Relief System for Adverse Drug Reactions

- Brief history and outline of the Relief System -

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PMDA

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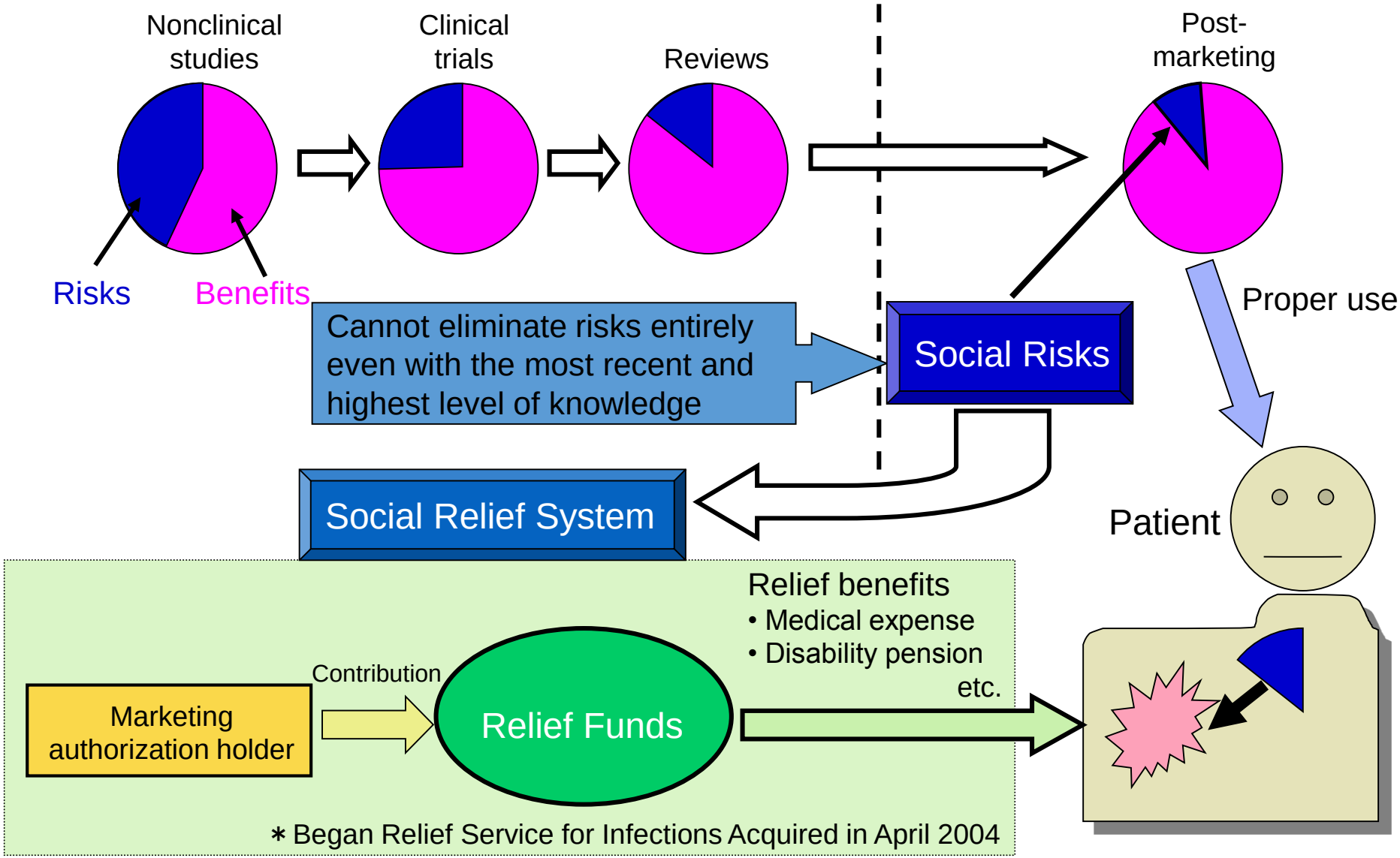
1. PMDA and Relief System for Adverse Health Effects

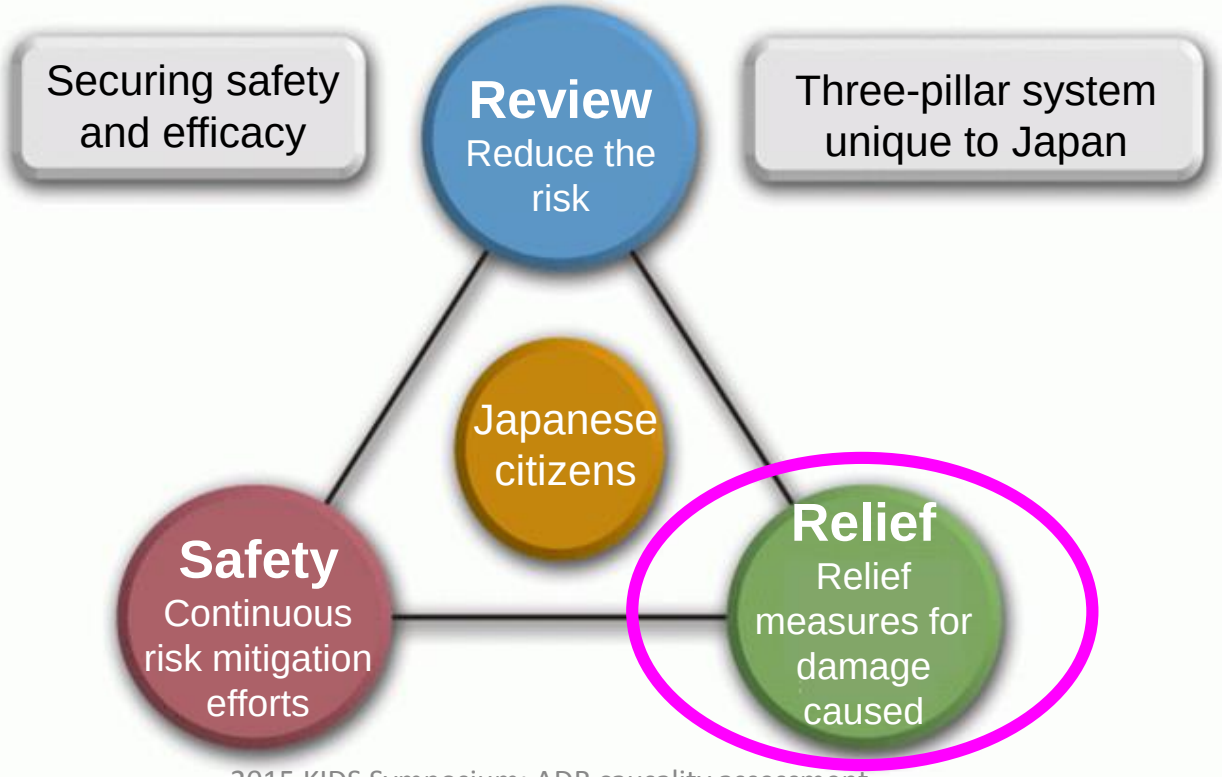
Drug Risks and Relief System for Adverse Health Effects



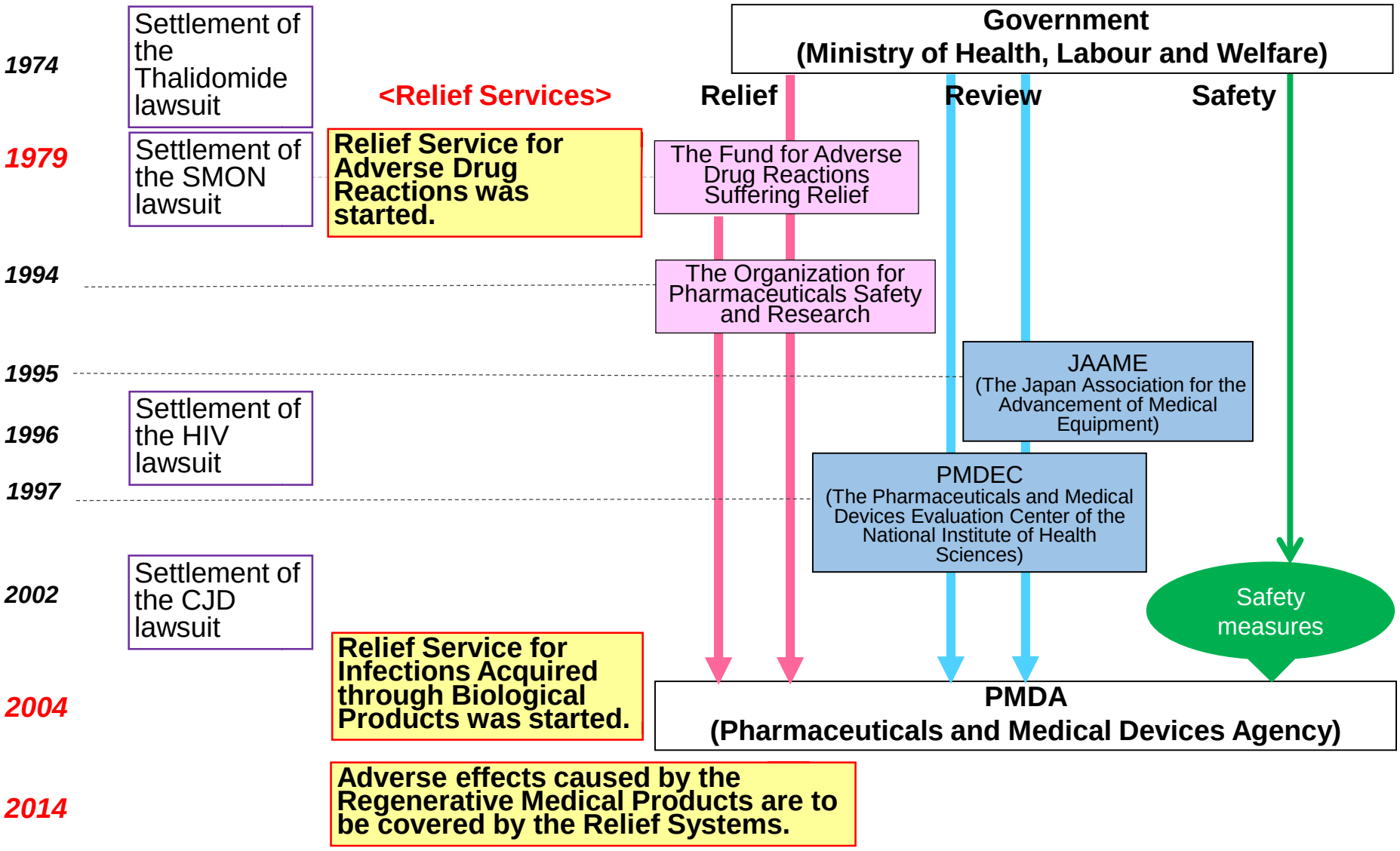
PMDA Functions

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 –



History of PMDA and Relief Systems



2. Relief System for Adverse Drug Reactions

Lawsuit Cases Related to Adverse Drug Reactions (Cases that reach a settlement)

Oct. 1974 Settlement reached for Thalidomide lawsuit

Sep. 1979 Settlement reached for SMON lawsuit

1983–1986 HIV Incident (HIV contaminated raw materials used for Factor VIII and IX products used to treat hemophilia)

<Lawsuit filed in 1989>

Mar. 1996 Settlement reached for HIV lawsuit

Nov. 1996 Creutzfeldt-Jakob disease lawsuit filed

Mar. 2002 Settlement reached for Creutzfeldt-Jakob disease lawsuit

Oct. 2002 Drug-induced hepatitis lawsuit filed

Feb. 2008 Settlement reached for drug-induced hepatitis

Occurrence of Two Major Adverse Drug Reactions

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

Thalidomide lawsuit <Action taken>

○ "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.

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

SMON lawsuit

<Outline>

<Outline>

SMON (Subacute Myelo-Optico-Neuropathy) (*1) developed when quinoform (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, ananastasia, 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>

<History>

1953.6– Production was approved

1955– Symptoms began to be identified in patients undergoing treatment for bowel disease, and drew attention as a nationwide social issue with no known cause.

1969.9 Ministry of Health and Welfare established “Association for SMON Investigation”. The highest incidence was reported that year.

1970.8 A university professor published a report that identified the correlation between the amount of quinoformuse and the incidence of SMON

1970.9 Sales of quinoform were discontinued. The incidence dramatically decreased after this, and there were virtually no new cases.

1971.5 Complaint was filed.

1979.9 Court ruling

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

<Action taken>

○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.

<Action taken>

○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.”

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

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

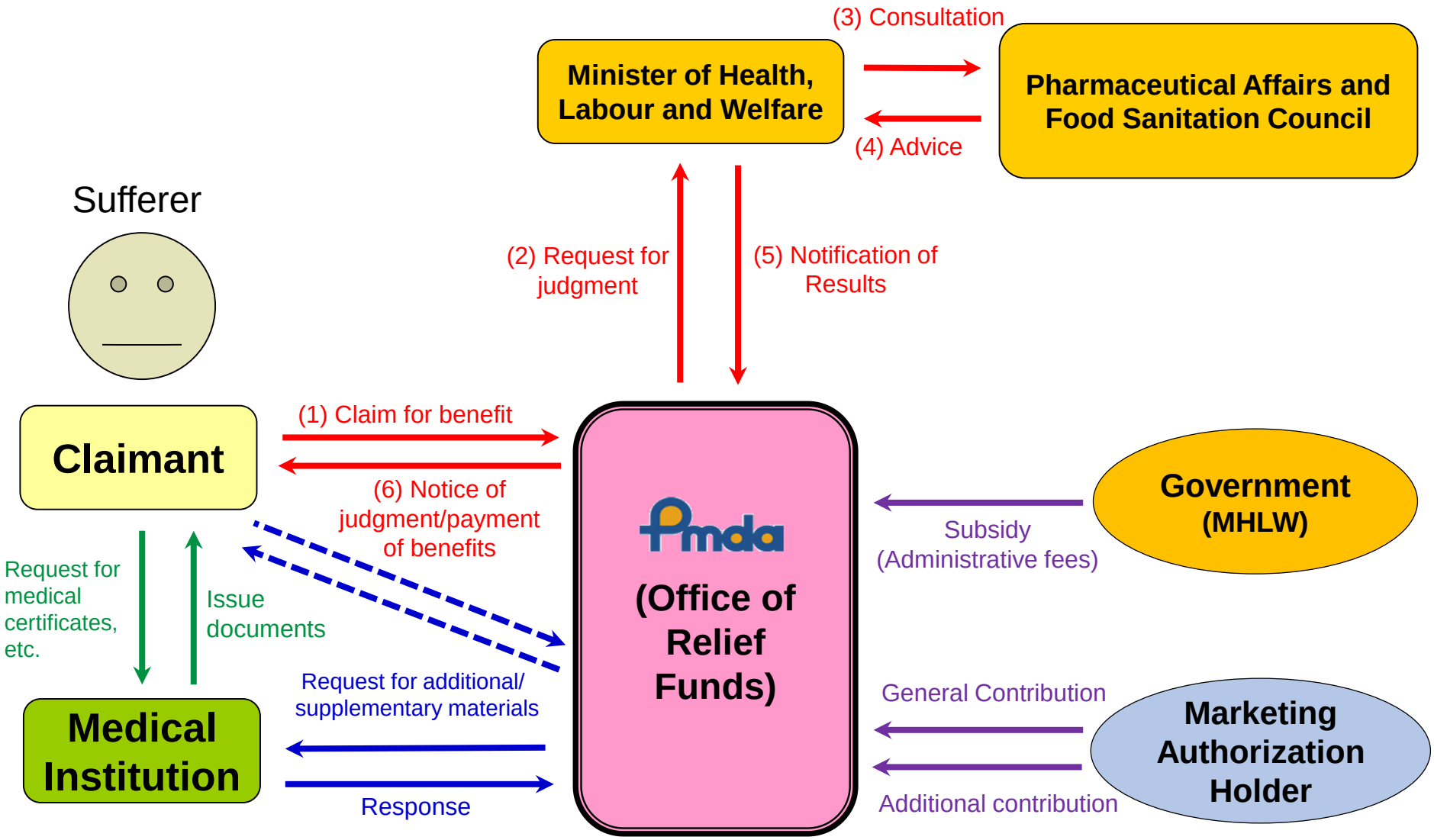
- Established: May 1, 1980

- 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



Type and content of relief benefits ①

As of April 1, 2015

	In case of Disease (requiring hospitalization)			
Type of benefit	Medical expenses	Medical allowances		
Content of benefit	Compensation for the actual cost of treating the disease (as borne by the patient, excluding the amount covered by health insurance)	Benefit paid for costs other than medical costs associated with treatment of the disease		
Amount of Benefit Paid	Costs as borne by the patient, excluding the amount covered by health insurance	If hospitalized	8 or more days in 1 month	Monthly: ￥36,000
			Less than 8 days in 1 month	Monthly: ￥34,000
		On an outpatient basis*	3 or more days in 1 month	Monthly: ￥36,000
			Less than 3 days in 1 month	Monthly: ￥34,000
		If hospitalized and on an outpatient basis		Monthly: ￥36,000
Deadline for Application	Within 5 years of paying the medical expenses that would be covered by the benefit.	Within 5 years since day one of the month following the day for which the medical care invoiced was provided.		

*On an outpatient basis refers to when patients receive treatment requiring hospitalization on an outpatient basis.

Type and content of relief benefits ②

As of April 1, 2015

	In case of Disability (causing serious Impairment in daily life)			
Type of benefit	Disability pensions (for those 18 and above)		Pensions for raising handicapped children	
Content of benefit	Benefit provided to compensate for living costs, etc. of patients aged 18 or older, who suffer from a certain degree of disability		Benefit provided for those who raise patients younger than 18, who suffer from a certain degree of disability	
Amount of Benefit Paid	Grade 1	Annually: ￥2,736,000 (Monthly: ￥228,000)	Grade 1	Annually: ￥855,600 (Monthly: ￥71,300)
	Grade 2	Annually: ￥2,188,800 (Monthly: ￥182,400)	Grade 2	Annually: ￥684,000 (Monthly: ￥57,000)
Deadline for Application	No deadline		No deadline	

Type and content of relief benefits ③

As of April 1, 2015

	In case of Death		
Type of benefit	Bereaved family pensions	Lump-sum benefits for bereaved family	Funeral expenses
Content of benefit	Benefits provided for bereaved families to rebuild their lives following the death of their main provider	Benefits provided for bereaved families as a gesture of sympathy following the death of a family member who is not the main provider	Benefits provided to cover the costs of holding a funeral
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.

Contributions for adverse drug reactions

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)

[Calculation formula] Products' transaction value (shipment amounts by item × unit price × coefficient[*]) × 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.

[Calculation formula] Actual amount of ADR relief benefit approved in the previous fiscal year (*) × 1/4
(Limited to total value of shipment of the company × 1/100)

***Estimated amount of benefit for lifetime for disability pensions, pensions for raising children with disabilities, and bereaved family pensions**

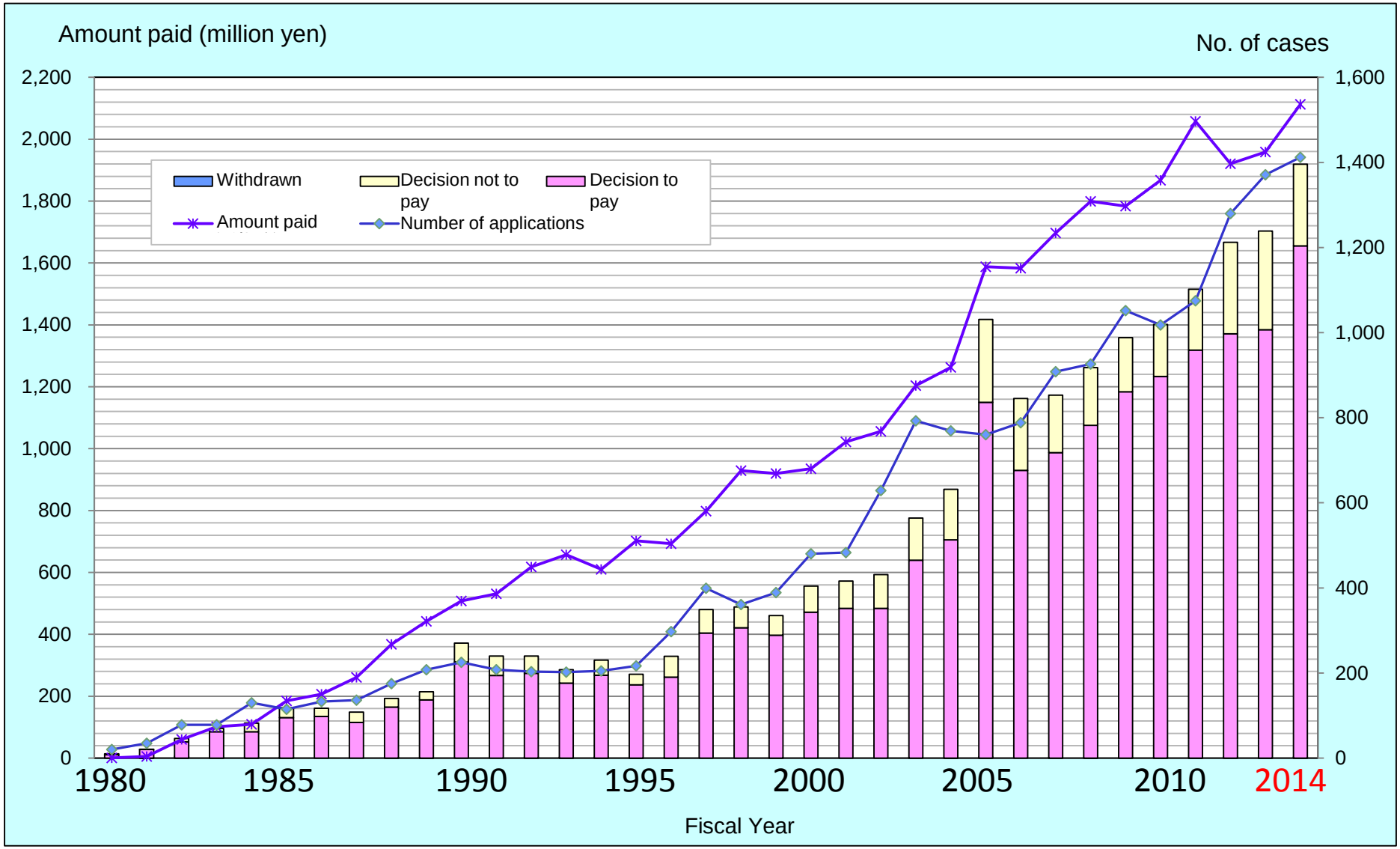
Reference Materials

(Actual performance of relief systems etc.)

- 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



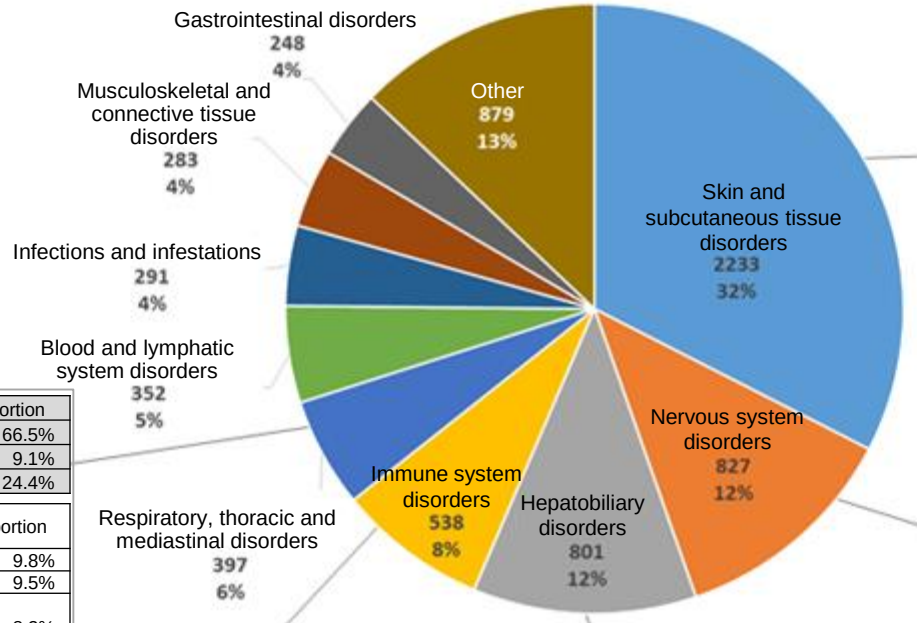
Number of Applications by Types of Benefits (for Adverse Drug Reactions)

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

*Note: Includes cases where 1 application was turned in for multiple benefits.

Breakdown of Health Damages due to Adverse Drug Reactions Classified by Standard Organ System (from Fiscal Year 2010–2014)

- 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.



Breakdown (LLT)	Proportion
Erythema multiforme	25.9%
Hypersensitivity syndrome	24.3%
Toxic epidermal necrolysis	12.8%
Oculomucocutaneous syndrome	12.7%
Other	24.3%

Therapeutic subcategory of causative drug	Proportion
Antiepileptics	18.8%
Antipyretic analgesics	14.9%
Mainly acting on gram-positive/negative bacteria	9.8%
Agents for peptic ulcer	6.8%
Gout preparations	4.2%
Common cold drugs	4.0%
Other	41.5%

Breakdown (LLT)	Proportion
Pneumonia interstitial	66.5%
Pulmonary embolus	9.1%
Other	24.4%

Therapeutic subcategory of causative drug	Proportion
Chinese herbal	9.8%
Antipyretic analgesics	9.5%
Metabolic drugs that cannot be classified in other categories	8.2%
Mainly acting on gram-positive/negative bacteria	7.5%
Other	65.0%

Breakdown (LLT)	Proportion
Hypoxic encephalopathy	19.5%
Neuroleptic malignant syndrome	7.6%
Other	72.9%

Therapeutic subcategory of causative drug	Proportion
Psychotropics	45.6%
Topical anesthetics	5.2%
Vaccines	4.6%
X-ray contrast agent	3.8%
Other	40.8%

Breakdown (LLT)	Proportion
Anaphylactoid shock	68.2%
Anaphylactoid reaction	23.6%
Other	8.2%

Therapeutic subcategory of causative drug	Proportion
X-ray contrast agent	22.2%
Mainly acting on gram-positive/negative bacteria	13.8%
Antipyretic analgesics	10.7%
Synthetic antibacterials	8.2%
Other	45.1%

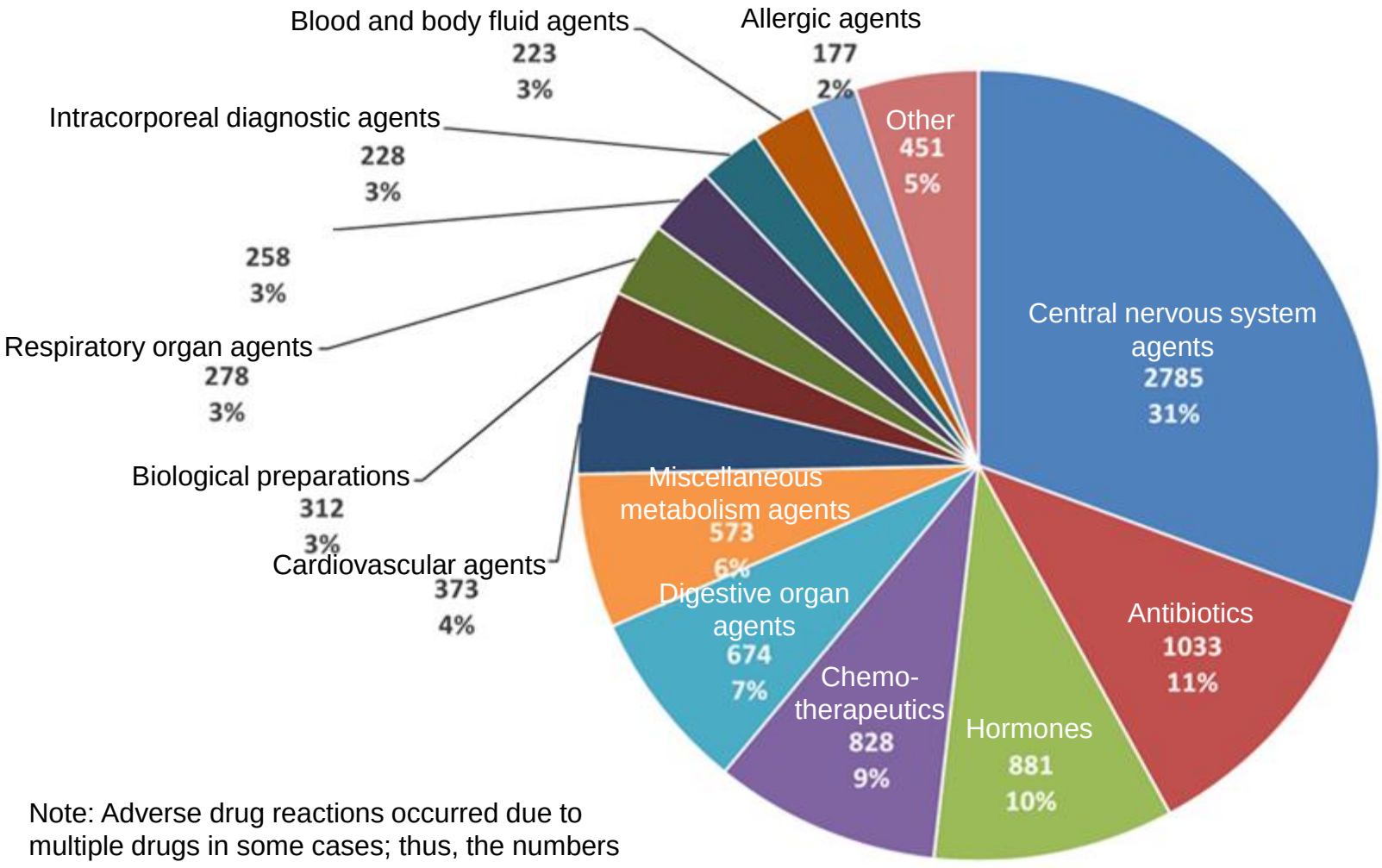
Breakdown (LLT)	Proportion
Hepatic function disorder	92.1%
Hepatitis fulminant	5.7%
Other	2.1%

Therapeutic subcategory of causative drug	Proportion
Antipyretic analgesics	12.3%
Agents for peptic ulcer	9.9%
Chinese herbal	8.5%
Mainly acting on gram-positive/negative bacteria	6.5%
Other	62.7%

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)

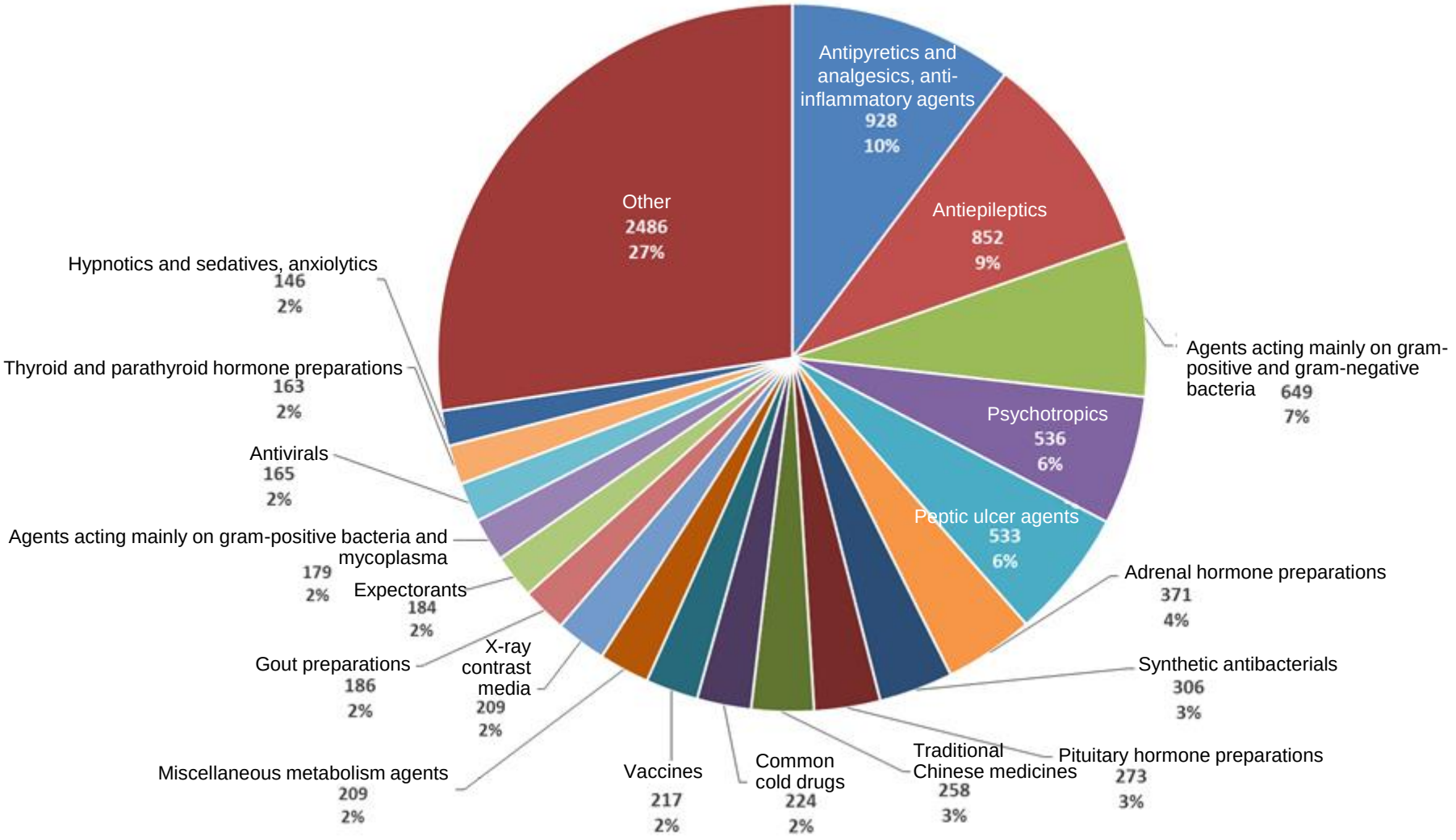
Indicates drug class of causal drugs (a total of 9,074 products) for which relief benefits were provided (5,064 cases) in the period FY2010-2014)



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

Breakdown of Drug Subclasses for Causal Drugs of Adverse Drug Reactions (for Fiscal Year 2010–2014)

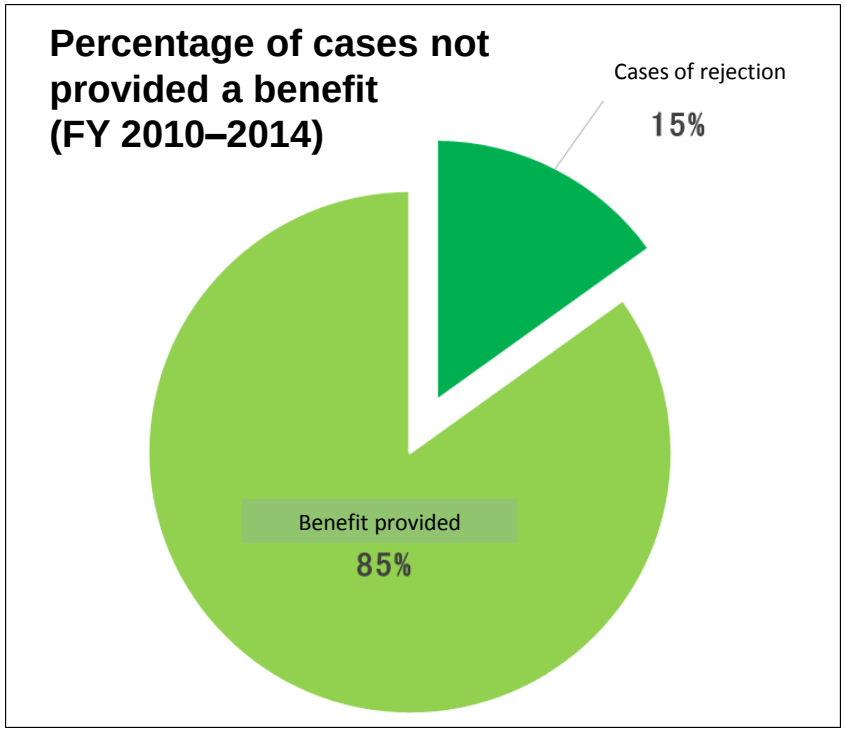
Indicates drug class (subclass) of causal drugs (a total of 9,074 products) for which relief benefits were provided (5,064 cases) in the period FY2010-2014).

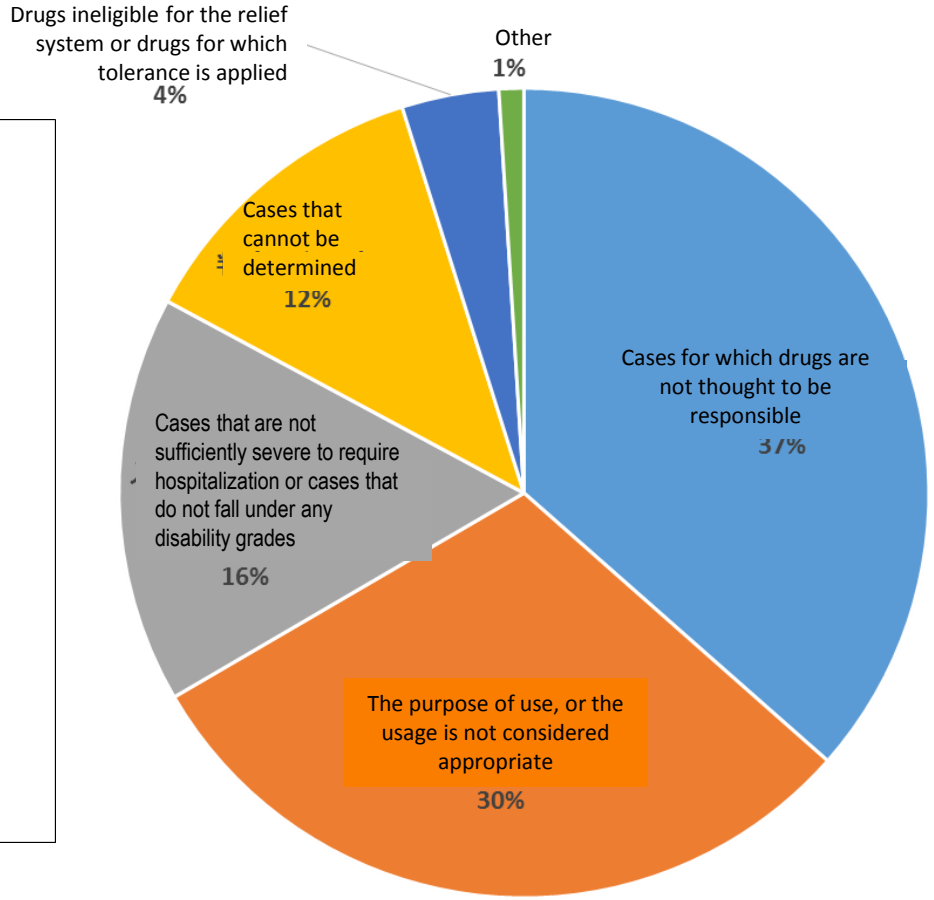


(Reference) Operating performance of relief system for adverse drug reactions (4)

Breakdown of reasons for not providing a benefit (FY 2010–2014)

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.





Information on Decisions Disclosed on Website

PMDA website

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

Gender	Age at application (*)	Brand name	Generic name	Name of adverse drug reactions	Types of benefit	Reasons for not providing benefits
Female	60–69	Predonine tablet 5 mg	Japanese Pharmacopoeia Prednisolone tablet	Disease: Steroid-induced diabetes	Medical expenses/ medical allowances	
Male	60–69	Imuran tablet 50 mg	Japanese Pharmacopoeia Azathioprine tablet	Disease: Maculopapular drug eruption	Not provided	Drugs not considered eligible for benefits
		Baktar Combination tablets	Sulfamethoxazole-Trimethoprim (tablet)			

平成26年度決定 (5月分)

整理番号	性別	請求時年齢(※)	医薬品販売名	一般名	副作用名称等	給付の内容	不支給理由
14-0251	女	60～69	プレドニン錠5mg	局・プレドニゾロン錠	疾病:ステロイド離脱病	医療費・医療手当	
14-0252	男	60～69	イムラン錠50mg	局・アザチオプリン錠	疾病:播種状紅斑丘疹型薬疹	不支給	対象除外医薬品である
			バクタ配合錠	スルファメトキサゾール・トリメトプリム(錠)			
14-0253	女	30～39	チウラジール錠50mg	(局)プロピルチオウラシル錠	疾病:抗好中球細胞質抗体(ANCA)関連血管炎症候群	医療費・医療手当	
14-0254	男	0～9	テグレトール錠100mg	カルバマゼピン(錠)	疾病:多形紅斑型薬疹	医療費・医療手当	
14-0255	男	20～29	－	－	障害:－	不支給	投与された医薬品により発現したとは認められない
14-0256	男	30～39	レクチゾール錠25mg	ジアフェニルスルホン(錠)	疾病:薬剤性過敏症症候群(DIHS)	医療費・医療手当	
14-0257	女	60～69	テグレトール錠100mg	カルバマゼピン(錠)	疾病:薬剤性過敏症症候群(DIHS)	医療費・医療手当	
14-0258	女	10～19	テグレトール錠200mg	カルバマゼピン(錠)	疾病:薬剤性過敏症症候群(DIHS)	医療費・医療手当	
14-0259	女	30～39	ラミクタール錠25mg	ラモトリギン(錠)	疾病:薬剤性過敏症症候群(DIHS)	医療費・医療手当	
14-0260	女	50～59	イオメロン300注シリンジ100mL	イオメプロール(注射液)	疾病:播種状紅斑丘疹型薬疹	医療費・医療手当	
14-0261	女	40～49	アザルフィジンEN錠250mg	サラゾスルファピリジン(腸溶錠)	疾病:薬剤性過敏症症候群(DIHS)	医療費・医療手当	
14-0262	女	70～79	プレドニゾロン錠「タケダ」5mg	局・プレドニゾロン錠	疾病:ステロイド精神病	医療費・医療手当	
14-0263	女	50～59	ラミクタール錠25mg	ラモトリギン(錠)	疾病:巨細胞型薬疹	不支給	医薬品の使用方法が適正とは認められない
			ピーエイ配合錠	非ピリン系感冒剤(4)(錠)			
14-0264	男	40～49	ラミクタール錠25mg	ラモトリギン(錠)	疾病:薬剤性過敏症症候群(DIHS)	医療費・医療手当	
14-0265	女	30～39	プロパジール錠50mg	局・プロピルチオウラシル錠	疾病:播種状紅斑丘疹型薬疹、薬物性肝障害	医療費・医療手当	
14-0266	女	10～19	イオソール注300シリンジ100mL	イオヘキソール(キット)	疾病:尋麻疹型薬疹	医療費・医療手当	
14-0267	女	40～49	ジプレキサ錠2．5mg	オランザピン(錠)	障害:尿閉による排尿障害に伴う日常生活障害	不支給	政令で定める程度の障害とは認められない