Regulatory scientific significance of Japan's ADR relief system

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DIA driving insights to action!

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DIA driving insights to action!

Japan's ADR Relief System

1. Streamlined rescue for ADR sufferers
2. To promote safer use of medicines
3. To ease societal apprehension about new drugs and to help innovation

Coverage of Japan’s Relief System

- Adverse Drug Reactions (ADRs) and Infections
- drugs, biologics, and regenerative medicine products (e.g. cellular, tissue, and gene therapies),
- prescription and over-the-counter (OTC) drugs, but not anti-cancer agents and immunosuppressants.
- known and unknown ADRs etc. necessitating hospitalization or graver.

Relief Fund

- Fund for Relief Services for Adverse Drug Reactions is maintained through mandatory annual contributions from the marketing approval holders.

Rationale of the Relief System

- There are unpreventable drug-related harms.
- In response to such drug-related harms, the manufacturer of the relevant medicine may not be held liable under generally-applicable product liability doctrine.
- Even in cases where civil liability may be pursued, sufficiently proving the necessary element of causality and fault in civil litigation is generally very difficult and places tremendous time, mental, physical, and financial burdens on victims.
- There is a societal obligation to provide relief to victims of drug-related harms who are unable to obtain relief from other sources. Or, because no individual party can bear full responsibility for harms caused by unpreventable drug-related harms, it becomes the duty of society as a whole to provide this relief to victims.
- Because drug manufacturers are responsible for ensuring as much as possible the safety and efficacy of the products, they should bear primary responsibility for financing relief payments.

Criteria for compensation eligibility

A) reasonably plausible causal relationship b/w the drug & the adverse event
   a. Expert staff at PMDA and MHLW primarily examine the chronology of the suspected medication use, and compare this to the timing of symptom onset
   b. Unless the possibility of a causal relationship is wholly eliminated, the benefit of the doubt is afforded to the claimant.

B) the use(s) of the medication associated with the adverse event were "proper".
   a. The drug must have been administered according to the approved dosage and other usage instructions (e.g. instructions requiring that the patient undergo periodic blood tests, etc.), with some allowance for deviation in the light of current medical science.

Drug product liability as alternative to Relief System

Pathway with Product Liability Act needs;

(a) the existence of a defect in a manufactured or processed good

(b) actual harm suffered

(c) causation

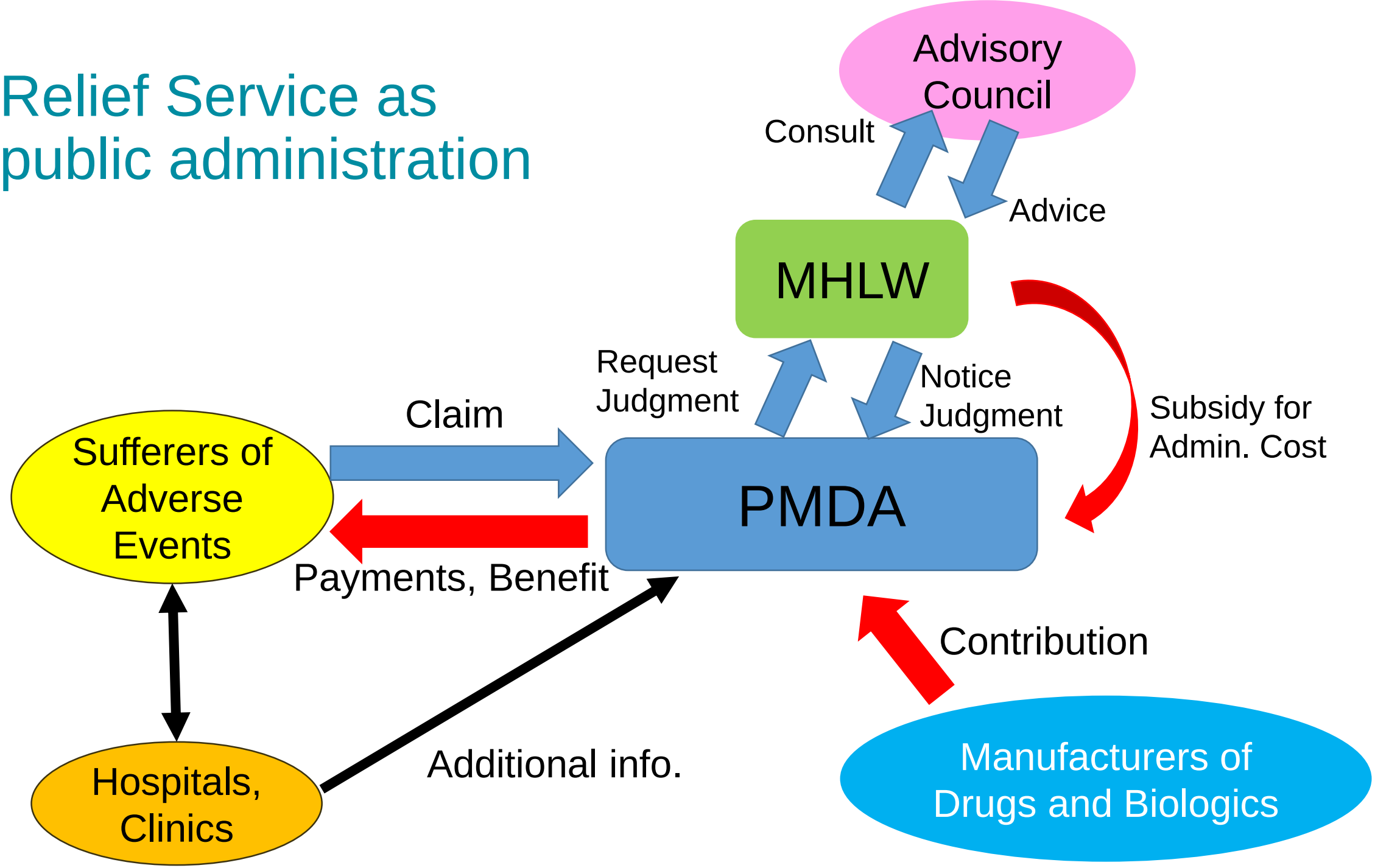
– But no need to prove negligence .

However

– Manufacturers can avoid liability if they can prove that discovering the relevant defect was impossible at the time of delivery to the user.

– information-gathering activities in Japan are far more restricted than in USA.

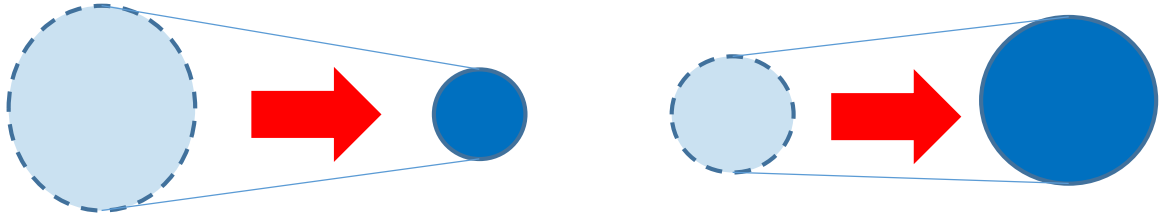
Relief Service as public administration



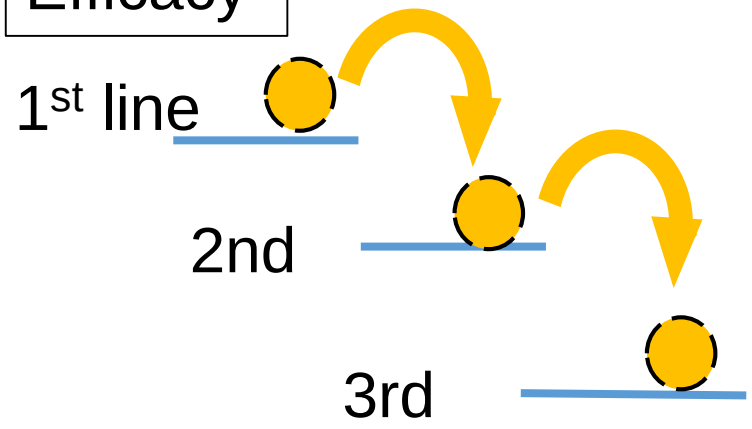
Society, drug use, and ADR as cost

Inevitable “trial and error” in establishing a drug’s usage

target population



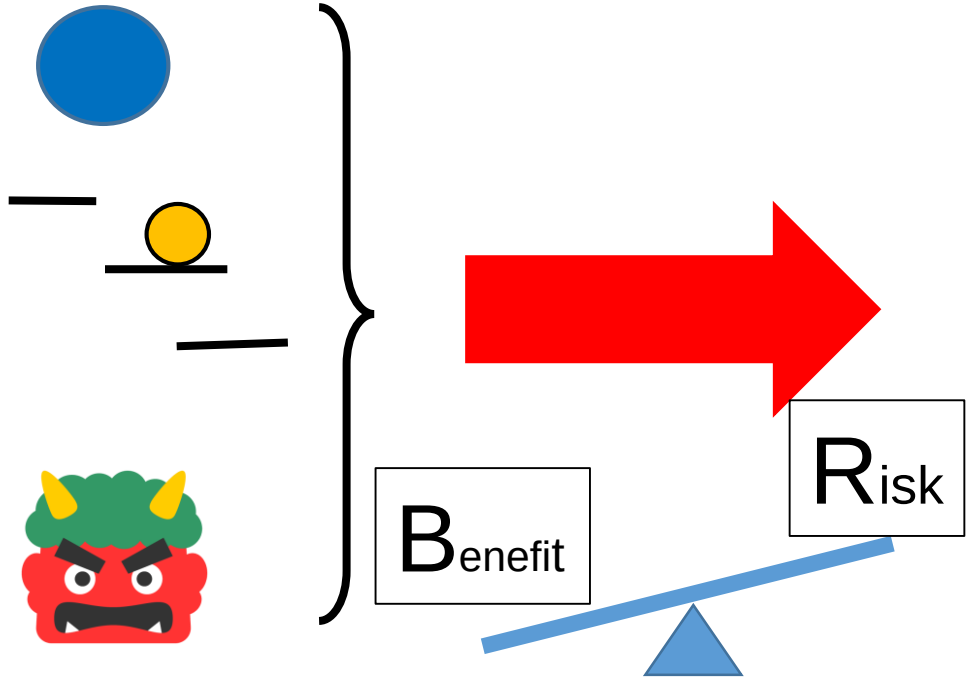
Efficacy



Safety (ADR)

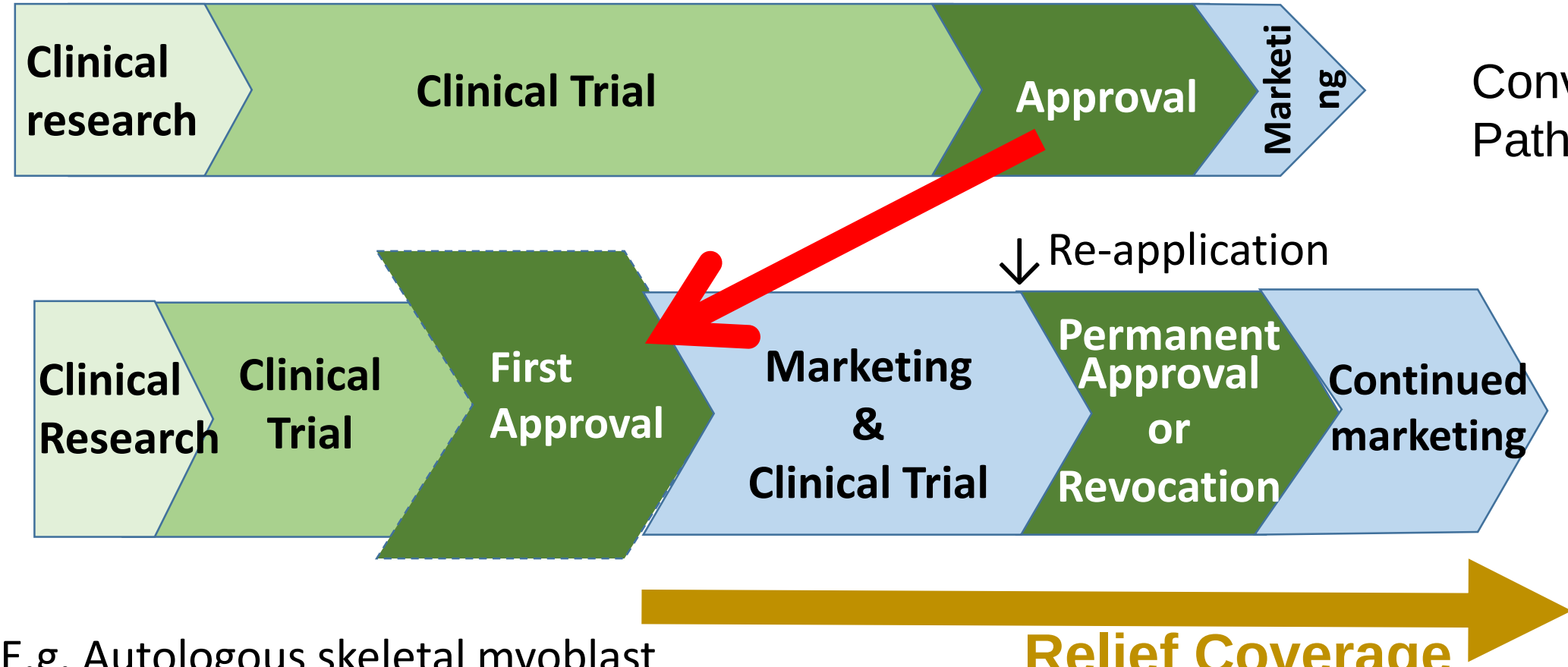
Inevitable ADR cases as cost to establish usage

Even with the drug’s usage established, known ADRs do occur

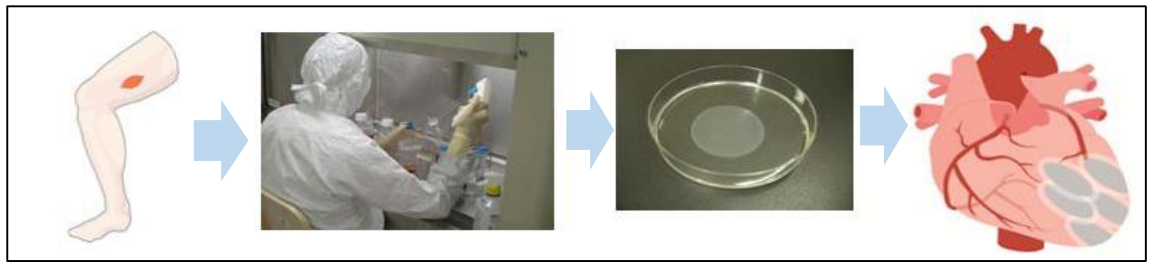


Inevitable ADR cases as cost to maintain on the market

Japan's conditional & time-limited authorization for cellular, tissue, and gene therapy products (regenerative medicine products).



E.g. Autologous skeletal myoblast



Innovative products are often with greater uncertainties when marketed

- Coverage by the Relief System should encourage use of drugs with reasonable caution and without excessive fear.
- Coverage decreases risk of product liability litigation for manufacturers of innovative products

➢ Coverage is expected to progress a drug's lifecycle, especially in post-market evidence acquisition (e.g. for adaptive pathway) and promote innovation.

Contribution to Safety Measures

1. Relief cases are also reportable in spontaneous ADR reporting. In theory PMDA receives duplicative reports/claims
2. Relief claims frequently contain more information than spontaneous reports, especially the claimant's medical history long before the occurrence of the event.
3. MHLW/PMDA's Relief Service Offices and Post-market Safety Offices combine ADR information from multiple sources and formulate safety measures.
4. Viewpoint: signal detection from multiple spontaneous reports vs. causal relationship in the claimant.
5. The condition of "proper use" implies that a doctor's failure to take suitable precautionary measures could cost a claimant's chance of financial compensation. This encourages health care professionals' compliance.

Example 1: Adefovil pivoxil (anti Hepatitis B) & Fanconi Syndrome

Fanconi Syndrome

Avg. 18 months

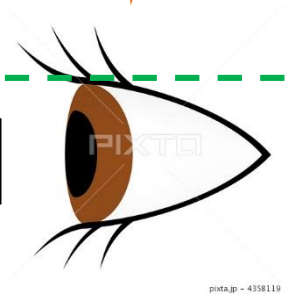
Muscle Weakness

Bone Fracture

Renal Damage (on re-absorption of Phosphate, etc.)

Joint Pain

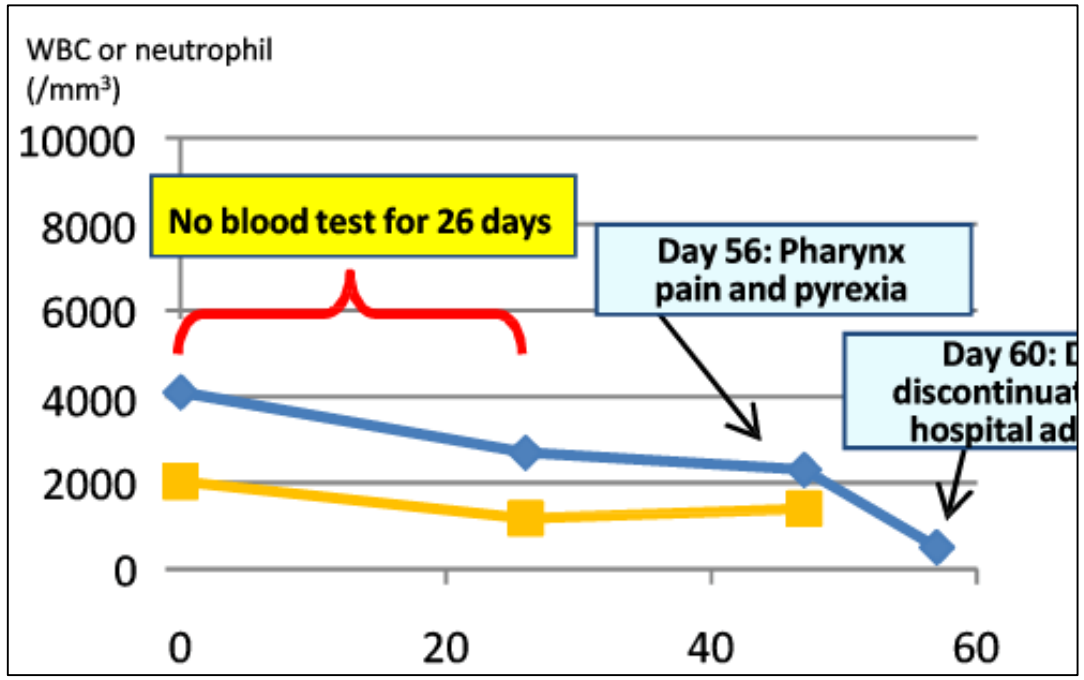
Patient's History in Relief Claim data

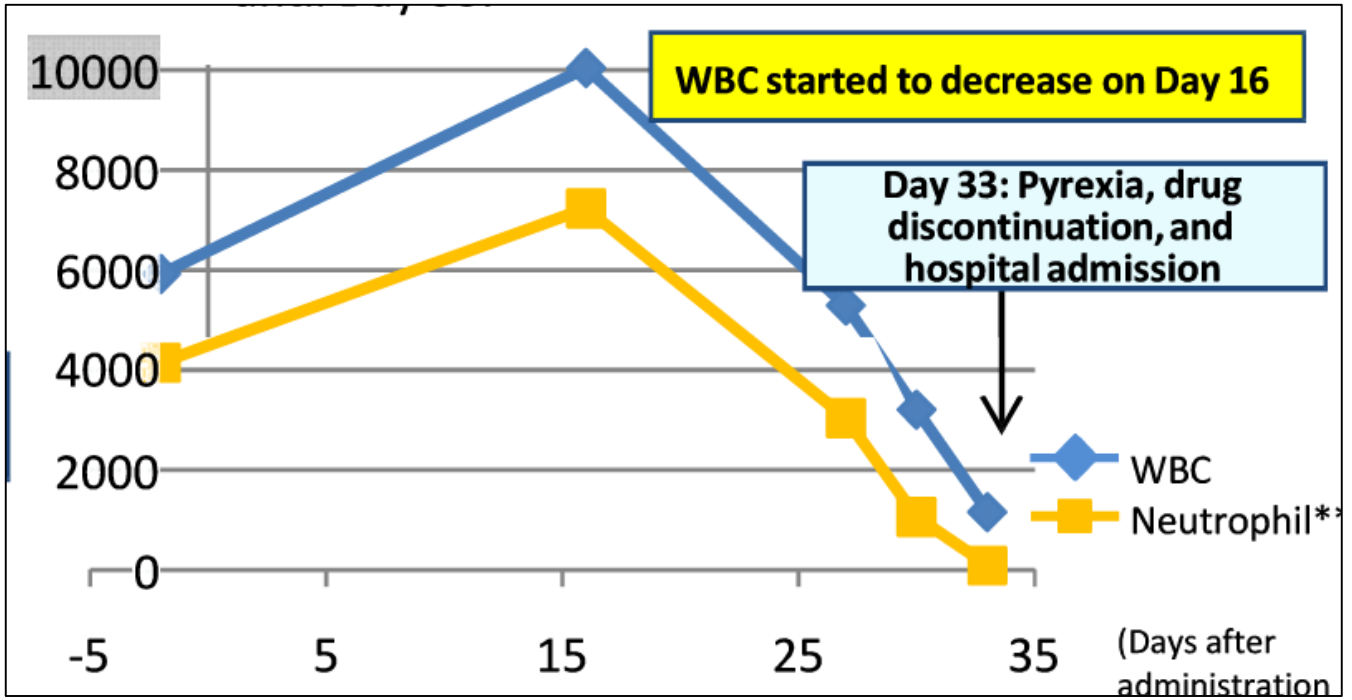


Labelling Change (2012)

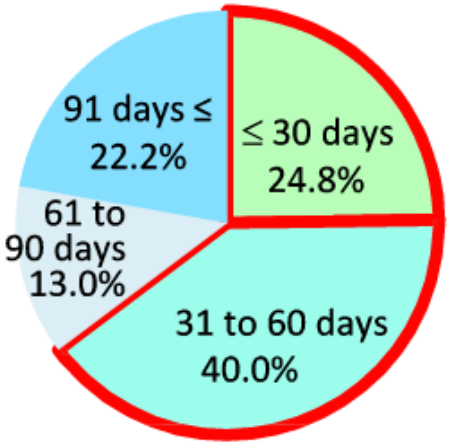
- Warned Possible course of events from hypophosphatemia to osteomalacia and bone fracture
- Mandated observation of serum phosphate and alkaline phosphate

Example 2 : Thiamazole and Agranulocytosis





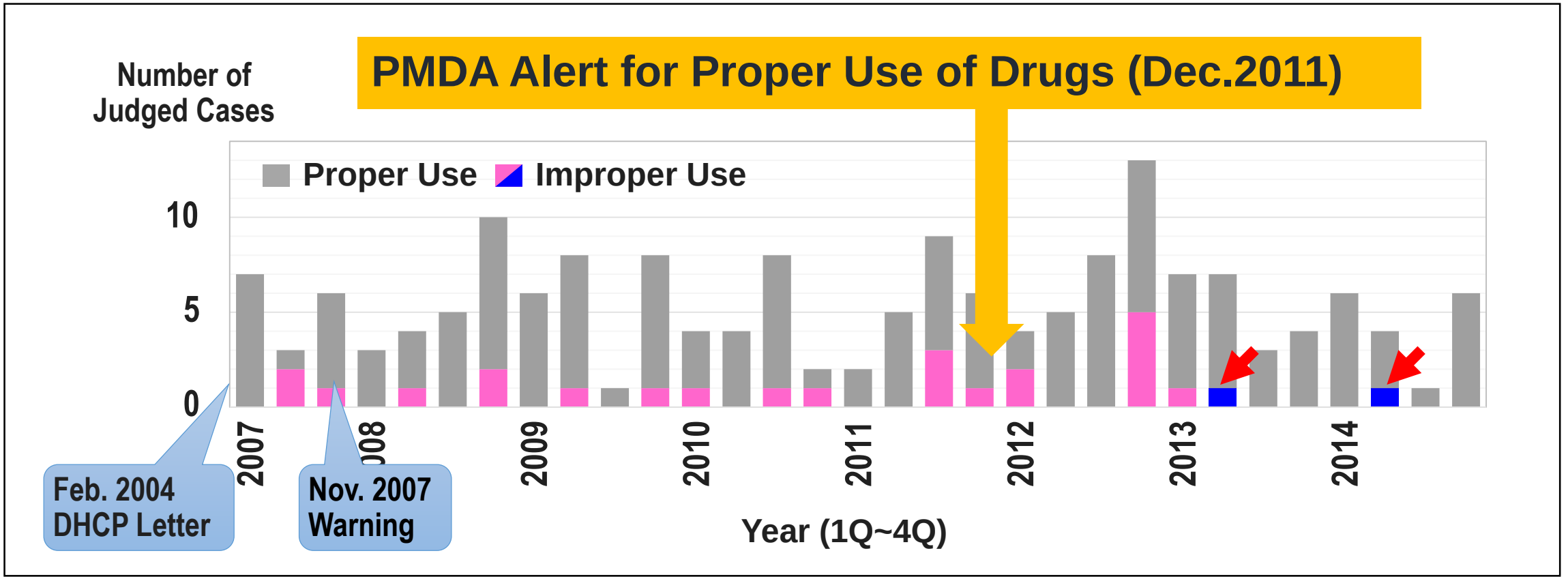
Time of onset of agranulocytosis



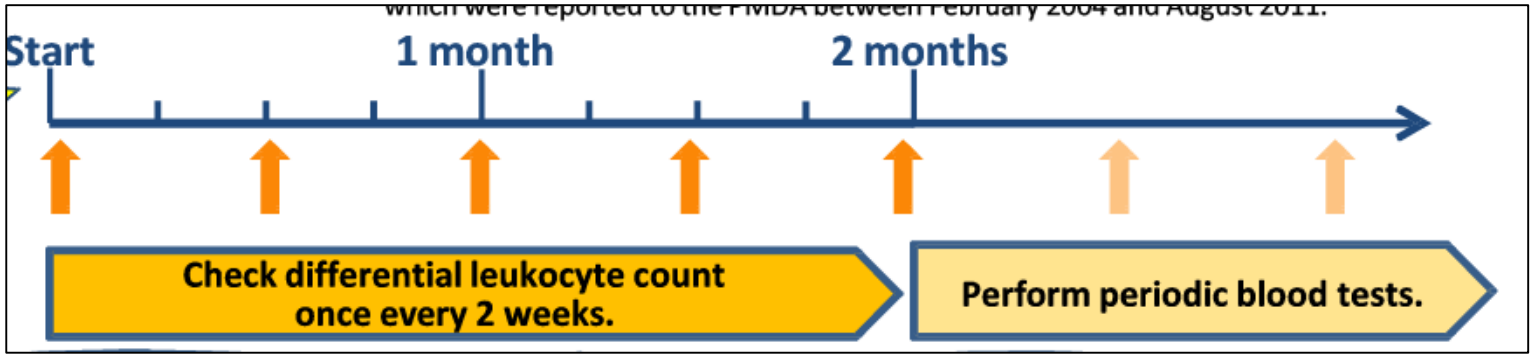
PMDA Alert for Proper Use of Drugs (2011)

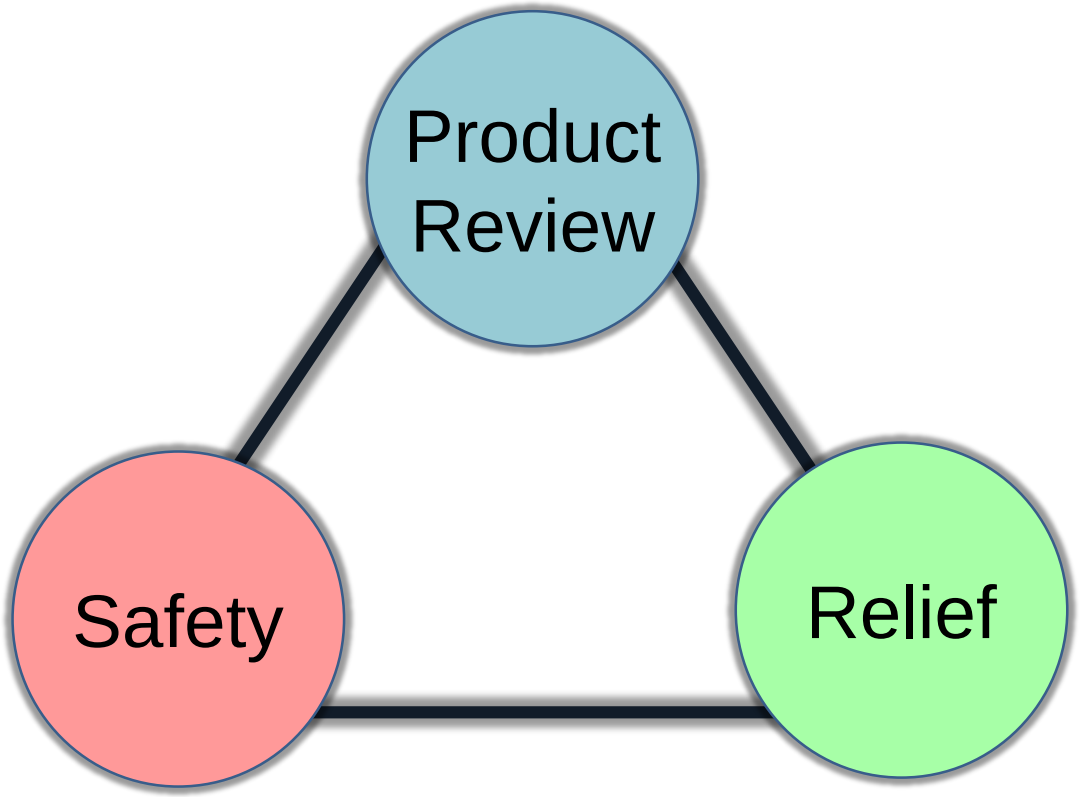
1. Strongly recommended
   - Periodic blood test (esp. once/2 weeks, first 2 months)
   - Symptoms including pharynx pain, etc.
2. Warned the doctors
   - Without blood tests, your patients are NOT eligible for Relief.

The Effect of PMDA Alert for Proper Use of Drugs (2011)



Recommended timing of leukocyte counts





PMDA's Safety Triangle

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