Risk Assessment through the Life Cycle of Medicinal Products

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OUTLINE

1. Risks Related to Use of the Medicinal Product
2. Life Cycle Management of Medicinal Products
3. Benefit-Risk Balance
4. Continuous B-R Assessment
5. Risk Management
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 is 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

- New Drug Discovery
- Preclinical Testing
- IND
- NDA
- Marketing
- Safety & Quality Surveillance
- PIC/S GMP
- PIC/S GMP
- Good Review Practices (GRevP)
- GLP/GTP
- GCP
- REMS / RMP
- Pre-Market Approvals
- Post-Market Management

- Good Laboratory Practices (GLP)
- Non-clinical Laboratory Studies / Good Tissue Practice (GTP)
- Good Clinical Practice (GCP)

International Council for Harmonisation (ICH)
### Risks (side effects) such as potential adverse drug effects (ADR)

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>Category</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Fatal</td>
<td><em>e.g.</em> Acetaminophen overdose</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td><em>e.g.</em> Phenothiazides: abnormal heart rhythm</td>
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<tr>
<td>Low</td>
<td>Moderate</td>
<td><em>e.g.</em> NSAIDs: Hypertension and edema</td>
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<tr>
<td></td>
<td>Minor</td>
<td><em>e.g.</em> Some antihistamines: Drowsiness</td>
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</table>
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

Intrinsic Risks

Extrinsic Risks

Safety

Efficacy

Optimize B-R

Quality

Safety Risk Monitor

Risk Management

Benefit-Risk Assessment

Signal Measurement
Benefit-Risk Balance

1. Do the benefits outweigh the risks?

Example 1: Thalidomide

- Thalidomide was first marketed in the 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
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
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*.....


**Risk Management**
- 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

  - Labeling change: indication unified, add boxed warning

- **2010**
  - Health Insurance pay for HLA-B*1502 gene screening (2010.06)
  - Mandatory printed warning on the drug bag and require pharmacists to remind the sADR when provide the prescriptions (2010.07)

- **2011**
  - Implementation of RMP (2011.09)
Risk Management
Post-Marketing Safety and Quality Surveillance

Surveillance

Quality surveillance

Risk Management
- Risk communication
- Labeling change
- Restriction of use
- Withdrawal/Recall

Active
- Quality surveillance Program
- GMP Inspection

Passive
- Drug product quality defect reporting system
- Informed by Drug Company

Active
- Global Safety Information Monitoring
- Post marketing studies
- Retrospectively Review Safety Issues from Health Insurance Database
- *PBRER by Drug Companies

Passive
- ADR reporting system
- Drug Injury Relief Database

*Risk Management

Pharmacovigilance

Global Drug Quality Information Monitoring

Informed by Drug Company

Global Safety Information Monitoring

Retrospectively Review Safety Issues from Health Insurance Database

*Periodic Benefit-Risk Evaluation Report (PBRER), ICH E2C(R2)
Global Drug Quality Information Monitoring

2018 Drug Quality Info. Monitoring

<table>
<thead>
<tr>
<th>Category</th>
<th>Total</th>
<th>GMP Violations (Imported)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Products</td>
<td>199</td>
<td>70(5)</td>
</tr>
<tr>
<td>API</td>
<td>54</td>
<td>26(9)</td>
</tr>
</tbody>
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- PIC/S Rapid Alert: 58%
- FDA warning letter: 31%
- EDQM: 9%
- Other: 2%
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


New ADR System encouraging reporting (2013)
For more information, please go to: http://www.fda.gov.tw