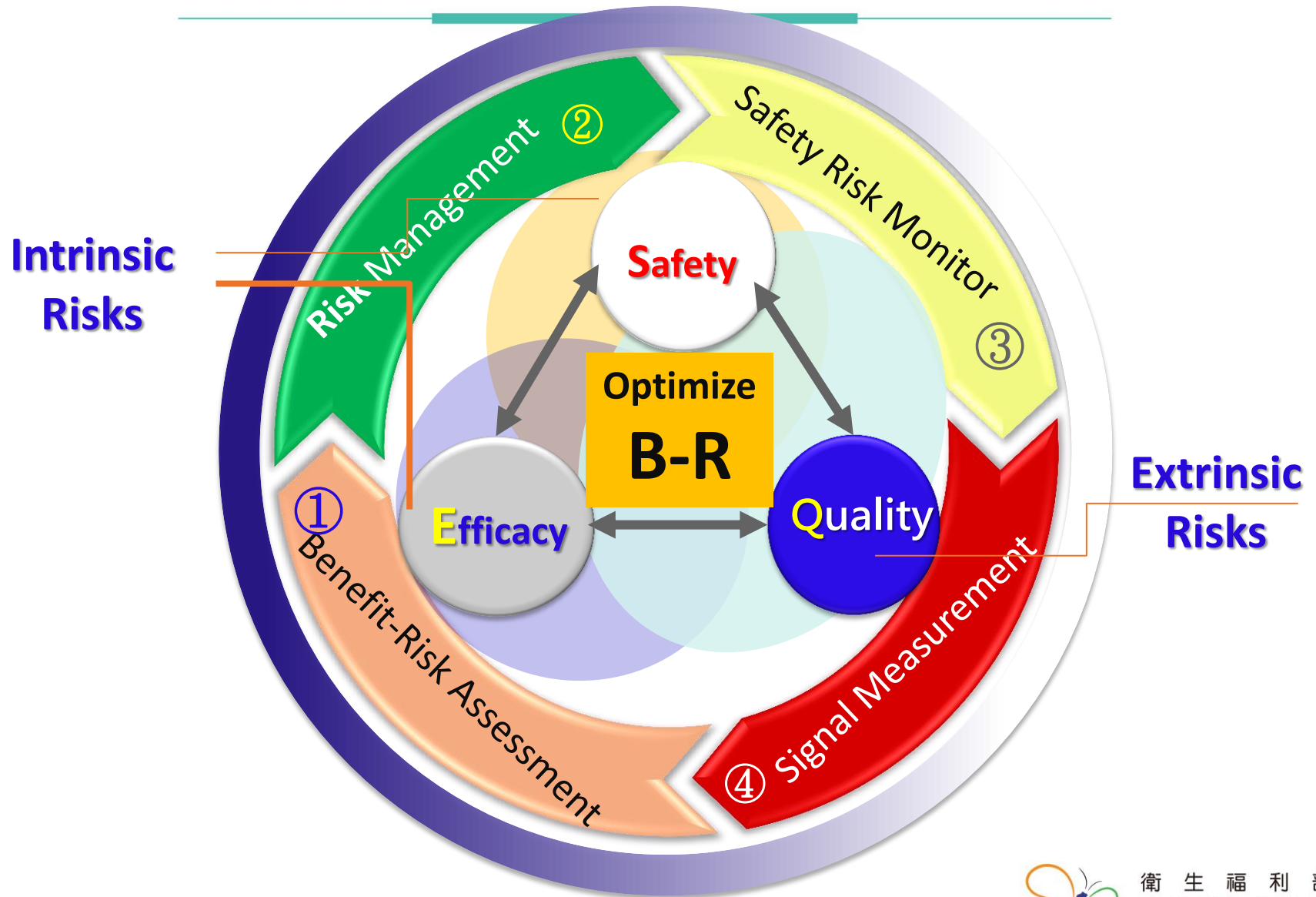
Risk (Side Effects)

Probability that harm the patient



Continuous B-R Assessment

Optimizing benefits throughout the lifecycle of a medicinal product

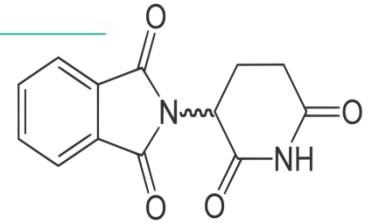


Benefit-Risk Balance

1. Do the benefits outweigh the risks?

Example 1 : Thalidomide

- Thalidomide was first marketed 1950s prescribed as a **sedative** or **hypnotic** etc. Afterwards, it was used against **nausea** and to alleviate **morning sickness** in pregnant women. Approx. 10 000 children affected with congenital anomalies e.g. **phocomelia** during late 50s and 60s leading to its **withdrawal** (1961)



Benefit
(against **nausea** and to
alleviate **morning
sickness**)

Risk
(**phocomelia**)



Benefit-Risk Balance

2. Is the uncertainty around B - R acceptably low?

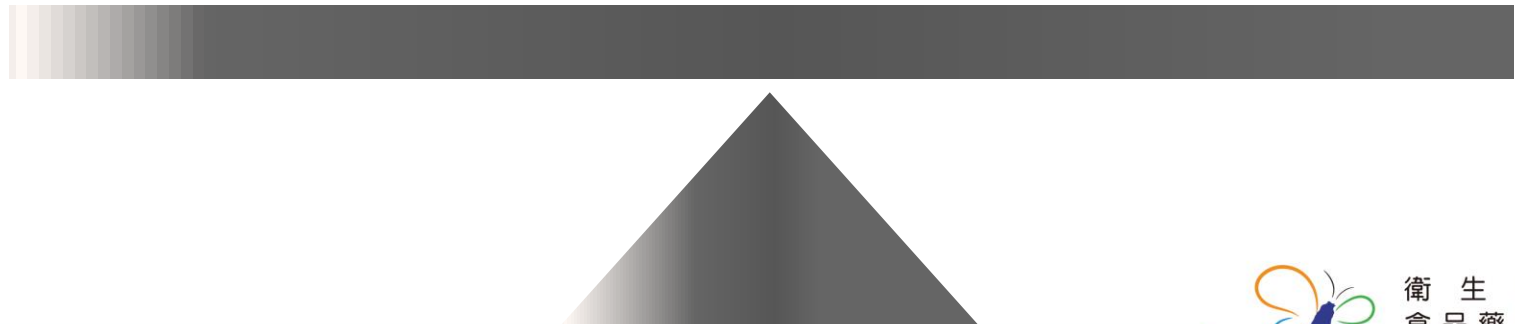
Example 1 : Thalidomide (continued)

Benefit

- Over the years some beneficial effects of thalidomide have been recognised and it has been used for treatment for multiple myeloma, erythema nodosum leprosum, aphthous ulcers in HIV-infected patients, chronic graft-versus-host-disease and a variety of tumors.

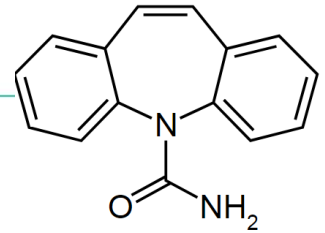
Risk

- To minimize the risk of Thalidomide exposure during pregnancy in women,
Risk management program including:
 - Education
 - Managed Distribution
 - Registration of Physicians, Pharmacists, Patients
 - Periodic Pregnancy Test
 - Periodic Confirmation of Understanding
 - ...etc



Benefit-Risk Balance

Is the uncertainty around B - R acceptably low?



Example 2 : Carbamazepine (CBZ)

Benefit

CBZ is an antiepileptic drug, first marketed in 1960s, is used to prevent and control seizures. This medication is known as an anticonvulsant or anti-epileptic drug. It is also used to relieve certain types of nerve pain (such as trigeminal neuralgia).

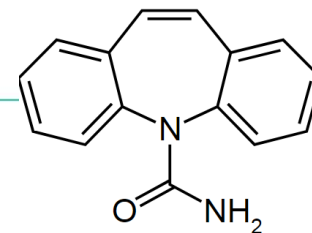
Risk (SJS/TEN)

- **SADR : Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis (SJS/TEN)**
- 3rd cause of drug injury relief cases



Benefit-Risk Balance

Is the uncertainty around B - R acceptably low?



Example 2 : Carbamazepine (CBZ) (continued)

The risks and benefits of CBZ therapy should be weighed before considering CBZ in patients known to be positive for **HLA-B*1502** (*Human Leukocyte Antigen (HLA) complex, encoded by the HLA gene family, plays a critical role in immunity*).
*Carbamazepine-Induced Toxic Effects and HLA-B*1502*

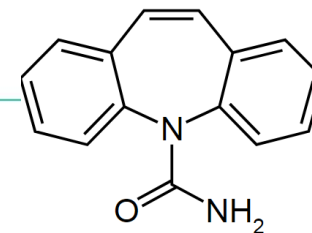
March 24, 2011 *N Engl. J Med* 2011; 364:1126-1133 ; DOI: 10.1056/NEJMoa1009717

Risk Management

- labeling revision, **black boxed warning added...**(2004、2007、2008、2010)
- **HLA-B*1502 gene screening included in NHI(2010.06)**
- Mandatory change labels, **Pharmacists are required to remind the patients of potential side effects** when fill out the prescriptions (2010.07)
- **RMP by pharmaceutical companies** (2011.09)

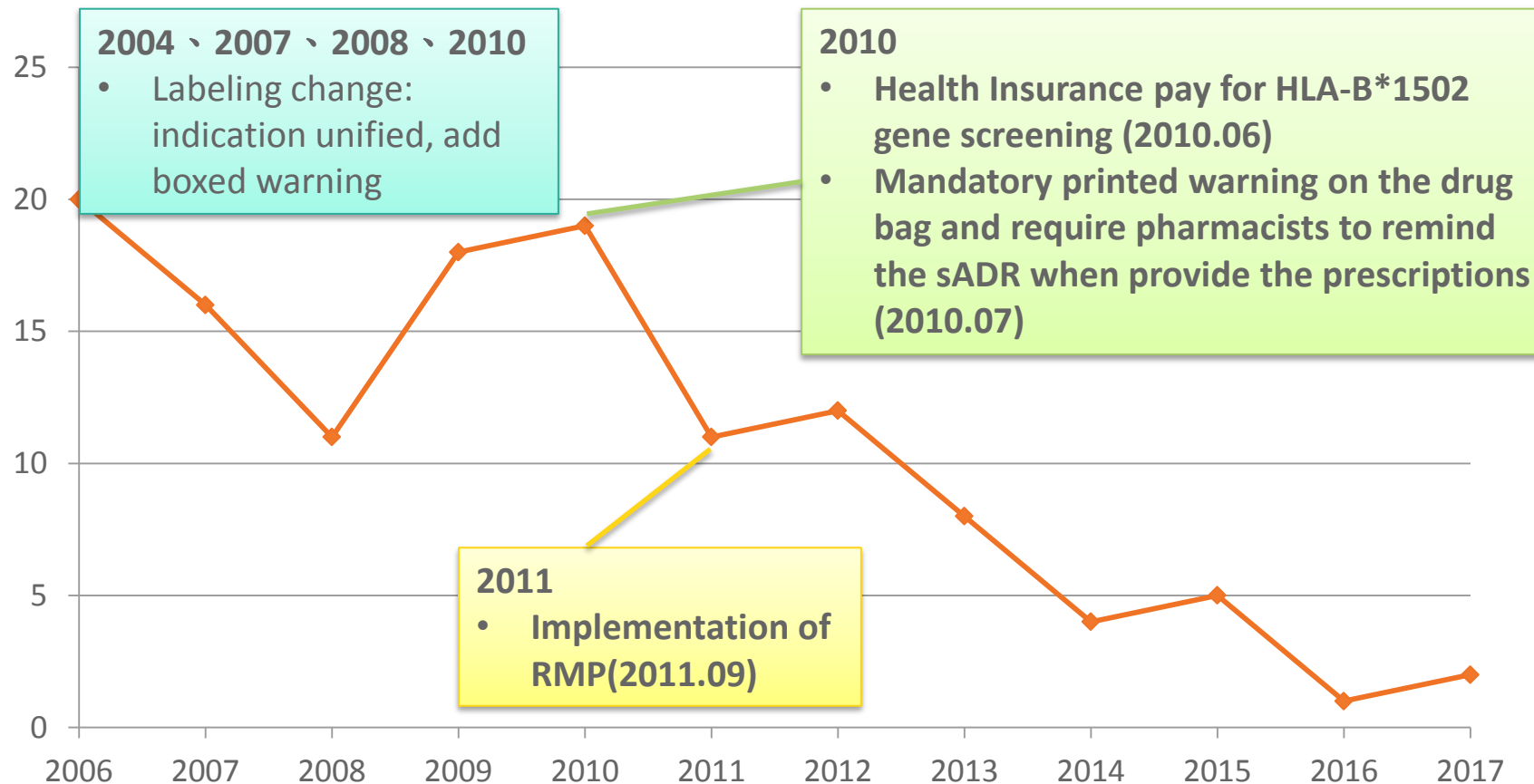
Benefit-Risk Balance

Is the uncertainty around B - R acceptably low?



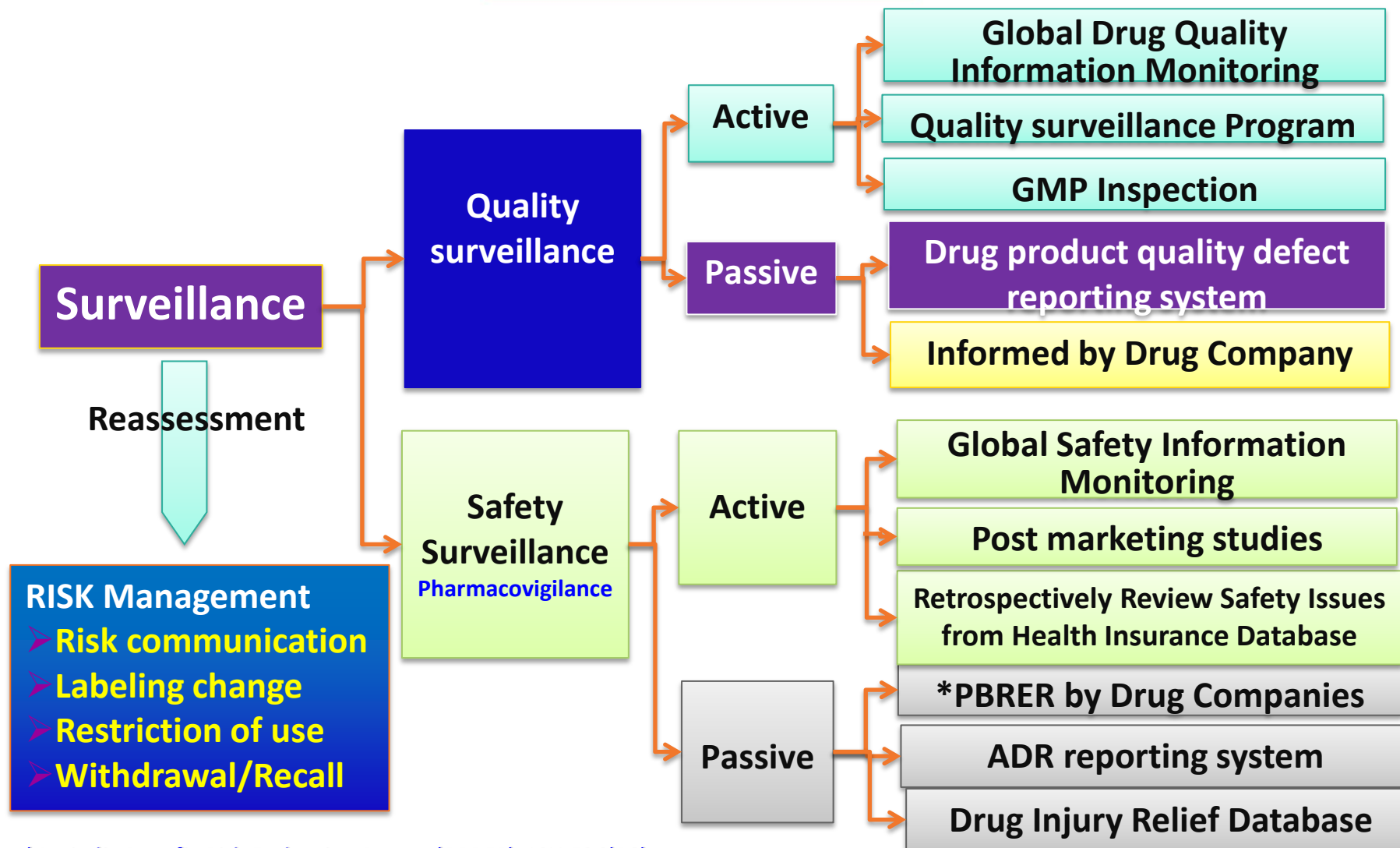
Example 2 : Carbamazepine (CBZ) (continued)

Drug injury relief case of SJS/TNS caused by carbamazepine



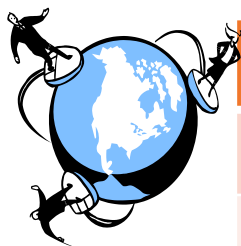
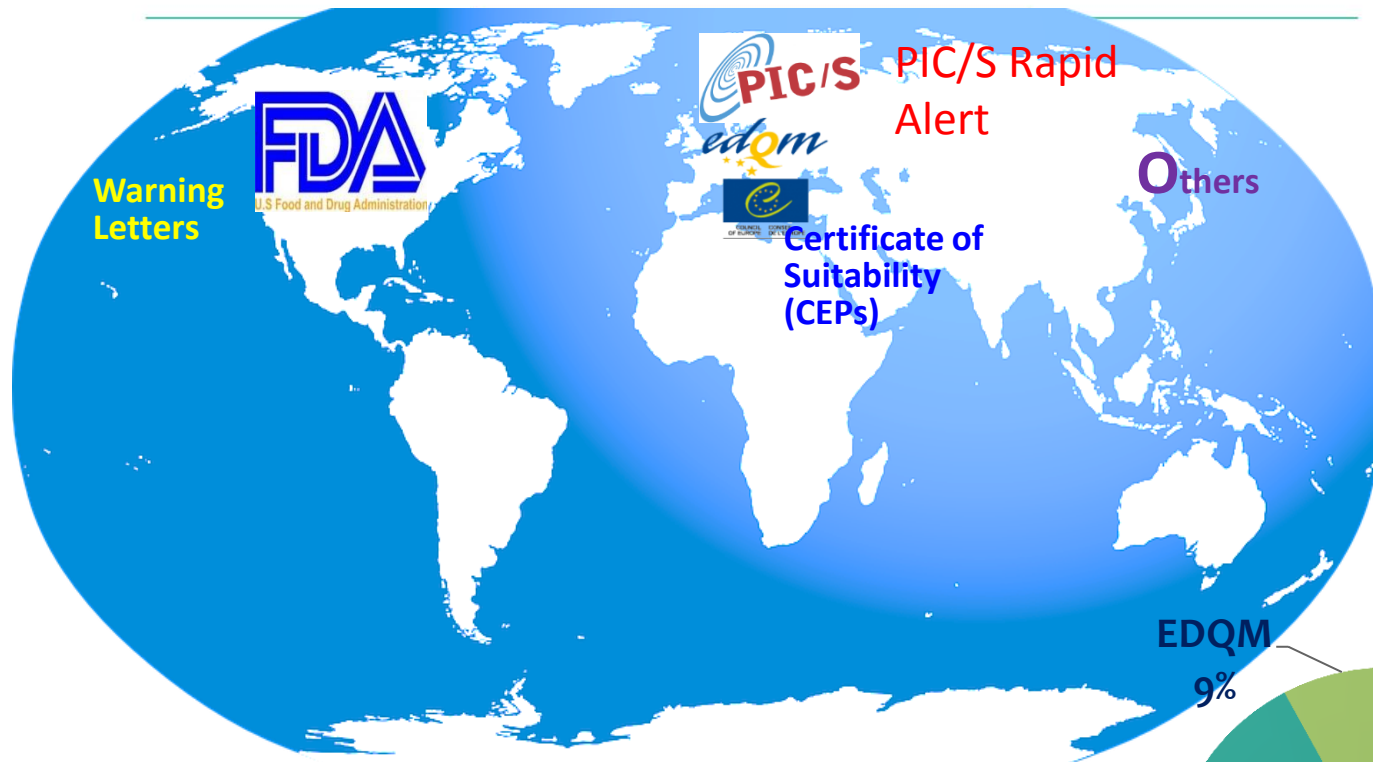
Risk Management

Post-Marketing Safety and Quality Surveillance



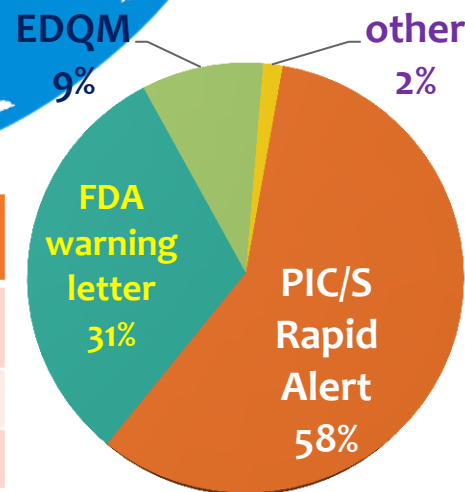
*Periodic Benefit-Risk Evaluation Report (PBRER), ICH E2C(R2)

Global Drug Quality Information Monitoring



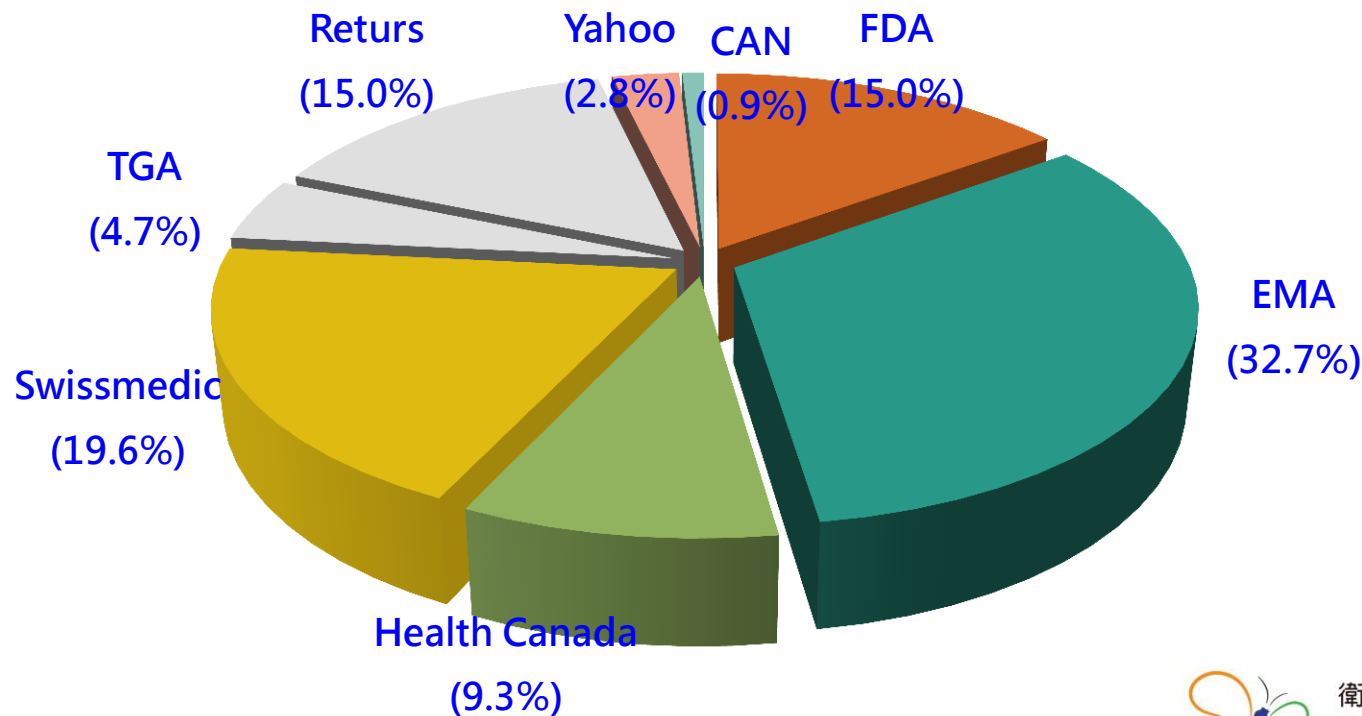
2018 Drug Quality Info. Monitoring

Category	Total	GMP Violations (Imported)
Products	199	70(5)
API	54	26(9)

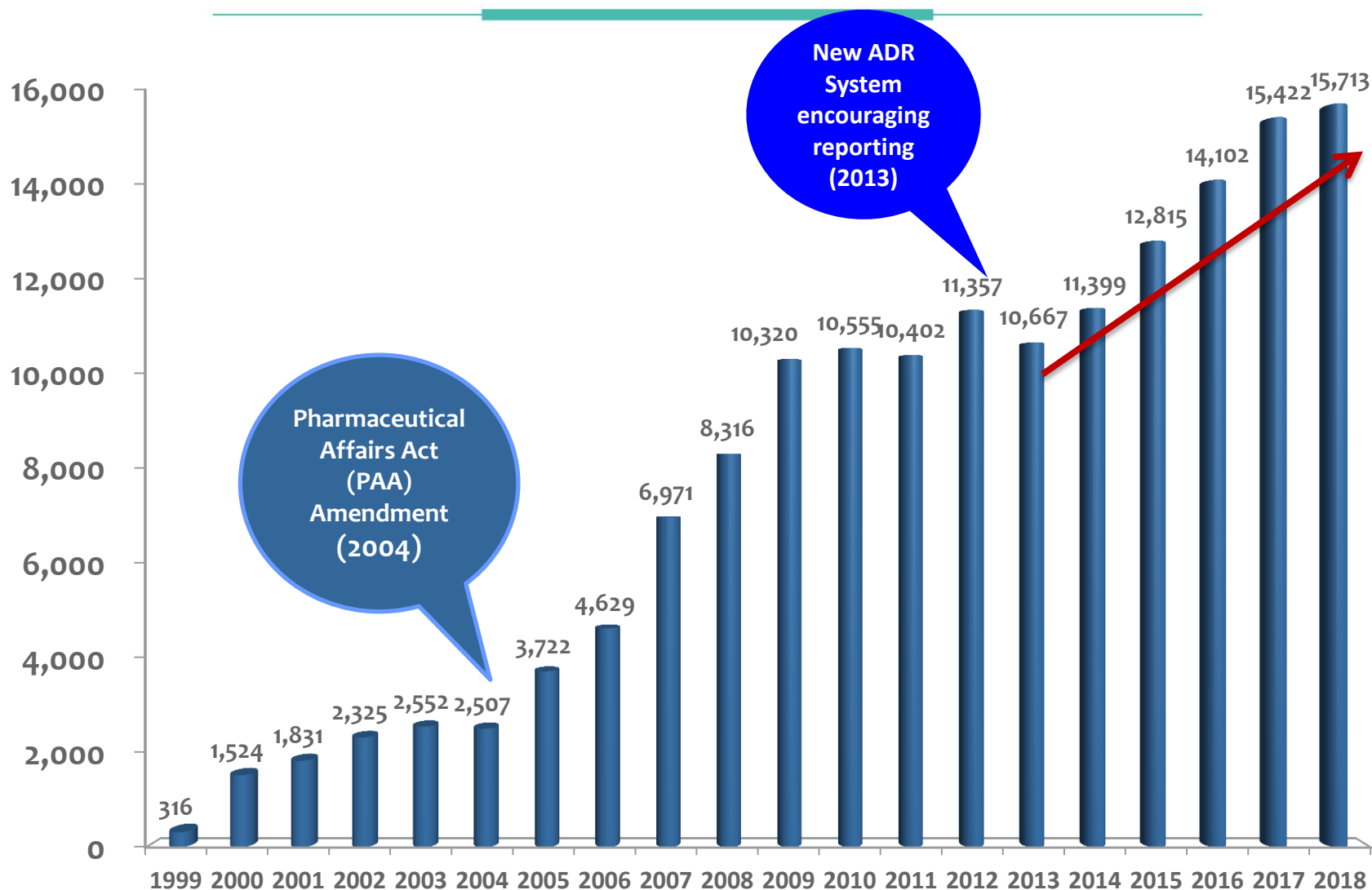


Global Safety Information Monitoring

- Actively Monitor Global Safety Information and news daily.
 - If there is a suspect safety signal, we will deliver risk communication letter and start drug safety re-evaluation.
- 107 drug alerts in 2018



Trends of ADR Reporting





Thank You for Your Attention



For more information, please go to: <http://www.fda.gov.tw>



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食品藥物管理署
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