Relief System for Sufferers from Adverse Drug Reactions

- Medical/pharmaceutical judgment -

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Office of Relief Funds
PMDA
Today’s Content

1. Medical/pharmaceutical judgment
2. PMDA Safety Triangle
Flow of operation

Claimant

(1) Claim
(12) Benefit
(4) Response
(3) Request for additional/supplementary data
(4) Response

Medical institution

(2) Accepted document
(7) Investigation report, etc.

Investigation Division

(5) Request for investigation
[Expert consultation]
(6) Opinion

PMDA Office of Relief Funds

(9) Consultation
(10) Report

Minister of Health, Labour and Welfare

Pharmaceutical Affairs and Food Sanitation Council First and Second Committees

2015 KIDS Symposium; ADR causality assessment and relief system in Asia, November 19, 2015
Documents required for filing a claim can be downloaded from PMDA homepage. 
http://www.pmda.go.jp/kenkouhigai/fukusayo_dl/

2015 KIDS Symposium; ADR causality assessment and relief system in Asia,
November 19, 2015
Flow of relief benefit & flow of Investigation work

**Benefit claimants**

- **(1) Benefit claim**
  - Request for additional materials/data
  - Additional materials/data submission
- **(4) Notification/benefit**
  - Request for additional/supplementary documents
  - Additional/supplementary documents submission

**Medical institutions**

- Claim for medical certificate
- Issuance of medical certificate
- Request for materials/data
- Submission of materials/data

**Pharmaceuticals and Medical Devices Agency**

- **Prior investigation/organization of facts**
  - (2) Application for judgment (Investigation report)
  - (3) Notification of judgment

**MHLW (Pharmaceutical Affairs and Food Sanitation Council)**

**External expert**

Additional comments:

- (Act on Pharmaceuticals and Medical Devices Agency, Article 24)

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Role sharing between PMDA and MHLW

[MHLW] Planning/drafting of basic policies, implementation of administrative measures such as approval and administrative orders based on laws.

(Example)
• Relief judgment (Judgment on eligibility)
• Discussions at councils, final judgment for approval
• Direction to issue a recall and emergency safety information
  Implementation of safety measures concerning urgent and significant cases

[PMDA] Review, investigation, and data processing, etc. that do not require administrative judgment.

(Example)
• Collection of contributions; provision of relief benefits
• Investigation prior to application for relief judgment
• Review/investigation on drug, etc., clinical trial consultation
• Acceptance/collection/organization/investigation of ADR reports, provision of ADR information

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Flowchart of relief services
Application Review Division (2 – 6), and Relief Division (1, 7 – 11)

1. Day when claim form is accepted

2. Prior organization
   • Confirm the content of claim form
   • Prepare case summary
   • Organize previous and ongoing cases

   Prior investigation
   • Review the content of claim form
   • Check known information in package inserts and literature, etc.
   • Search and review previous cases
   • Control the progress of prior investigation
   • Prepare the request form of additional/supplementary information, request
   • Accept and review additional/supplementary information

3. Expert consultation

4. Prepare investigation report

5. PMDA briefing

6. Prepare for proposal of judgment

7. Proposal of judgment

8. Judgment Committee (MHLW)

9. Accept the judgment

10. Confirm with claimant (Adjustment of high medical expenses, etc.)

11. Decision on payment

4.5 months; PMDA

Standard Administrative Processing Time:
At least 60% of cases processed within 180 days

1 month; MHLW

0.5 month; PMDA

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Works of the Application Review Division
–Part 1–

In the Relief System for Adverse Drug Reactions,

- Investigation prior to request for judgment
  - Prepare case summaries and narratives over time
  - Check known information with package inserts, etc.
  - Search and review previous cases/literature, etc.
  - Request additional/supplementary information/review of response

- Expert consultation
  (consultation for medical/ pharmaceutical opinions concerning causality, proper use, and severity of the damage, etc.)

- Preparation of investigation reports
Works of the Application Review Division
–Part 2–

• Other
  • Investigation prior to claim, organization, expert consultation, and preparation of investigation report for Relief System for Infections Acquired through Biological Products
  • Collaboration with other divisions (e.g. safety divisions, review divisions)
  • Collaboration with MHLW (Safety Division, Office of Drug Induced Damage, Blood and Blood Products Division, etc.)
  • Accumulation and analysis of data
  • PR activities for healthcare professionals
  • Actions taken in relation to lawsuits
Additional or supplementary information

• To obtain all relevant data when assessing the causality and proper use, etc., of a drug, additional or supplementary information may be requested by medical institutions and claimants themselves.

• For example…
  • Clinical laboratory test result before and after the occurrence of adverse event are not sufficient.
  • The information on treatment (intended use, dosage, period of taking the drug, etc.) concerning a causative drug is not clear.
  • Clinical course after the occurrence of adverse event is not described, and information necessary for diagnosis of ADR cannot be obtained.
  • Other factors such as infection can be considered.
Expert consultation

To investigate and organize the facts, medical and pharmaceutical opinions are sought from experts who use causative drugs and experts on the ADR.

- Confirms data needed to evaluate causality, proper purpose and proper use, etc.
Issues that require medical/pharmaceutical judgment I

(1) Is there a causal relationship between the drug and the health damage? [Causality]

(2) Was the drug used for the intended purpose? [Proper purpose]

(3) Was the drug used correctly? [Proper use]

(4) Should the health damage incurred be tolerated by the patient? [Tolerance]

* 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.
Issues that require medical/pharmaceutical judgment II

(5) Is the level of medical care equivalent to the level of hospitalization? [Certification of medical benefit]

(6) Is the status of health damage certified as disability? [Certification of disability]

(7) Does the degree of disability fall under the classes of disability specified by the cabinet order? [Certification of the class of disability, etc.]

* From these viewpoints (I, II), after deliberation by MHLW Pharmaceutical Affairs and Food Sanitation Council (Judgment Committee on Adverse Drug Reactions and Infections), PMDA makes decisions regarding approval or not of relief benefits based on the result of judgment by MHLW.
(1) Causality assessment –Part 1–

- What is happening to sufferers from adverse health effects?
- Is the health damage considered to have happened due to an adverse drug reaction?
- Relationship with the initiation/discontinuation of drug, onset of ADR, and time course of recovery
- Relationship with primary disease and complications
- Elimination of other factors
(1) Causality assessment –Part 2–

Investigation of ADR and suspected drug

• Investigation of ADR
  • Check with manuals for management of individual serious adverse drug reactions, and diagnostic criteria, etc.
  • Refer to physician’s comments etc. contained in the medical certificate, etc.

• Investigation of causative drugs
  • Temporal relationship between the period during which the drug was used and occurrence of adverse reactions
  • Present descriptions provided in the package inserts
  • Investigation of medically relevant information, literature, guidelines from professional societies
  • Result of patch test, etc.
(2) Evaluation of proper purpose

- Was the causative drug used for the indication specified in the package inserts?
- Was the causative drug used for a proper purpose based on sufficient evidence even though this purpose was not specified in the indications section of package inserts?
  (Described in textbooks, etc.)

The above are to be investigated.
(3) Evaluation of proper use

Was the causative drug used properly?

① Did the use fall under the contraindications contained in the package inserts?

② Was the dosage of the drug correct?

③ Were the precautions complied with?
What is “Improper purpose or improper use”?

- Cases where a drug was used for the purpose other than the indications approved by the Minister of Health, Labour and Welfare, and caused Adverse Drug Reactions (ADR), which led to health damage, and cases where the usage did not comply with the precautions contained in package inserts.

- “Precautions” are the information necessary to ensure the safety of patients for whom the drug is indicated, and promote the proper use of the drug. If the drug is used without complying with the precautions, the health damage, if it occurs, may not be eligible for coverage under the health damage relief system.

Excerpt from Pharmaceuticals and Medical Devices Safety Information No.262 (October, 2009)
(4) Evaluation of tolerance

Cases where the patient should tolerate adverse effects…

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.

- Should the occurrence of health damage be tolerated or not?
- Did the health damage occur due to drugs not eligible for relief benefits?

Example: oncology drugs, immunosuppressant, etc.
What drugs are not eligible for relief benefits?

- Pharmaceuticals used for the purpose of the treatment of cancer and certain other diseases designated by the Minister of Health, Labour and Welfare. (159 items as of July 3, 2015)

- Pharmaceuticals that may not cause suffering due to adverse reactions such as pharmaceuticals not directly designed for human use or without pharmacological action.
(5) Evaluation of medical benefit

The relief system is applied to cases with medical care equivalent to the level of hospitalization.

• Was the medical care given in the period covered by the claim medical care targeting the treatment of an ADR?

• Was the level of medical care equivalent to the level of hospitalization?
(6) Evaluation of disability
Refer to the standard for national pension/employees’ pension insurance disability certification

• What criteria must the disability meet?
• What symptoms are regarded as equivalent to a disability?
• Do symptoms of the disability continue for at least 18 months after their onset? Or, have the symptoms resolved?
• Is there a causal relationship between the ADR and the disability?
• What is the name of disability?
(7) Evaluation of grades of disability

This system provides relief for severe disabilities classified as grade 2 or higher.
→Will the disability presented in the claim be Grade 1 or 2?

**Grade 1: The patient's capacity is limited to barely being able to take care of him/herself.**

- Example 1) Lower limb function disability
  - Life in hospital → Scope of activity is basically limited to a bed, etc.
  - Life at home → Scope of activity is basically limited to within the home, etc.

- Example 2) Vision impairment
  - The largest character or symbol cannot be identified at the closest distance from the visual acuity chart.

**Grade 2: The patient's capacity is confined to performing limited activities in hospital and at home (e.g. making breakfast, washing underwear). Scope of activity is basically limited to indoors.**

- Example 3) Lower limb function disability
  - Life in hospital → Scope of activity is basically limited to the ward, etc.
  - Life at home → Scope of activity is basically limited to within the home, etc.

- Example 4) Vision impairment
  - The largest character or symbol can only be identified at a distance of 3 meters from the visual acuity chart.
## Operating performance of relief system for adverse drug reactions (1)

<table>
<thead>
<tr>
<th>Year</th>
<th>FY 2009</th>
<th>FY 2010</th>
<th>FY 2011</th>
<th>FY 2012</th>
<th>FY 2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of claims</td>
<td>1,052 cases</td>
<td>1,018 cases</td>
<td>1,075 cases</td>
<td>1,280 cases</td>
<td>1,371 cases</td>
</tr>
<tr>
<td>No of cases for which a decision was made</td>
<td>990 cases</td>
<td>1,021 cases</td>
<td>1,103 cases</td>
<td>1,216 cases</td>
<td>1,240 cases</td>
</tr>
<tr>
<td>Benefit provided</td>
<td>861 cases</td>
<td>897 cases</td>
<td>959 cases</td>
<td>997 cases</td>
<td>1,007 cases</td>
</tr>
<tr>
<td>Benefit not provided</td>
<td>127 cases</td>
<td>122 cases</td>
<td>143 cases</td>
<td>215 cases</td>
<td>232 cases</td>
</tr>
<tr>
<td>Rejected</td>
<td>2 cases</td>
<td>2 case</td>
<td>1 case</td>
<td>4 cases</td>
<td>1 case</td>
</tr>
</tbody>
</table>

Within 8 months

- Percentage of cases handled
  - FY 2009: 733 cases (74.0%)
  - FY 2010: 765 cases (74.9%)
  - FY 2011: 809 cases (73.3%)
  - FY 2012: 923 cases (75.9%)
  - FY 2013: 1,063 cases (85.7%)

Within 6 months

- Percentage of cases handled
  - FY 2009: 360 cases (36.4%)
  - FY 2010: 434 cases (42.5%)
  - FY 2011: 534 cases (48.4%)
  - FY 2012: 553 cases (45.5%)
  - FY 2013: 754 cases (60.8%)

No. of cases processed

- FY 2009: 746 cases
- FY 2010: 743 cases
- FY 2011: 715 cases
- FY 2012: 779 cases
- FY 2013: 910 cases

Period of processing (median)

- FY 2009: 6.8 months
- FY 2010: 6.4 months
- FY 2011: 6.1 months
- FY 2012: 6.2 months
- FY 2013: 5.8 months

*1 Percentage of cases processed within 8 months of cases decided in the relevant year
*2 Percentage of cases processed within 6 months of cases decided in the relevant year
*3 Value at the end of each fiscal year
PMDA Safety Triangle

PMDA engages in activities designed to create a sound foundation that allows the government to perform pharmaceutical administration through the concerted efforts of three divisions.

**Review**
Reduce the risk

- Share information among divisions
  - Personnel reshuffle
  - Co-assignment of duties among divisions
  - Daily briefings

- Utilize the information on approval/rejection of relief benefit for review
- Utilize risk information obtained through review process for evaluation of the content of the relief claim

**Safety**
Minimize post-marketing risk

- Safety divisions participate in review
- Utilize safety information for review
- Utilize ADR risk information that is clarified during the process of reviewing of safety measures

**Japanese citizens**

**Relief**
Provide relief for damage caused

- Utilize the information on the approval/rejection of relief benefit for revision of package inserts

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Promotion of collaboration among divisions

Further risk reduction is facilitated by promoting collaboration with safety divisions, and providing information obtained through emergency interventions to safety divisions.

1. Since November 25, 2014, information is organized and investigated so as to utilize cases applying for relief benefit for post-marketing safety measures based on the Drug and Medical Device Act.

2. In particular, the following cases are utilized for safety measures.
   - ADRs that are not described in package inserts
   - Improper use repeated despite the precaution being stated in package inserts, etc.
   - Revision of package inserts
   - “PMDA Request for Proper Use of Drugs” posted on the Medical Product Information web page, explaining points for safe use of drugs, etc. in an easy-to-understand way that allows healthcare professionals to readily use the information, in order to further promote the proper use of drug products.
**Contribution to the safety measures**

Relief Services revealed following drug-safety information by collaborating with the safety section;

- **Newly defined clinically significant ADRs added to package inserts:**
  - Fanconi syndrome associated with Adefovir (2012)
  - Stevens–Johnson syndrome associated with Alogliptin benzoate (2012)
  - Interstitial pneumonia associated with Anastrozole (2011) etc.

- **Inappropriate drug usage (ex, neglected laboratory tests):**
  - PMDA Alert for Proper Use of Drugs: Thiamazole (2011), Lithium carbonate (2011), etc.