Relief System for Adverse Drug Reactions

- Brief history and outline of the Relief System -

Yutaka Onda
Office of Relief Funds
PMDA
1. PMDA and Relief System for Adverse Health Effects
2. Relief System for Adverse Drug Reactions
3. Reference Materials
1. PMDA and Relief System for Adverse Health Effects
Drug Risks and Relief System for Adverse Health Effects

Social Relief System

Cannot eliminate risks entirely even with the most recent and highest level of knowledge

Social Risks

Post-marketing

Proper use

Patient

Relief benefits
- Medical expense
- Disability pension
- etc.

Marketing authorization holder

Relief Funds

Contribution

Nonclinical studies → Clinical trials → Reviews

Risks

Benefits

* Began Relief Service for Infections Acquired in April 2004

2015 KIDS Symposium; ADR causality assessment and relief system in Asia, November 19, 2015
PMDA is an independent government agency working together with the Ministry of Health, Labour and Welfare and aims to contribute to improving public health. It is responsible for conducting approval reviews and safety measures and for providing health damage reliefs for drugs and medical devices based on the Pharmaceuticals and Medical Devices Act.

**PMDA Safety Triangle**

― Comprehensive Risk Management Through the 3 Functions ―

- **Review**: Reduce the risk
- **Securing safety and efficacy**
- **Three-pillar system unique to Japan**
- **Safety**: Continuous risk mitigation efforts
- **Japanese citizens**
- **Relief**: Relief measures for damage caused

2015 KIDS Symposium; ADR causality assessment and relief system in Asia, November 19, 2015
History of PMDA and Relief Systems

1974
- Settlement of the Thalidomide lawsuit

1979
- Settlement of the SMON lawsuit

1994

1995
- Settlement of the HIV lawsuit

1996
- Settlement of the CJD lawsuit

2002
- Settlement of the CJD lawsuit

2004
- Relief Service for Infections Acquired through Biological Products was started.

2014
- Adverse effects caused by the Regenerative Medical Products are to be covered by the Relief Systems.

Relief Service for Adverse Drug Reactions was started.

PMDA (Pharmaceuticals and Medical Devices Agency)

Government (Ministry of Health, Labour and Welfare)

Safety measures

Relief

Review

Safety

The Fund for Adverse Drug Reactions Suffering Relief

The Organization for Pharmaceuticals Safety and Research

JAAME (The Japan Association for the Advancement of Medical Equipment)

PMDEC (The Pharmaceuticals and Medical Devices Evaluation Center of the National Institute of Health Sciences)
2. Relief System for Adverse Drug Reactions
<table>
<thead>
<tr>
<th>Date</th>
<th>Event Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oct. 1974</td>
<td>Settlement reached for Thalidomide lawsuit</td>
</tr>
<tr>
<td>Sep. 1979</td>
<td>Settlement reached for SMON lawsuit</td>
</tr>
<tr>
<td>1983–1986</td>
<td>HIV Incident (HIV contaminated raw materials used for Factor VIII and IX products used to treat hemophilia)</td>
</tr>
<tr>
<td>Mar. 1996</td>
<td>Settlement reached for HIV lawsuit</td>
</tr>
<tr>
<td>Nov. 1996</td>
<td>Creutzfeldt-Jakob disease lawsuit filed</td>
</tr>
<tr>
<td>Mar. 2002</td>
<td>Settlement reached for Creutzfeldt-Jakob disease lawsuit</td>
</tr>
<tr>
<td>Oct. 2002</td>
<td>Drug-induced hepatitis lawsuit filed</td>
</tr>
<tr>
<td>Feb. 2008</td>
<td>Settlement reached for drug-induced hepatitis</td>
</tr>
</tbody>
</table>
1. Thalidomide Incident

In the 1950s, mothers who took thalidomide (hypnotic-sedative agent, etc.) in the early stages of pregnancy gave birth to children with severe disabilities affecting the extremities. (Thalidomide lawsuit filed in 1963)

Teratogenicity became worldly known
Became a momentum to review drug laws and pharmaceutical administrative organizations in every country

2. SMON Incident (Quinoform Incident)

Subacute Myelo-Optico-Neuropathy (SMON) developed due to quinoform (antiflatulent) administration (Adverse drug reactions occurred in the 1950s)

Difficulty in walking, ananastasia, and vision impairment caused by degenerated bone marrow, optic nerve, and peripheral nerves.
(SMON lawsuit filed in 1971)

Took a long time until measures were implemented because the causal relationship between the damage and the drug was difficult to prove. Resulted in many victims and dire damages.
Thalidomide lawsuit

Outline and history

Outline
In the 1950s, mothers who took thalidomide (hypnotic-sedative agent, etc.) in the early stage of pregnancy gave birth to children with severe disabilities (referred to as thalidomide embryopathy) affecting the extremities, face, and internal organs, etc.

History
1957.10 Production was approved
1961.11 Warning from Dr. Lenz (pointing out that an increasing number of babies were being born in the former West Germany with severe deformation of the extremities caused by thalidomide)
1962.5 Market release was suspended.
1962.9 Product was recalled.
1963.6 Complaint was filed.
1974.10 Court ruling
Number of persons covered by ruling: 309 (at the time of ruling: 62 persons)

Excerpt from reference material in Reference Material 5 concerning October 27, 2008 “Convening of the Sixth Committee for Investigation of Drug-induced Hepatitis Cases and Appropriate Regulatory Administration to Prevent Similar Suffering”; from MHLW HP
“Basic guidelines concerning drug marketing approval” were issued in order to clarify the policies governing approval examination, which had simply followed conventional practice (1967).

- The scope of material necessary for application for approval was specified (Submission of data on testing on pregnant animals, etc. became mandatory).
  *Concerning thalidomide, safety regarding teratogenicity was not confirmed.
- Separate prescription drugs and general drugs, and review in consideration of individual characteristics.

ADR reporting system was started (1967)

- ADR reporting system from companies to MHLW was started under the government’s guidance.
  *Initially, new drugs were subject to reporting, but existing drugs were also covered from 1971.
- ADR monitoring system was started by medical institutions assigned to perform this task.
SMON lawsuit

<Outline>

** SMON (Subacute Myelo-Optico-Neuropathy) (**1) developed when quinoiform (antiflatulent (**2)) was taken orally.

(**1) Abdominal symptoms such as diarrhea and abdominal pain, etc. are followed by neurological manifestations, which started with numbness and paresthesia in the peripheral lower extremities, gradually advanced to paralysis, causing difficulty in walking, anastastasia, etc., and is associated with vision impairment. A disease refractory to treatment that causes intolerable patient distress.

(**2) The indication was gradually expanded from amoebic dysentery.
### SMON lawsuit

<History>

<table>
<thead>
<tr>
<th>Year</th>
<th>Event Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1953.6</td>
<td>Production was approved</td>
</tr>
<tr>
<td>1955</td>
<td>Symptoms began to be identified in patients undergoing treatment for bowel disease, and drew attention as a nationwide social issue with no known cause.</td>
</tr>
<tr>
<td>1969.9</td>
<td>Ministry of Health and Welfare established “Association for SMON Investigation”. The highest incidence was reported that year.</td>
</tr>
<tr>
<td>1970.8</td>
<td>A university professor published a report that identified the correlation between the amount of quinoformuse and the incidence of SMON</td>
</tr>
<tr>
<td>1970.9</td>
<td>Sales of quinoform were discontinued. The incidence dramatically decreased after this, and there were virtually no new cases.</td>
</tr>
<tr>
<td>1971.5</td>
<td>Complaint was filed.</td>
</tr>
<tr>
<td>1979.9</td>
<td>Court ruling</td>
</tr>
</tbody>
</table>

Number of persons covered by the ruling: 6,490 (at the time of ruling: 4,819)

Excerpt from reference material in Reference Material 5 concerning October 27, 2008 “Convening of the Sixth Committee for Investigation of Drug-induced Hepatitis Cases and Appropriate Regulatory Administration to Prevent Similar Suffering”; from MHLW HP
1979: Revision of the Pharmaceutical Affairs Act (PAA)

- PAA explicitly aims to ensure the quality, efficacy and safety of drugs, etc.
- The re-examination system for new drugs was established for the government to re-confirm the efficacy, etc. within a specified period after receiving approval.
- The re-evaluation system was established by the government in order to review the efficacy, safety, and quality of existing drugs with a view to supporting medical and pharmaceutical advancement, which had previously been conducted under administrative guidance.
- Provisions were newly established requiring that companies must report ADRs, which had previously been conducted under administrative guidance.
- Provisions for emergency order and recall order were newly established.
- Provisions were newly established requiring that companies must make efforts to provide information to distributors etc.
1979 Fund for Relief Services for Adverse Drug Reactions was established

Relief System for Adverse Drug Reactions was started. In order to provide prompt relief for patients suffering from adverse drug reactions, the Fund for Adverse Drug Reactions Suffering Relief was established to provide relief benefits such as medical expenses, disability pension, and bereaved family pensions. (October 1, 1979)

ADRs due to drugs used after May 1, 1980 are eligible under the relief system.

- Pharmaceutical companies make contributions to the relief benefit.
- Drugs used for cancer etc. and other specific disease with a high incidence of severe ADRs are excluded from the relief system (e.g. anticancer drug).
- Infections due to contamination by viruses, etc. in raw materials are not regarded as “ADRs.”
Background to Establishment of the Relief System for Adverse Drug Reactions

It has become a prime task and social demand to tighten the approval system and safety measures for pharmaceuticals outlined in the Pharmaceutical Affairs Act after the Thalidomide and SMON incidents, and promptly relieve sufferers.

Health damages due to adverse drug reactions
1. Some adverse drug reactions are things that cannot be prevented.
2. Damages due to these adverse drug reactions are not considered civil liabilities based on current doctrine of negligence liability.
3. Extreme expert knowledge and massive amounts of time and money are required to prove causal relationships between damages and drugs.
4. Even if the pharmaceutical company is negligent, it is not easy to prove that negligence occurred.
5. Resolution through lawsuits require a lot of time.
6. Companies have social responsibilities to supply drugs that are safe and efficacious.
Relief System for Adverse Drug Reactions

- Established: May 1, 1980

- Official system that provides relief benefits such as for medical expense, medical allowance, disability pension, etc. to sufferers of severe diseases or disabilities requiring hospitalized treatment due to the occurrence of adverse drug reactions even after proper use of drugs (*).

- Money required for relief benefits will be funded by contributions paid by drug marketing authorization holders as part of their social responsibility.

*”Drugs” mentioned in this system refer to pharmaceuticals and proprietary drugs sold by marketing authorization holders approved by the MHLW. (However, there are certain drugs that are not eligible including antiepileptics and immunosuppressants.)
Mechanism of Relief System and Flow of Application

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## Type and content of relief benefits

### In case of Disease (requiring hospitalization)

<table>
<thead>
<tr>
<th>Type of benefit</th>
<th>Medical expenses</th>
<th>Medical allowances</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Content of benefit</strong></td>
<td>Compensation for the actual cost of treating the disease (as borne by the patient, excluding the amount covered by health insurance)</td>
<td>Benefit paid for costs other than medical costs associated with treatment of the disease</td>
</tr>
<tr>
<td><strong>Amount of Benefit Paid</strong></td>
<td>Costs as borne by the patient, excluding the amount covered by health insurance</td>
<td></td>
</tr>
<tr>
<td><strong>Deadline for Application</strong></td>
<td>Within 5 years of paying the medical expenses that would be covered by the benefit.</td>
<td>Within 5 years since day one of the month following the day for which the medical care invoiced was provided.</td>
</tr>
</tbody>
</table>

*On an outpatient basis refers to when patients receive treatment requiring hospitalization on an outpatient basis.*
### Type and content of relief benefits

#### In case of Disability (causing serious Impairment in daily life)

<table>
<thead>
<tr>
<th>Type of benefit</th>
<th>Content of benefit</th>
<th>Amount of Benefit Paid</th>
<th>Deadline for Application</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Disability pensions</strong> (for those 18 and above)</td>
<td>Benefit provided to compensate for living costs, etc. of patients aged 18 or older, who suffer from a certain degree of disability</td>
<td>Grade 1: Annually: ¥2,736,000 (Monthly: ¥228,000)</td>
<td>No deadline</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Grade 2: Annually: ¥2,188,800 (Monthly: ¥182,400)</td>
<td></td>
</tr>
<tr>
<td><strong>Pensions for raising handicapped children</strong></td>
<td>Benefit provided for those who raise patients younger than 18, who suffer from a certain degree of disability</td>
<td>Grade 1: Annually: ¥855,600 (Monthly: ¥71,300)</td>
<td>No deadline</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Grade 2: Annually: ¥684,000 (Monthly: ¥57,000)</td>
<td></td>
</tr>
</tbody>
</table>

As of April 1, 2015
## Type and content of relief benefits

<table>
<thead>
<tr>
<th>Type of benefit</th>
<th>In case of Death</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bereaved family pensions</strong></td>
<td>Benefits provided for bereaved families to rebuild their lives following the death of their main provider</td>
</tr>
<tr>
<td><strong>Lump-sum benefits for bereaved family</strong></td>
<td>Benefits provided for bereaved families as a gesture of sympathy following the death of a family member who is not the main provider</td>
</tr>
<tr>
<td><strong>Funeral expenses</strong></td>
<td>Benefits provided to cover the costs of holding a funeral</td>
</tr>
</tbody>
</table>

### Amount of Benefit Paid

|                                | Annually: ¥2,392,800* (Monthly: ¥199,400) | ¥7,178,400 | ¥206,000 |

### Deadline for Application

- **Within 5 years** since the death of the patient.
- However, if payment for benefits relating to medical expenses, medical allowances, disability pension, or pension for raising children with disability was decided, within 2 years after death.

*Pensions are paid for 10 years. However, if the patient that died was receiving disability pension and the duration the patient received this pension was less than 7 years, the family would be paid the pension for 10 years minus the number of years the disability pension was paid. If the disability pension was paid for 7 years or more, the bereaved family pension will be paid for 3 years.
Cases where the relief system is not applicable (1)

● Cases of adverse health effects resulting from standard vaccination practice. (Cases of adverse health effects resulting from voluntary vaccinations are eligible for relief benefits.)

● Cases where it is clear who is responsible for adverse health effects, including in the case marketing authorization holders of the pharmaceutical or biological product are clearly liable.

● Cases where it is necessary to use the pharmaceutical or biological product in an amount exceeding the approved dosage for the purpose of saving the patient’s life, even if it was recognized beforehand that adverse health effects may occur.
Cases where the relief system is not applicable (2)

- Cases where health damage does not require hospital admission; disability does not cause significant activity limitation during daily life; the deadline for claiming the relief benefits has passed.
- Cases where the drug was not used for the proper purpose or where usage was incorrect.
- Cases where health damages were caused by drugs not eligible for relief benefits.
- Cases of health damage caused Cases that are not approved by the Pharmaceutical Affairs and Food Sanitation Council of MHLW based on medical and pharmaceutical judgment.
Contributions for Adverse Drug Reactions

Financial resources for ADR relief benefits are from contributions (general contributions and additional contributions) made by the marketing authorization holder. These are pledged and paid to PMDA by each marketing authorization holder.

① General Contribution:
Pledged and paid by the marketing authorization holder according to the total shipped quantity of approved drugs the previous year. Approximately 3.2 billion yen in fiscal year 2014.

② Additional Contribution:
Pledged and paid by the marketing authorization holder in addition to the general contributions and is calculated based the actual amount of benefits approved by PMDA the previous year for ADR caused by own product. Approximately 570 million yen in fiscal year 2014.
1. Purpose

In order to secure funds necessary for ADR relief benefits and infection relief benefits, marketing authorization holders pledge and pay contributions for ADR and contributions for relief for infections.

2. Contributors

Business operators that are marketing authorization holders for drugs, biological products, or regenerative medical products as of April 1 each year (PMDA Act, Articles 19 and 21)

3. Deadline for Payment

July 31 of each fiscal year (PMDA Act, Enforcement Order, Articles 18)
4. Calculation method for Contributions

Contributions for Adverse Drug Reactions

Targets include drugs and regenerative medical products.
Except for drugs not eligible for relief benefits.

(1) General contribution

Calculated based on the value of shipments in the previous fiscal year
(ratio of contribution 0.27/1,000)

\[
\text{[Calculation formula]} \quad \text{Products’ transaction value (shipment amounts by item } \times \text{ unit price } \times \text{ coefficient[\*]) } \times \text{ ratio of contribution}
\]

\*Coefficient: new drugs 2, oral drugs, etc. 1, other 0.6
- General drugs/drugs requiring guidelines: 0.1
- Regenerative medical products/new regenerative medical products, etc. 2.0
- Regenerative medical products besides the aforementioned products 1.0

(2) Additional contribution

Calculated based on the relief benefits for an ADR caused by the own product, and for which provision is decided in the previous fiscal year.

\[
\text{[Calculation formula]} \quad \text{Actual amount of ADR relief benefit approved in the previous fiscal year (\*}) \times \frac{1}{4}
\]

(Limited to total value of shipment of the company \( \times \frac{1}{100} \))

\*Estimated amount of benefit for lifetime for disability pensions, pensions for raising children with disabilities, and bereaved family pensions
• This tabulation is the result of a summary of cases for which a benefit was provided by the health damage relief system, but does not indicate a general trend regarding ADRs etc.

• More than one causative drug and ADR in a single case are aggregated in the total.
Annual Shift in Number of Cases Provided Relief Benefits for Adverse Drug Reactions and Amount Paid

Fiscal Year

Amount paid (million yen)

No. of cases

Withdrawn
Decision not to pay
Decision to pay
Amount paid
Number of applications


1,600 1,400 1,200 1,000 800 600 400 200 0

1,800 1,600 1,400 1,200 1,000 800 600 400 200 0

2,000 2,200

0 200 400 600 800 1,000 1,200 1,400 1,600 1,800 2,000

0 200 400 600 800 1,000 1,200 1,400 1,600 1,800 2,000

2015 KIDS Symposium; ADR causality assessment and relief system in Asia, November 19, 2015
### Number of Applications by Types of Benefits
(for Adverse Drug Reactions)

<table>
<thead>
<tr>
<th>Type of Benefit</th>
<th>Fiscal year</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of applications</td>
<td></td>
<td>1,018</td>
<td>1,075</td>
<td>1,280</td>
<td>1,371</td>
<td>1,412</td>
</tr>
<tr>
<td>Medical expenses</td>
<td></td>
<td>854</td>
<td>909</td>
<td>1,101</td>
<td>1,200</td>
<td>1,221</td>
</tr>
<tr>
<td>Medical allowances</td>
<td></td>
<td>911</td>
<td>964</td>
<td>1,168</td>
<td>1,252</td>
<td>1,290</td>
</tr>
<tr>
<td>Disability pension</td>
<td></td>
<td>74</td>
<td>77</td>
<td>83</td>
<td>88</td>
<td>95</td>
</tr>
<tr>
<td>Pensions for raising handicapped children</td>
<td></td>
<td>4</td>
<td>4</td>
<td>1</td>
<td>7</td>
<td>12</td>
</tr>
<tr>
<td>Bereaved family pensions</td>
<td></td>
<td>46</td>
<td>47</td>
<td>46</td>
<td>49</td>
<td>41</td>
</tr>
<tr>
<td>Lump-sum benefits for bereaved family</td>
<td></td>
<td>54</td>
<td>63</td>
<td>53</td>
<td>54</td>
<td>65</td>
</tr>
<tr>
<td>Funeral expenses</td>
<td></td>
<td>100</td>
<td>107</td>
<td>98</td>
<td>105</td>
<td>103</td>
</tr>
</tbody>
</table>

*Note: Includes cases where 1 application was turned in for multiple benefits.*
The following shows a breakdown of claimed health damages due to adverse drug reactions for which benefits were provided in the period FY2010-2014 (5,064 cases) classified by the MedDRA/J standard organ system (a total of 6,849 cases).

- MedDRA/J lowest level terms (LLT) of major adverse drug reactions and drug subclasses of major causal drugs are indicated for each System Organ Class.

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Breakdown (LLT)</th>
<th>Proportion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal disorders</td>
<td>Pneumonia interstitial</td>
<td>66.5%</td>
</tr>
<tr>
<td></td>
<td>Pulmonary embolus</td>
<td>9.1%</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>24.4%</td>
</tr>
<tr>
<td></td>
<td>Therapeutic subcategory of causative drug</td>
<td>Proportion</td>
</tr>
<tr>
<td></td>
<td>Chinese herbal</td>
<td>9.8%</td>
</tr>
<tr>
<td></td>
<td>Antipyretic analgesics</td>
<td>9.5%</td>
</tr>
<tr>
<td></td>
<td>Metabolic drugs that cannot be classified in other categories</td>
<td>8.2%</td>
</tr>
<tr>
<td></td>
<td>Mainly acting on gram-positive/negative bacteria</td>
<td>7.5%</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>65.0%</td>
</tr>
</tbody>
</table>

Note: The numbers above do not indicate trends in general adverse drug reactions but are an analysis of relief cases. The numbers indicated above are the total number of health damages with confirmed disease, disabilities, etc.
Breakdown of Drug Classes for Causal Drugs of Adverse Drug Reactions (for Fiscal Year 2010–2014)

Indicates drug class of causal drugs (a total of 9,074 products) for which relief benefits were provided (5,064 cases) in the period FY2010-2014)

- Central nervous system agents: 2785 (31%)
- Antibiotics: 1033 (11%)
- Hormones: 881 (10%)
- Chemo-therapeutics: 828 (9%)
- Digestive organ agents: 674 (7%)
- Cardiovascular agents: 373 (4%)
- Biological preparations: 312 (3%)
- Intracorporeal diagnostic agents: 228 (3%)
- Blood and body fluid agents: 223 (3%)
- Allergic agents: 177 (2%)
- Other: 451 (5%)

Note: Adverse drug reactions occurred due to multiple drugs in some cases; thus, the numbers do not match the number of benefits provided.

[Image: Pie chart showing the breakdown of drug classes]

Indicates drug class (subclass) of causal drugs (a total of 9,074 products) for which relief benefits were provided (5,064 cases) in the period FY2010-2014.
Concerning 904 cases not provided a benefit out of 5,980 cases decided from FY 2010–2014, the reasons for not providing a benefit are as follows.

- Benefit provided: 85%
- Cases of rejection: 15%
- Cases for which drugs are not thought to be responsible: 31%
- Cases that are not sufficiently severe to require hospitalization or cases that do not fall under any disability grades: 16%
- Cases that cannot be determined: 12%
- Drugs ineligible for the relief system or drugs for which tolerance is applied: 4%
- Other: 1%

The purpose of use, or the usage is not considered appropriate: 30%
Information on Decisions Disclosed on Website

PMDA website
http://www.pmda.go.jp/relief-services/adr-sufferers/0043.html

<table>
<thead>
<tr>
<th>Gender</th>
<th>Age at application</th>
<th>Brand name</th>
<th>Generic name</th>
<th>Name of adverse drug reactions</th>
<th>Types of benefit</th>
<th>Reasons for not providing benefits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>60–69</td>
<td>Predonine tablet 5 mg</td>
<td>Japanese Pharmacopoeia Prednisolone tablet</td>
<td>Disease: Steroid-induced diabetes</td>
<td>Medical expenses/medical allowances</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>60–69</td>
<td>Imuran tablet 50 mg</td>
<td>Japanese Pharmacopoeia Azathioprine tablet</td>
<td>Disease: Maculopapular drug eruption</td>
<td>Not provided</td>
<td>Drugs not considered eligible for benefits</td>
</tr>
</tbody>
</table>