# Post-marketing Safety Measures of medical devices

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## Today’s agenda

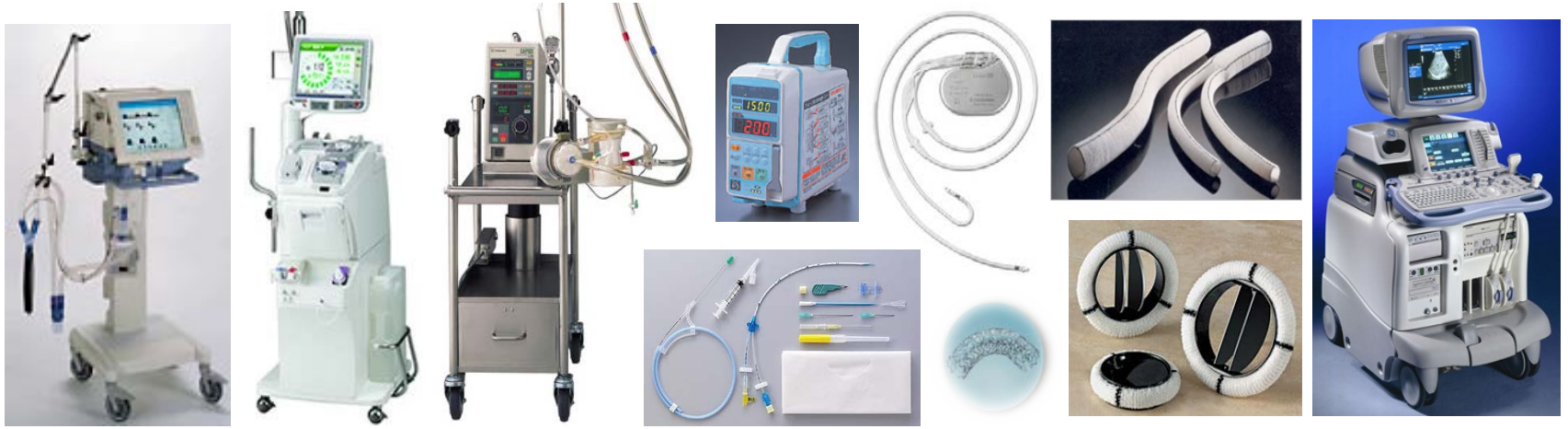
1. Risk management of medical devices
2. Safety vigilance of medical devices in Japan
3. Field safety corrective action of medical devices in Japan

# Risk management of medical devices

# Medical devices are…

The Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics (PMD Act)

Devices, etc. intended for use in the diagnosis, treatment or prevention of disease in humans or animals, or intended to affect the structure or functions of the body of humans or animals, and which are specified by the Cabinet Order (except for Regenerative and Cellular Therapy Products).



## The feature of medical devices are…( compared with pharmaceuticals )

- Variety of shape, structure and principle of operation
  ⇒**Various usage required for safety and efficacy**
  **Various malfunction mode**
- Variety of intended use/purpose and patient risk
  ⇒**Various health effect is assumed when a malfunction occurs**
- Repeated improvement/modification of the product or manufacturing process
  ⇒Difficult quality management (cf. number of recalls as referred later)
  ⇒Short life-cycle

Risk management based on these feature is desirable.

# Essential Principles of Safety and Performance of Medical Devices and IVD Medical Devices

- Initinally produced under the Global Harmonization Task Force (GHTF/SG1/N68:2012), and finally updated by International Medical Device Regulators Forum (IMDRF GRRP WG/N47:2018)

<introduction>
*The purpose of this IMDRF guidance is to provide harmonized Essential Principles that should be fulfilled in the design and manufacturing of medical devices and IVD medical devices to ensure that they are safe and perform as intended.*
*...*

- Contains harmonized Essential Principles applicable to all medical devices and IVD medical devices throughout the life-cycle
  - Mainly about designing and manufacturing process to ensure safety and efficacy of the product
  - Also includes the principles on **risk management process,** which successively required in post-marketing

PMD Act requires the compliance with Ministerial Notification “Essential Principles” (based on GHTF/IMDRF document)

# Risk management of medical devices

- “Essential Principles” - Article2 “Risk management”

*The solutions adopted by the manufacturer for the design and manufacture of the devices should conform to safety principles, taking account of the generally acknowledged state of the art.* ***When risk reduction is required, the manufacturer should control the risks so that the residual risk associated with each hazard is judged acceptable****. The manufacturer should apply the following principles in the priority order listed:*

- *identify known or foreseeable hazards and estimate the associated risks arising from the intended use and foreseeable misuse;*
- *eliminate risks as far as reasonable practicable through inherently safe design and manufacture;*
- *reduce as far as reasonably practicable the remaining risks by taking adequate protection measures, including alarms; and*
- *inform users of any residual risks.*

In pre-marketing review, the compliance with this article is to be explained with application of ISO 14971 by manufacturer

# Risk management of medical devices (ISO 14971)

- Risk analysis
- Risk evaluation
- Risk control
- Evaluation of overall residual risk
- Risk management review
- Production and **post-production activities**

**Information collection**
**Information review**
**Actions**

Propriety of these process is confirmed in the pre-marketing review

**Safety vigilance of post-marketing activities of manufacturer is required**

# Safety vigilance of medical devices in Japan

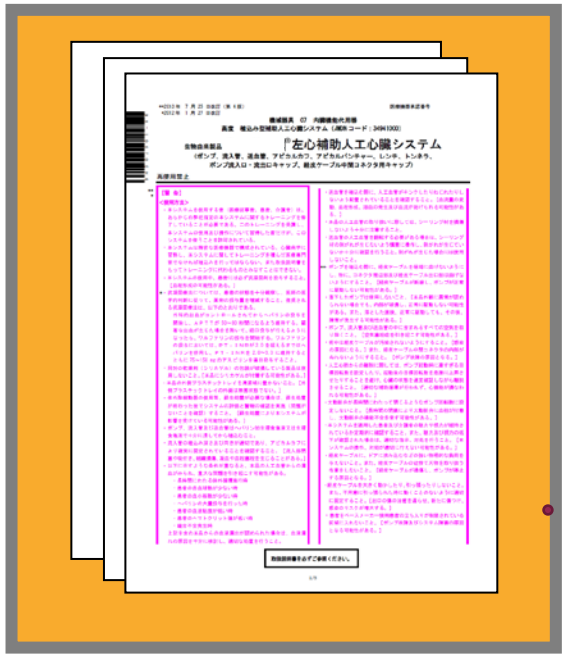
## Japanese system about safety vigilance of medical devices in Japan

- Online publication of accompanying document

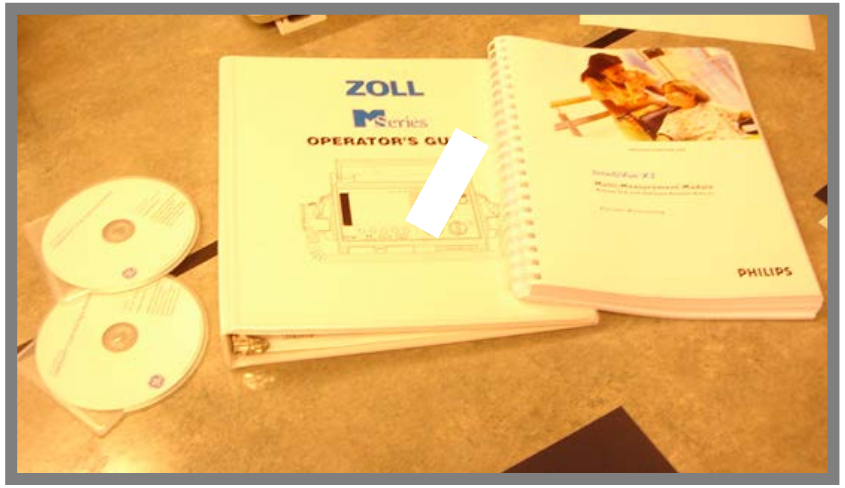
- Adverse Event Report System

# Accompanying documents of medical devices in Japan

Package insert
(“Tempu-Bunsho”)




Instructions for use


**Precautions for use**, etc.

From August 2021, digitizing and online publishing (via PMDA Website) of package insert is mendatory* by PMD. Act amendment

*all except some product categories are under obligation

# Devices Subjected to Submission

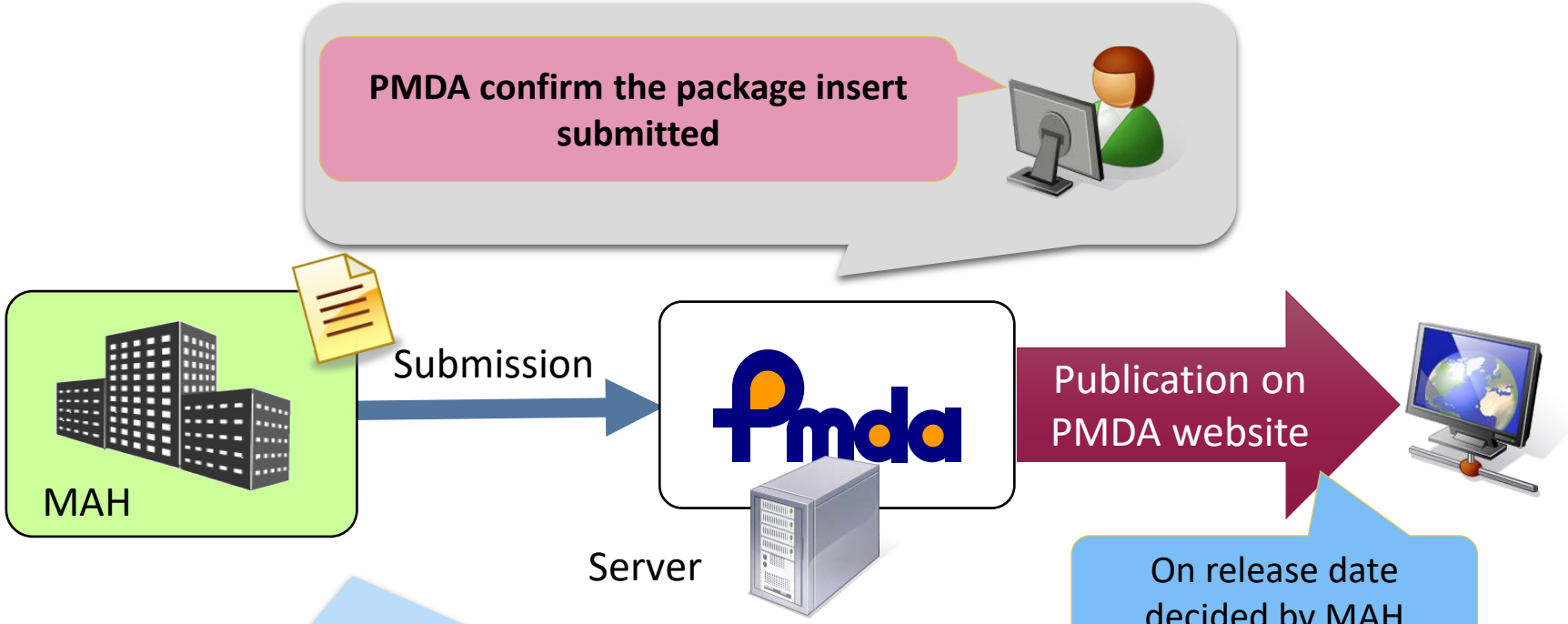
● Article 68-2-3, Paragraph 1 of PMD Act

Before marketing authorization holder (MAH) manufactures and sells medical devices which is specified by the Minister of Health, Labour and Welfare, the precautions information* which is specified by the Ordinance of MHLW must be submitted to PMDA. This is also applied when modifying existing package insert information.

*equivalent to "package insert information" before PMD. Act amendment

| | Submitted | Not Submitted (but published) |
|---|---|---|
| Devices | Class IV devices | Class I-III devices |
| Cellular and Tissue-based Products | All products | - |
| Drugs | Ethical drugs (except in vitro diagnostics, etc.) | OTC drugs, etc. |

# Preliminary consultation of the Package Insert



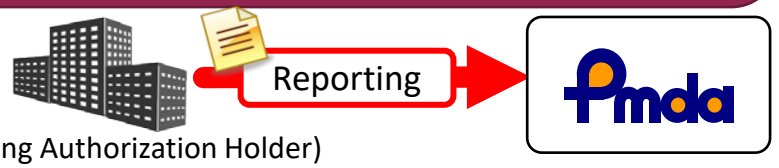

When the Package Insert is revised, MAH must consult PMDA before submission

Shorten the period from the submission to the publication

# Adverse Event Report System

- Article 68-10, Paragraph 1 of the PMD Act

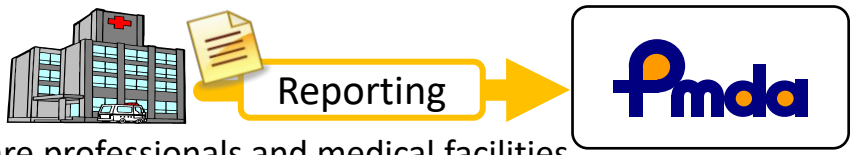
When a marketing authorization holder (MAH) learns of the occurrence of adverse events or similar that are suspected to be related to the efficacy and/or safety of medical devices, that MAH must report such information to PMDA within a certain period of time as stipulated in the relevant Ministerial Ordinance issued by the Ministry of Health, Labour and Welfare (MHLW).




MAH
(Marketing Authorization Holder)

- Article 68-10, Paragraph 2 of the PMD Act

When a healthcare professional learns of adverse events, etc. suspected to be related to medical devices and they confirm that it is necessary to take affirmative measures to prevent the onset or spread of risks to public health or safety, that healthcare professional must report such information to PMDA.




Healthcare professionals and medical facilities

# What's "adverse events"

- Notification about Ordinance for Enforcement Act 228-20

"Impact of malfunction"* is due to **a wide range of problems of the device** such as damage, failure, etc., and it **doesn't matter whether due to design, manufacturing and sales, distribution or use.**

*herein equivalent to "adverse events"

Any event which lessen the safety and efficacy of medical devices is called "adverse events".

- Examples

1. Breakage, failure, malfunction, etc. of the device
2. Problem with device specifications
3. Defective products
4. Health effect related to use of the device
5. Deficiency in information written in the package insert (IFU)

Regardless of occurrence of injury

If it might be the cause of use error

# When and What is Reported?

- Health impact
  - Serious adverse event
    1. Death
    2. Disability or permanent damage
    3. Life-threatening event
    4. Hospitalization (initial or prolonged)
    5. Congenital anomaly
    6. Other important medical events
  - Non-serious adverse event

Includes the cases that even if no serious adverse event actually doesn't occur, the event might lead to serious adverse event if the event recurs (could happen again).

- Description in the package insert
  - Listed ⇒ anticipated
  - Not listed ⇒ unanticipated

# Adverse Event Report (1)

- Malfunction, failure, breakage, leak, fault, etc. of a medical device

| Possibility of Health Damage | Description in the package insert/IFU | Report's due date |
|---|---|---|
| Serious | Unanticipated | 30 days |
| | Anticipated | 15 days (Uncomprehended elevation of the incidence rate of AE) |
| | | 30 days (Except reports shown above) |
| Non-Serious | Unanticipated | Annual reports |
| | Anticipated | — |

# Adverse Event Report (2)

- Health damage
  (in case relation with the medical device cannot be denied)

<table>
<tr><th colspan="2">Health Damage</th><th>Description in the package insert/IFU</th><th>Report’s due date</th></tr>
<tr><td rowspan="3">Serious</td><td>Death</td><td>Anticipated/<br>Unanticipated</td><td>15 days</td></tr>
<tr><td rowspan="2">Except death</td><td>Unanticipated</td><td>15 days</td></tr>
<tr><td rowspan="2">Anticipated</td><td>15 days<br>(Uncomprehended elevation of the incidence rate of AE)</td></tr>
<tr><td colspan="2">Non-Serious</td><td>Unanticipated</td><td>Annual report</td></tr>
<tr><td colspan="2"></td><td>30 days<br>(Except reports shown above)</td></tr>
<tr><td colspan="2"></td><td>Anticipated</td><td>—</td></tr>
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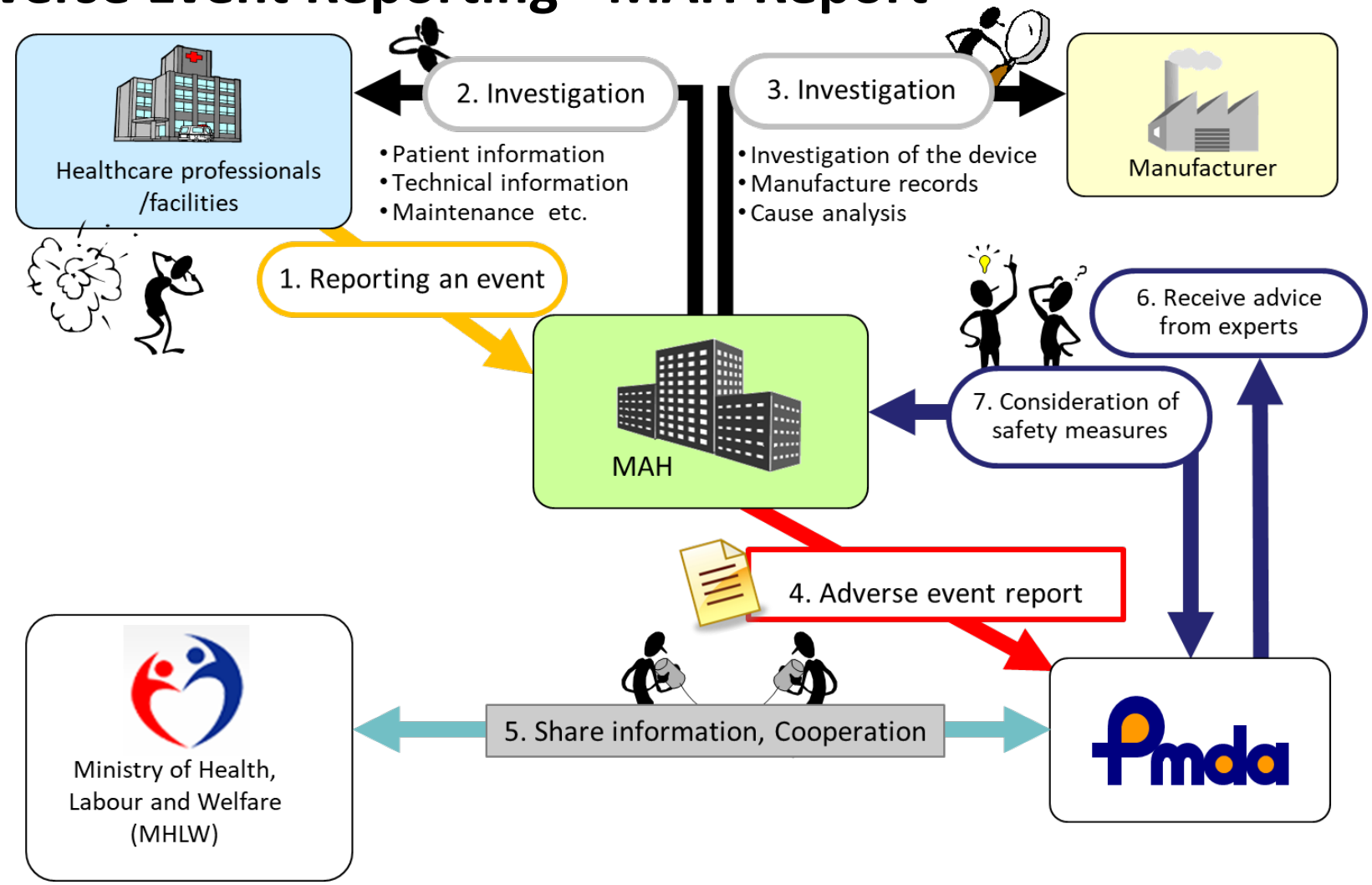
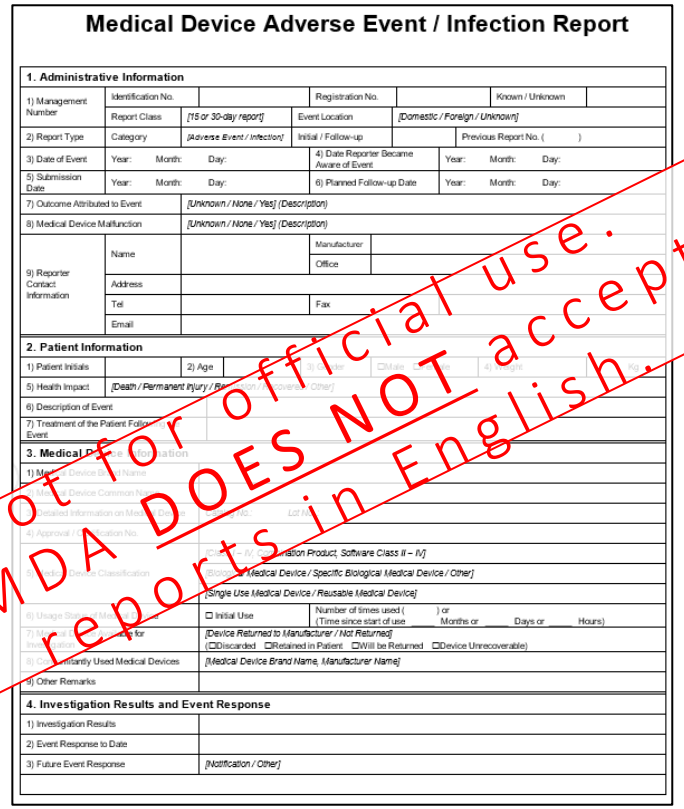
# Flow of Adverse Event Reporting - MAH Report



# Adverse Event Reporting Form （Japan）



**Medical Device Adverse Event / Infection Report**

| | | | | | |
|---|---|---|---|---|---|
| **1. Administrative Information** | | | | | |
| 1) Management Number | Identification No. | | Registration No. | | Known / Unknown |
| | Report Class | [15 or 30-day report] | Event Location | [Domestic / Foreign / Unknown] | |
| 2) Report Type | Category | [Adverse Event / Infection] | Initial / Follow-up | | Previous Report No. ( ) |
| 3) Date of Event | Year: Month: Day: | | 4) Date Reporter Became Aware of Event | Year: Month: Day: | |
| 5) Submission Date | Year: Month: Day: | | 6) Planned Follow-up Date | Year: Month: Day: | |
| 7) Outcome Attributed to Event | [Unknown / None / Yes] (Description) | | | | |
| 8) Medical Device Malfunction | [Unknown / None / Yes] (Description) | | | | |
| 9) Reporter Contact Information | Name | | Manufacturer | | |
| | | | Office | | |
| | Address | | | | |
| | Tel | | Fax | | |
| | Email | | | | |
| **2. Patient Information** | | | | | |
| 1) Patient Initials | | 2) Age | | | |
| 5) Health Impact | [Death / Permanent injury / Re | | | | |
| 6) Description of Event | | | | | |
| 7) Treatment of the Patient Follo Event | | | | | |
| **3. Medical P** | | | | | |
| 1) Me | | | | | |
| 2) Me | | | | | |
| Medical | | | | | |
| 4) Approval | | | | | |
| 5) Me Classification | [Class IV, Certification Product, Software Class II – IV] | | | | |
| | [Biological Medical Device / Specific Biological Medical Device / Other] | | | | |
| | [Single Use Medical Device / Reusable Medical Device] | | | | |
| 6) Usage Status of Medical | ☐ Initial Use | | Number of times used ( ) or (Time since start of use ____ Months or ____ Days or ____ Hours) | | |
| 7) Medical Device Returned for Malfunction Investigation | [Device Returned to Manufacturer / Not Returned] (☐Discarded ☐Retained in Patient ☐Will be Returned ☐Device Unrecoverable) | | | | |
| 8) Concomitantly Used Medical Devices | [Medical Device Brand Name, Manufacturer Name] | | | | |
| 9) Other Remarks | | | | | |
| **4. Investigation Results and Event Response** | | | | | |
| 1) Investigation Results | | | | | |
| 2) Event Response to Date | | | | | |
| 3) Future Event Response | [Notification / Other] | | | | |



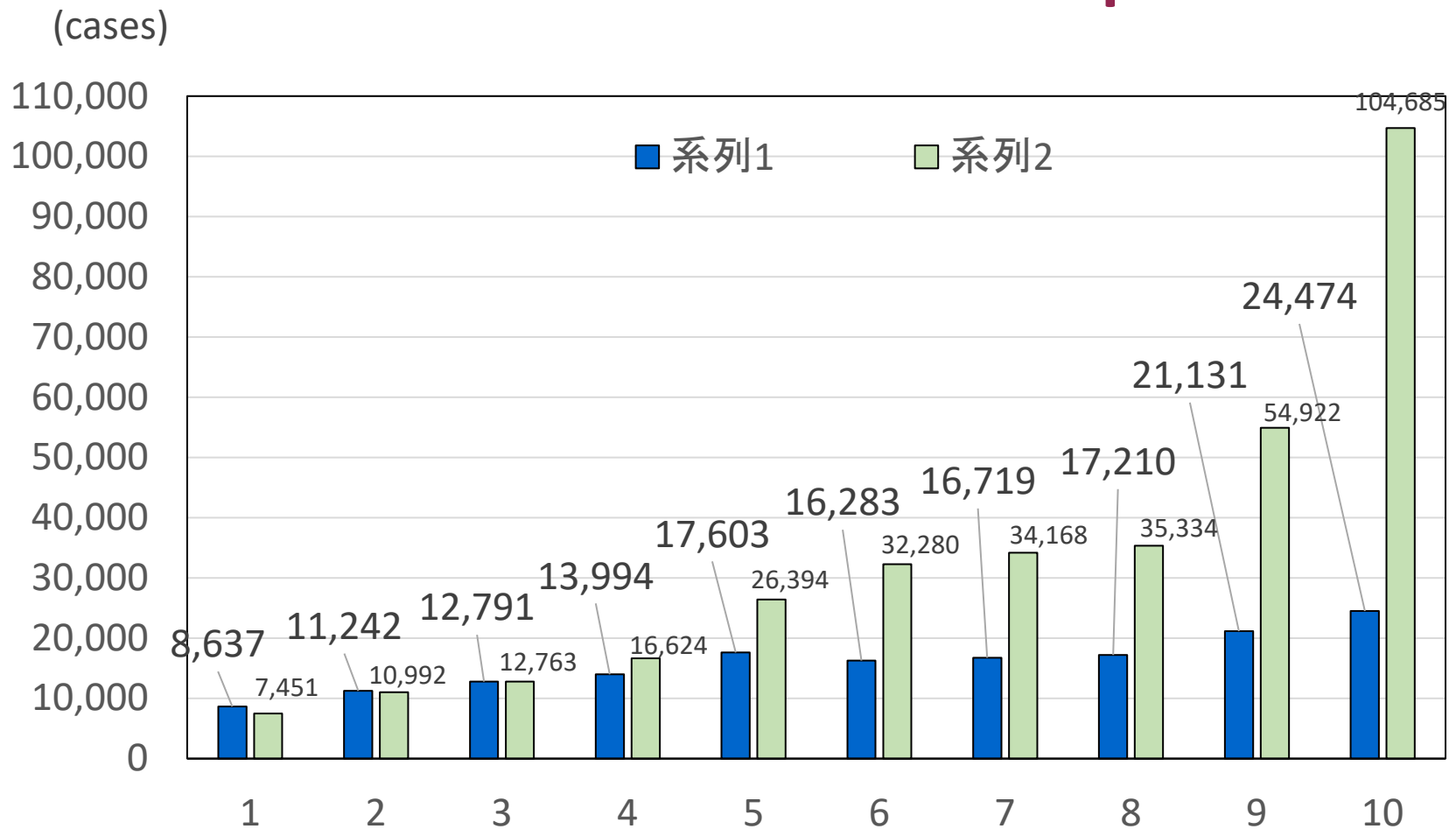
Ex.)

I. Administrative Information
II. Patient Information
III. Medical Device Information
IV. Investigation Results and Event Response
V. Comments

- **Terminology to use in the form is also under harmonization** in the IMDRF AE Terminology WG.

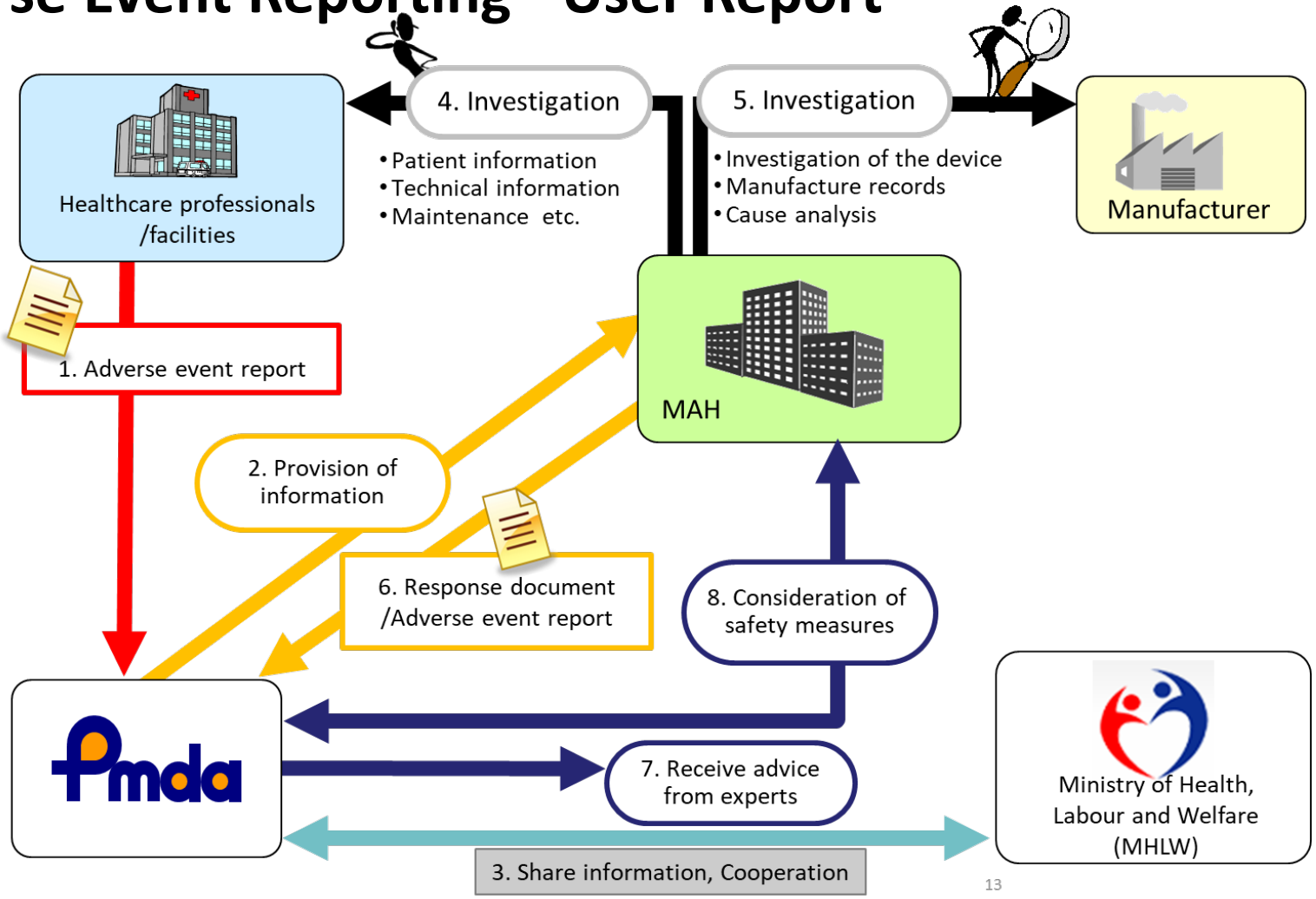
⇒**Efficiency in MAH's reporting and regulatory's reviewing potentially useful for analysis and signal detection**

# Number of Adverse Event Reports

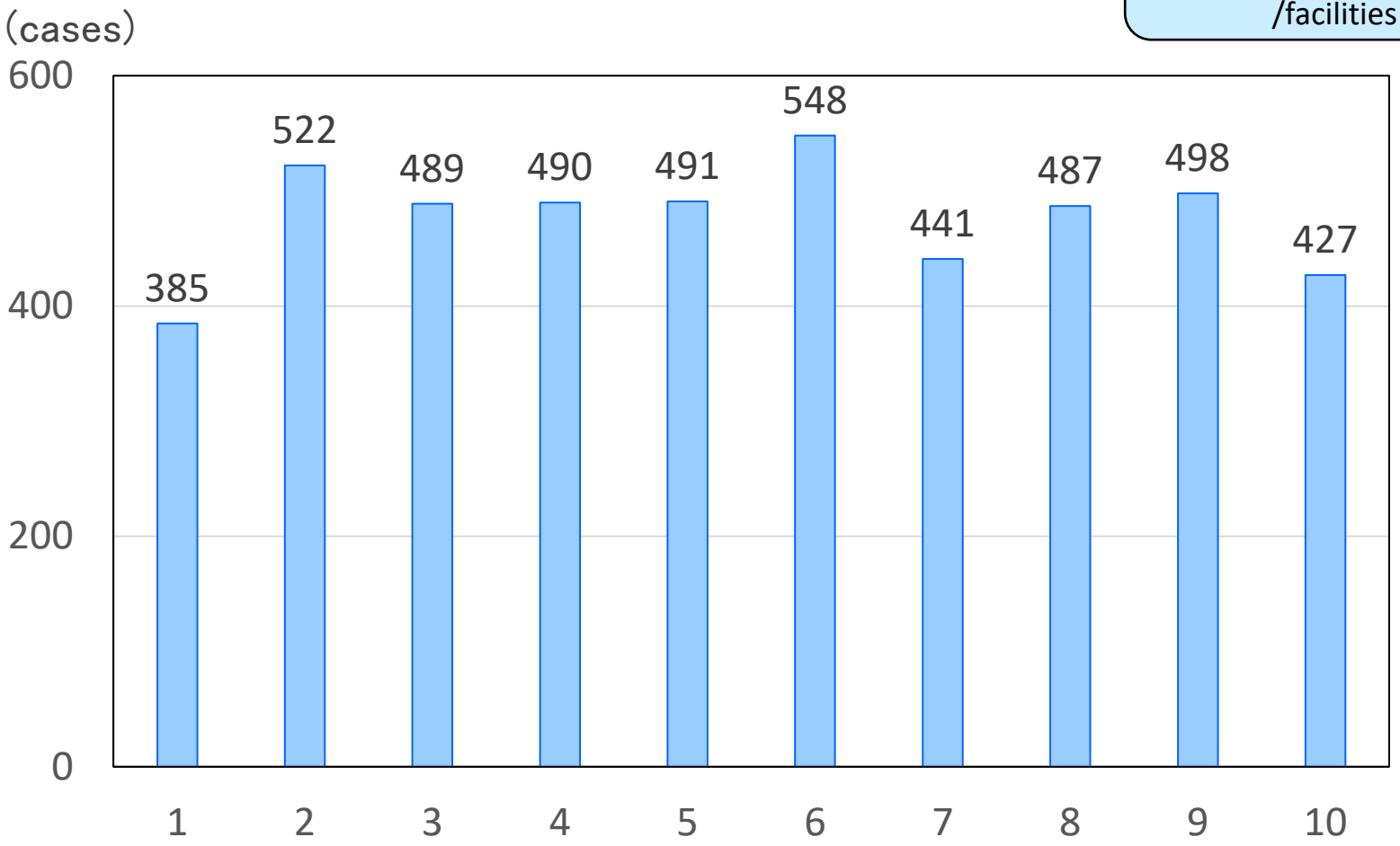



(PMDA Business Report, FY 2011 to FY 2020)

# Flow of Adverse Event Reporting - User Report

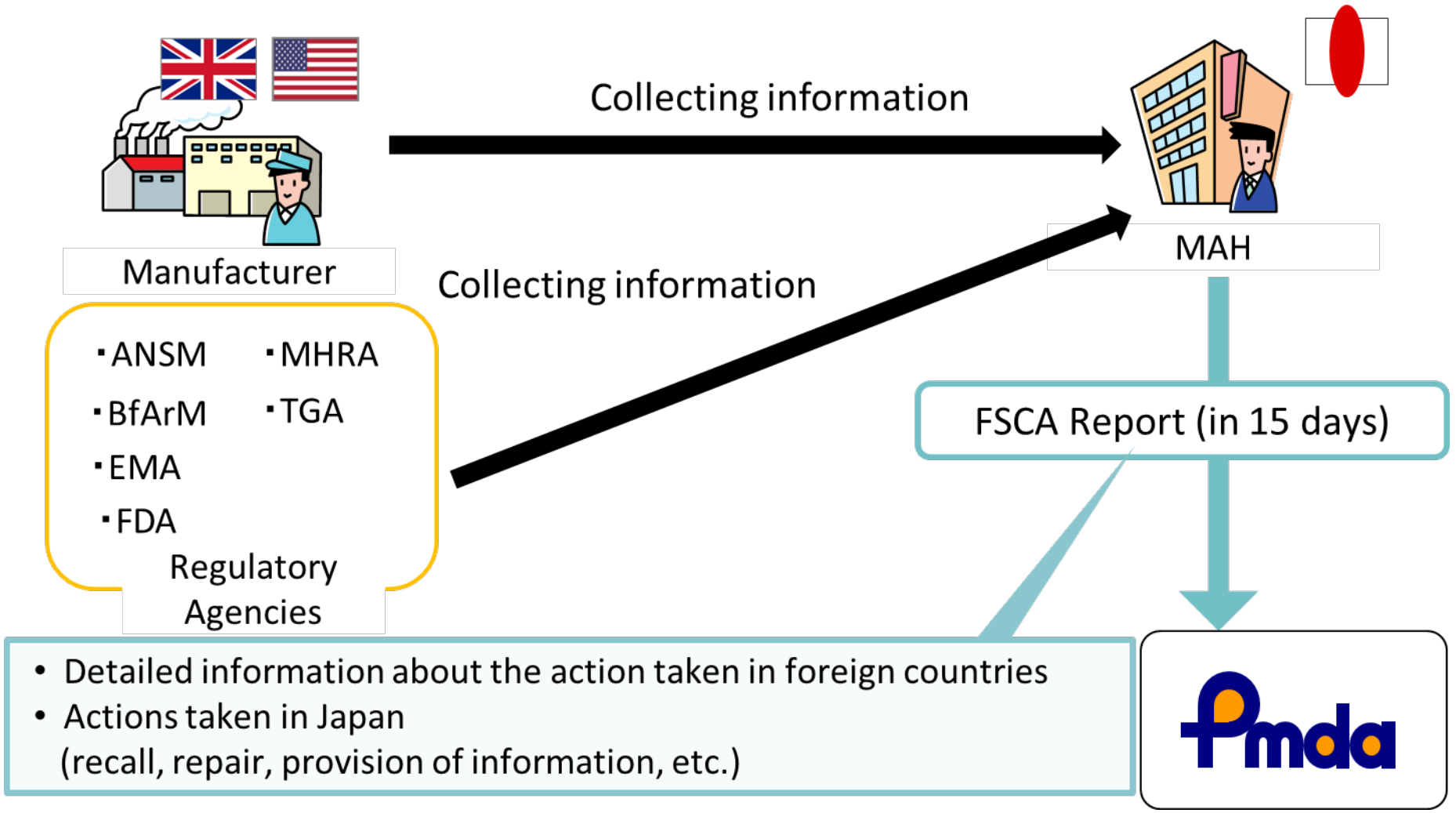


# Number of User Reports

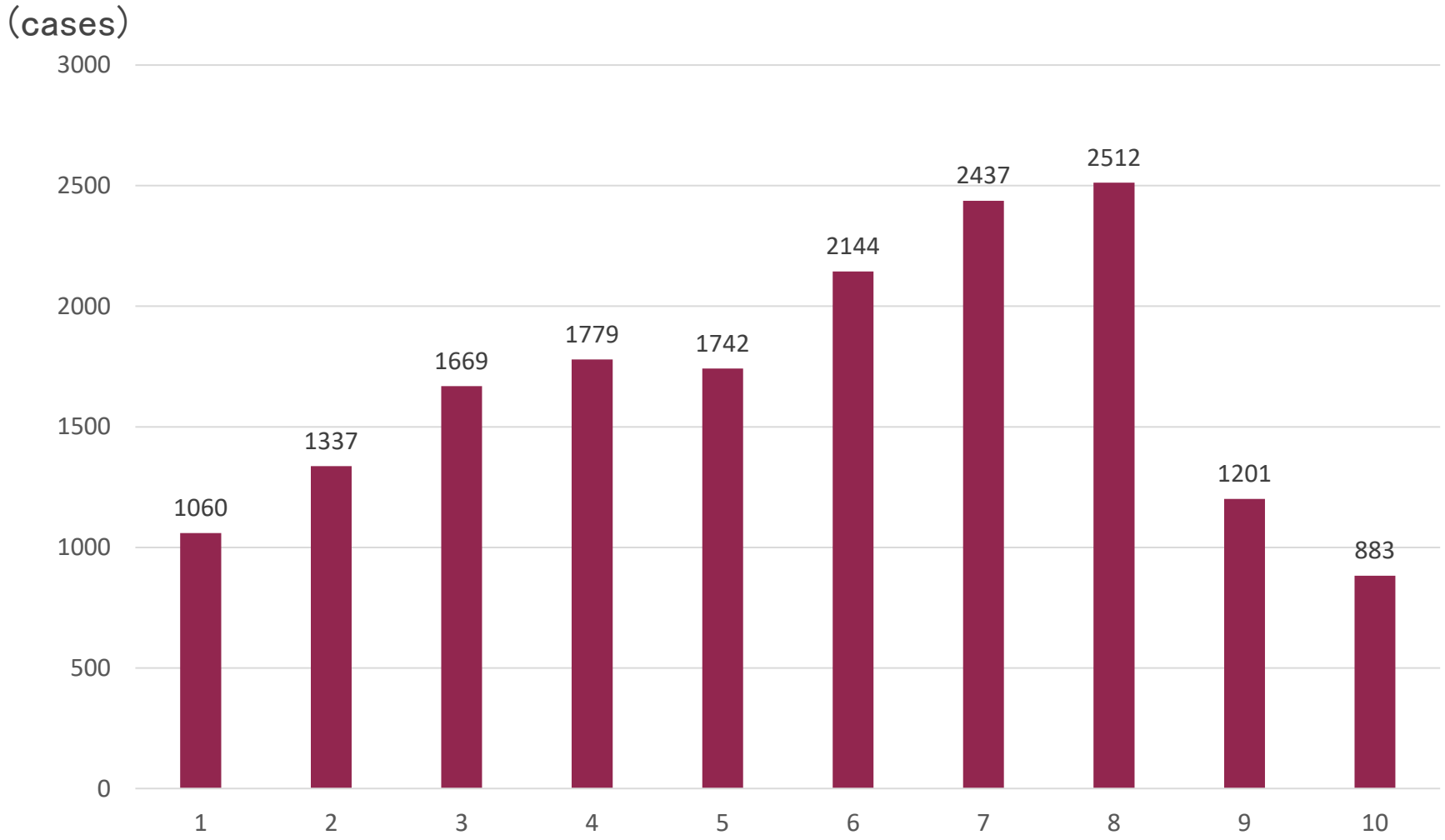




(PMDA Business Report, FY 2011 to FY 2020)

# Foreign Field Safety Corrective Action (FSCA) Report



# Number of Foreign Field Safety Corrective Action (FSCA) Report




(PMDA Business Report, FY 2011 to FY 2020)

# Causes of Adverse Events

## Problems of the device or MAH

1. Quality defect, problem with durability, strength
2. Sophistication / complication of the device
3. Lack of the information provided by the MAH

## Problems of use

4. Inexperienced or unskilled in using the device
5. Poor maintenance
6. Insufficient environmental management
7. Inappropriate use (off label use, contraindications)

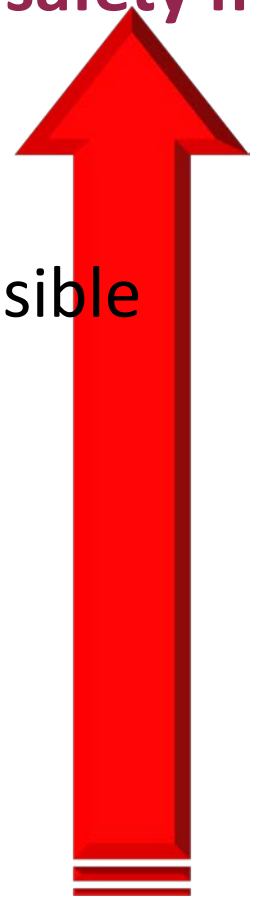
## Other

8. Patient condition (complication of diseases, allergy)

# Field safety corrective action of medical devices in Japan

## Post market safety measures of medical devices

Permanent
Costly
Not always feasible

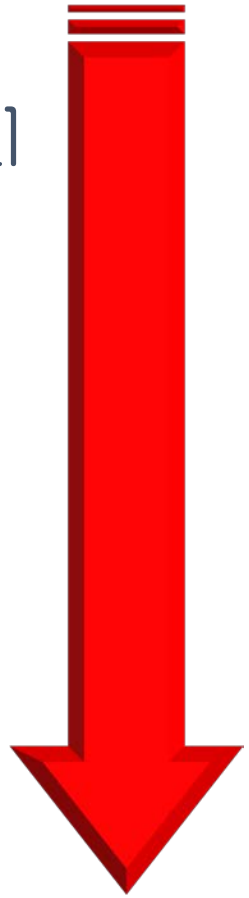


Recall
- physical removal
- modification

Labeling change

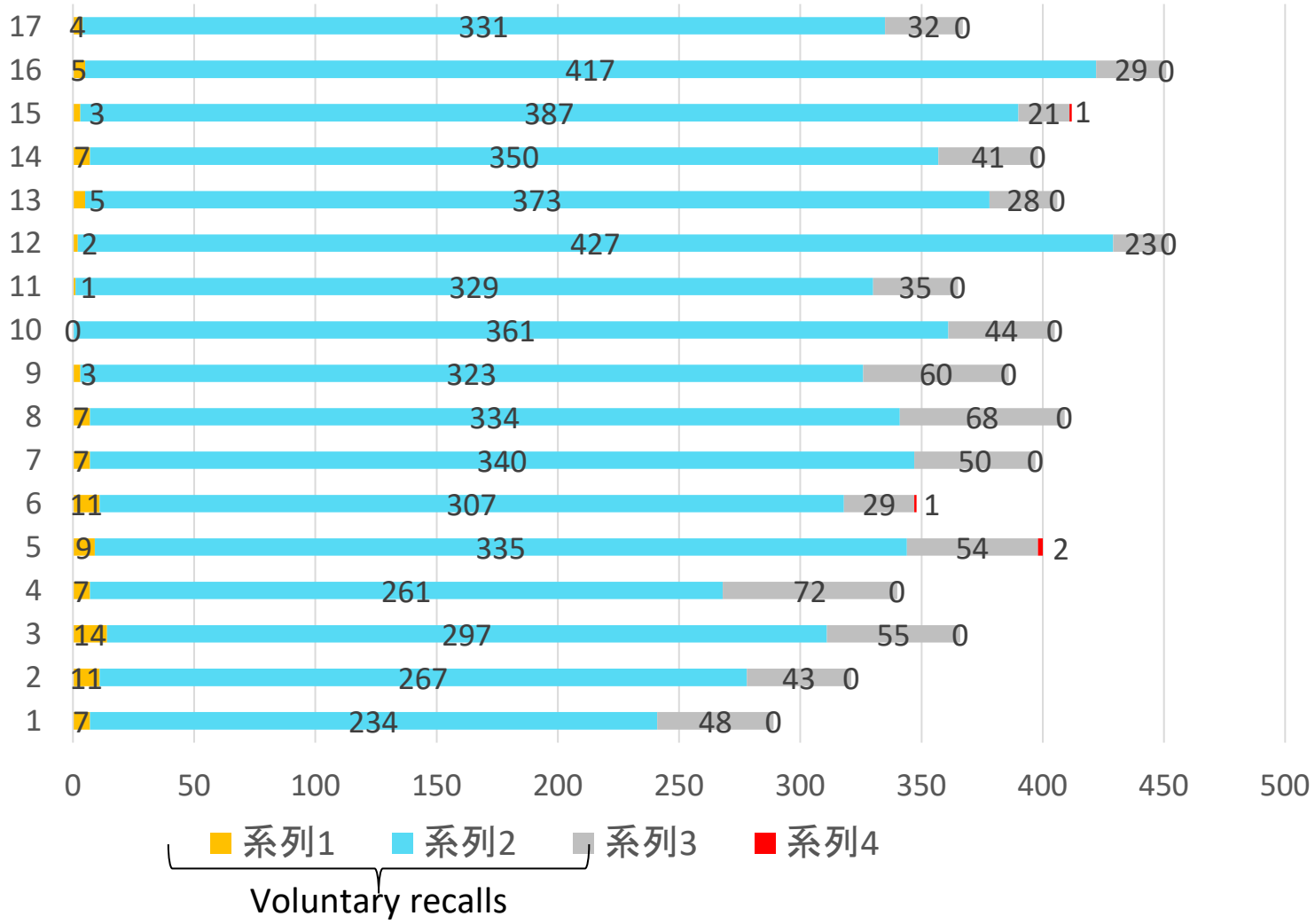
Field safety notices

Increased surveillance



In addition, condition of each jurisdiction is to be considerd.

# Number of Recalls/Repairs in Japan



# Ex. 1. Breast Implants and BIA-ALCL

# Introduction to Breast Implants

- Breast implants are medical devices used to increase breast size or rebuild breast tissue.
- The device consists of a silicone outer shell filled with saline or silicone gel.
- They vary in size, shape, shell thickness, and shell texture.

NATRELLE 410 Breast Implant (Allergan)

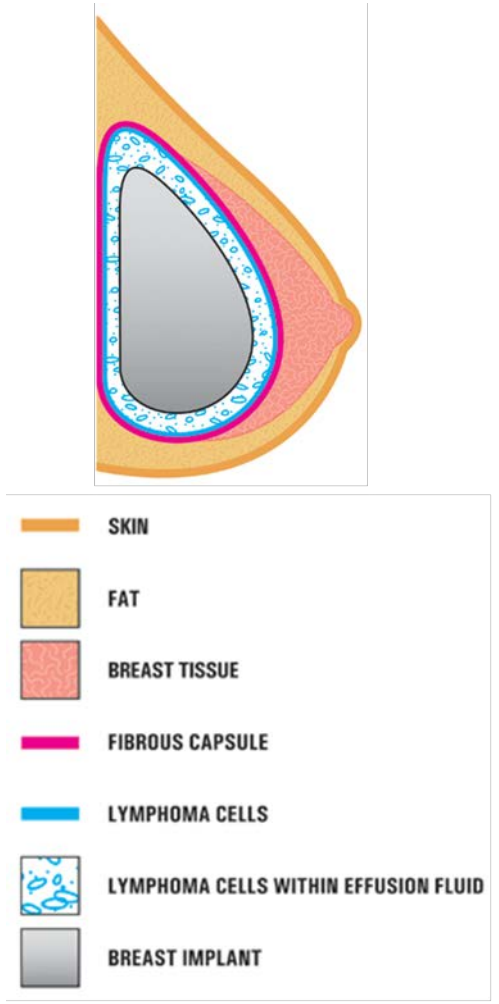
https://allergan-web-cdn-prod.azureedge.net/actavis/actavis/media/allergan-pdf-documents/labeling/natrelleus/410implants/natrelle-410-aug-patient-ldoc-03824rev05.pdf

# Risks of Breast Implant

- Additional surgeries, with or without removal of the device
- Capsular contracture, scar tissue that forms around the implant and squeezes the implant
- Breast pain
- Changes in nipple and breast sensation
- Rupture with deflation of saline-filled implants
- Rupture with or without symptoms (silent rupture) of silicone gel-filled implants
- “Breast Implant Illness” (e.g., memory loss, brain fog, fatigue, joint pain, rash)
- **Breast Implant Associated Anaplastic large cell lymphoma (BIA-ALCL), a type of non-Hodgkin's lymphoma (cancer of the immune system)**

# Breast Implant Associated Anaplastic Large Cell Lymphoma (BIA-ALCL)

- Lymphoma (cancer of immune system) usually found around the breast implant.
- Main symptoms are swelling or pain around the breast.
- Slow progression, but can lead to death if untreated.
- Most patients are cured by removal of the implant and surrounding scar tissue; some require additional treatment.
- The risk of BIA-ALCL is thought to be higher in textured breast implants.




(Figure arranged from FDA)

# Examples of Regulatory Actions regarding BIA-ALCL

| Date | Region | Action |
|---|---|---|
| 2011 Jan. | USA | Safety Communication: Preliminary warning on risk of BIA-ALCL |
| 2016 Sep. | Australia | Safety Communication: Warning on risk of BIA-ALCL |
| 2017 Oct. | EU | Advisory Committee (SCHEER): Recommended additional evaluation on risk of BIA-ALCL |
| 2017 Nov. | Canada | Safety Review: Continue monitoring for BIA-ALCL |
| 2018 Dec. | **EU** | **Recall: Allergan Textured Breast Implants (license not renewed).** |
| 2019 Feb. | Singapore | Expert Panel: Discuss risks and measures for BIA-ALCL |
| 2019 Mar. | USA | Advisory Committee: Discuss risks and measures for BIA-ALCL |
| 2019 Apr. | **France** | **Recall: Banned all textured implants as a precautionary measure** |
| 2019 Apr. | **Singapore** | **Recall: Banned Allergan textured breast implant as a precautionary measure** |
| 2019 May | **Canada** | **Recall: Banned Allergan textured breast implant as a precautionary measure** |
| 2019 May | USA | Statement: FDA does not feel that there is adequate evidence to ban textured breast implants |

# Breast Implant-related actions / events in Japan

| Date | Region | Action |
|---|---|---|
| 2011 Jan. | USA | Safety Communication: Preliminary warning on risk of BIA-ALCL |
| 2012 | Japan | Allergan Natrelle breast implant approved |
| 2013 | Japan | Allergan Natrelle 410 breast implant approved |
| 2013 | Japan | Establishment of patient registry for BIA-ALCL by relevant academic societies (Japan Oncoplastic Brest Surgery Society, etc.) |
| 2016 Sep. | Australia | Safety Communication: Warning on risk of BIA-ALCL |
| 2017 June | Japan | Warning of BIA-ALCL from relevant academic societies |
| 2017 Oct. | EU | Advisory Committee (SCHEER): Recommended additional evaluation on risk of BIA-ALCL |
| 2017 Nov. | Canada | Safety Review: Continue monitoring for BIA-ALCL |
| 2018 | Japan | Allergan Natrelle breast implant discontinued due to lack of demand |
| 2018 Dec. | **EU** | **Recall: Allergan Textured Breast Implants (license not renewed).** |
| 2019 Feb. | Singapore | Expert Panel: Discuss risks and measures for BIA-ALCL |
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| 2019 May | USA | Statement: FDA does not feel that there is adequate evidence to ban textured breast implants |
| **2019 May** | **Japan** | **Report of the first diagnosis of BIA-ALCL in Japan** |

# The situation in Japan as of June 1, 2019

Available Products:

- Natrelle 410 Breast Implant – (*Textured breast implant banned in some jurisdictions*)
- Natrelle 133 Tissue Expander

Estimated Number of Patients:

- Total number of patients who received breast implants: approx. 29,000
- Total number of patients who implanted a tissue expander: approx. 31,000
- Approx. 6,000 patients undergo breast implant surgery per year.

# Issue a Notification

Confirmed Cases of BIA-ALCL:

- **In May 2019, the Japan Oncoplastic Breast Surgery Society reported a case of BIA-ALCL diagnosed for the first time in Japan in a patient who had received a gel-filled breast implant that is not approved in Japan. This is the first case of BIA-ALCL in Japan.**

- In response to the case of BIA-ALCL diagnosed in Japan, **MHLW/PMDA requested that Allergan revise its package insert** to warn more strongly about BIA-ALCL in June 2019.

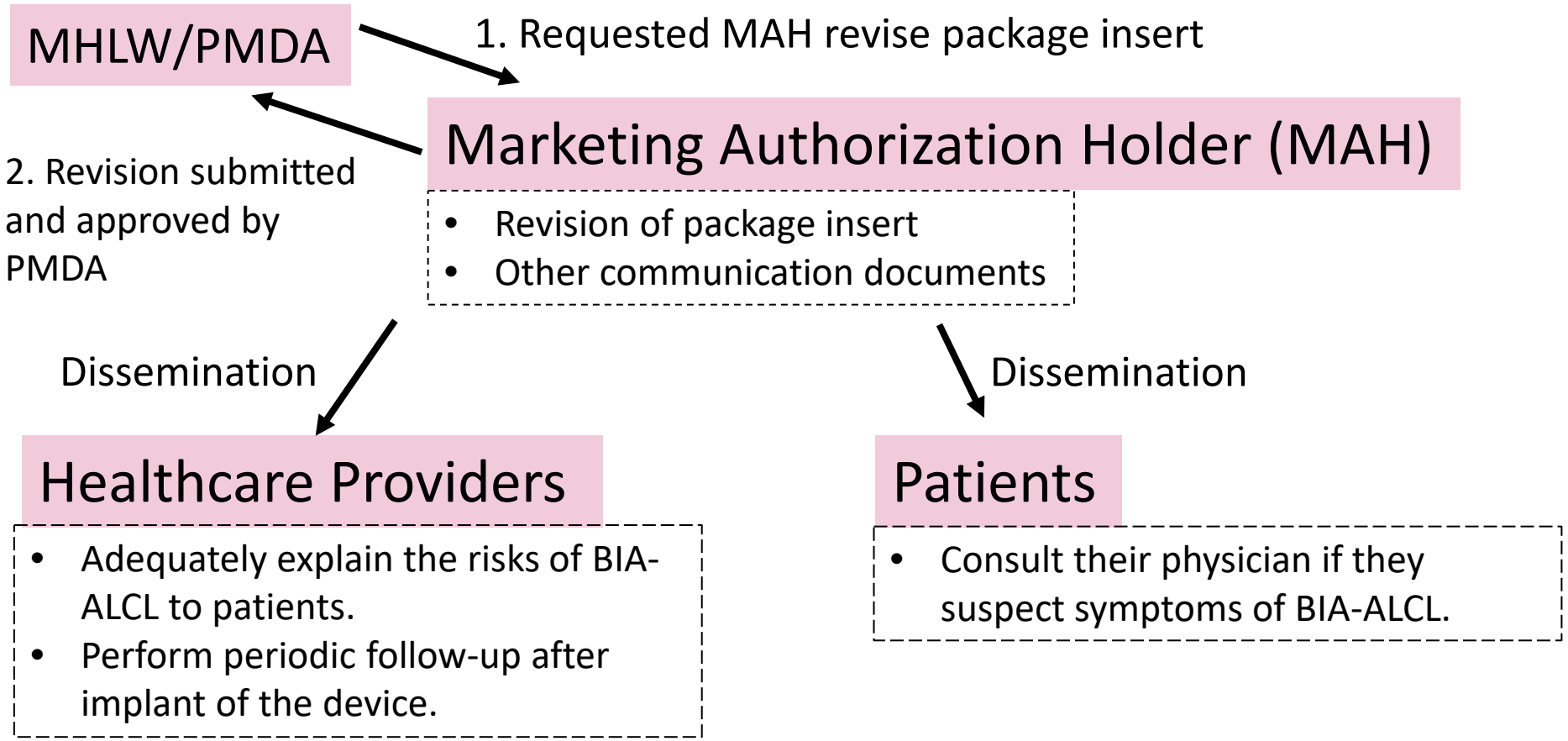
# Why a notification to revise the package insert?

- There was only 1 case of BIA-ALCL, and this 1 case was from a device that was implanted before approval in Japan. There are were no cases of BIA-ALCL from approved devices.

- As stated in the conditions for approval, breast implant surgery can only be performed in medical facilities that meet the criteria established by relevant academic societies, so good patient follow-up was thought to be possible. Furthermore, conditions for approval required that diagnoses of BIA-ALCL must be reported immediately, ensuring that if necessary, safety measures could be implemented.

- We prioritized providing accurate information to healthcare providers and patients to ensure informed consent and routine follow-up following surgery. Routine, long-term follow up is important for early detection of BIA-ALCL.

# System and Impact of Package Insert Revision




➢ **Ensure rapid dissemination of accurate information to protect patient safety**

## US FDA (Safety Communication, July 2019)

- **The FDA requested that Allergan recall all BIOCELL textured breast implants**; Allergan agreed on a global recall.
- **Of the 573 cases of BIA-ALCL, 481 are reported to have Allergan breast implants** at the time of diagnosis.
- **12 of 13 deaths** occurring in patients with BIA-ALCL where the manufacturer was known **occurred in patients implanted with an Allergan breast implant** at the time of their BIA-ALCL diagnosis (33 deaths total).
- The **risk of BIA-ALCL with Allergan BIOCELL textured implants is approximately 6 times** the risk of BIA-ALCL with textured implants from other manufacturers marketing in the U.S.

## Recall of Allergan Textured Breast Implants in Japan

- In response to the FDA Safety Communication in July 2019, **Allergan decided on a global recall of its textured implants**. This recall was carried out in Japan as well.
- Natrelle 410 breast implants were recalled, leaving Japanese patients with only Natrelle breast implants. But Natrelle breast implant manufacture had stopped over a year ago. Thus, **ensuring patient access to breast implants became extremely difficult.**

## Impact of the Recall

- Only one product was readily available at the time of recall, and this product was recalled, temporarily reducing the availability of breast implants.
- The treatment of approximately 3,500 patients implanted with tissue expanders and scheduled to use breast implants was interrupted.
- If patients wanted to undergo breast reconstruction surgery, healthcare providers and patients were forced to turn to alternative measures such as fat transfer surgery or waiting for an alternative breast implant to be approved.

## Response to the Recall (1)

- On August 28th, 24 patient groups submitted a document, “Requests Regarding Implants and Tissue Expanders for Breast Reconstruction” to the MHLW.
- Academic societies asked for rapid approval of an alternative implant and tissue expander.

- In response to these requests, MHLW/PMDA approved a smooth-type breast implant and expander on October 8th. A typical review takes 4 months, but these products were approved in 1 month.

## Response to the Recall (2)

- In addition, on October 1st, relevant academic societies issued additional information for patients including safety recommendations and alternatives to breast implants.
- The MHLW also informed local prefectural governments about this information to aid in widespread dissemination.

*In this way, an alternative product was rapidly approved, while also ensuring that appropriate safety information was readily available to patients.*

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| 2017 Nov. | Canada | Safety Review: Continue monitoring for BIA-ALCL |
| 2018 | Japan | Allergan Natrelle breast implant discontinued due to lack of demand |
| 2018 Dec. | **EU** | **Recall: Allergan Textured Breast Implants (license not renewed).** |
| 2019 Feb. | Singapore | Expert Panel: Discuss risks and measures for BIA-ALCL |
| 2019 Mar. | USA | Advisory Committee: Discuss risks and measures for BIA-ALCL |
| 2019 Apr. | **France** | **Recall: Banned all textured implants as a precautionary measure** |
| 2019 Apr. | **Singapore** | **Recall: Banned Allergan textured breast implant as a precautionary measure** |
| 2019 May | **Canada** | **Recall: Banned Allergan textured breast implant as a precautionary measure** |
| 2019 May | USA | Statement: FDA does not feel that there is adequate evidence to ban textured breast implants |
| **2019 May** | **Japan** | **Report of the first diagnosis of BIA-ALCL in Japan** |

# Breast Implant-related actions / events in Japan

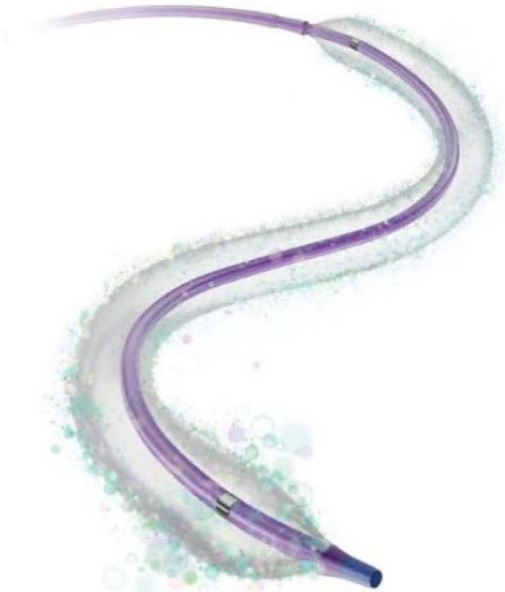
| Date | Region | Action |
|---|---|---|
| 2019 May | Japan | Report of the first diagnosis of BIA-ALCL in Japan |
| 2019 June | Japan | Notification issued instructing Allergan to revise their package insert |
| 2019 July | **USA/Global** | **Recall: FDA requests Allergan recall their textured breast implants; Allergan agrees with a global recall, including Japan.** |
| 2019 Aug. | Japan | Joint request from 24 patient groups submitted to MHLW: "Requests Regarding Implants and Tissue Expanders for Breast Reconstruction" |
| 2019 Oct. | Japan | **Alternative breast implants approved** / Additional safety recommendations provided to patients from relevant academic societies. |
| 2019 Oct. | USA | FDA issued a draft guidance "Breast Implants – Certain Labeling Recommendations to Improve Patient Communication" |

*Breast implants continue to be a closely monitored medical device, both by regulators and the public. There are still unresolved questions for BIA-ALCL, as well as additional issues such as widespread reports of Breast Implant Illness.*

# Ex. 2. Mortality risk of paclitaxel-coated devices

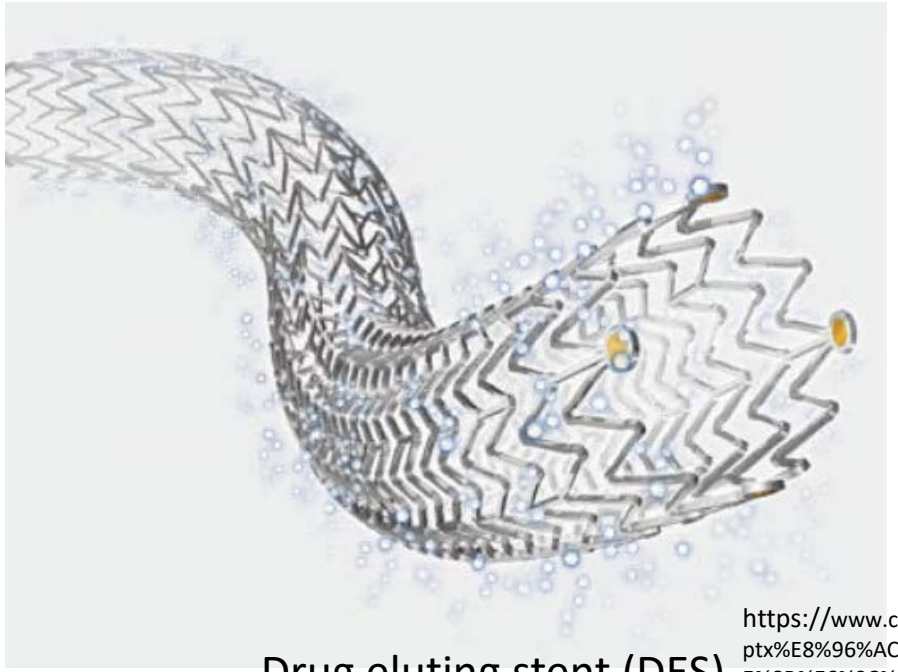
# About the paclitaxel-coated devices

- Balloons or stents for percutaneous transluminal angioplasty(PTA)
- Coated with the paclitaxel to reduce the rate of restenosis



Drug coated balloon (DCB)

https://europe.medtronic.com/xd-en/healthcare-professionals/products/cardiovascular/drug-coated-balloons/inpact-drug-coated-balloon.html

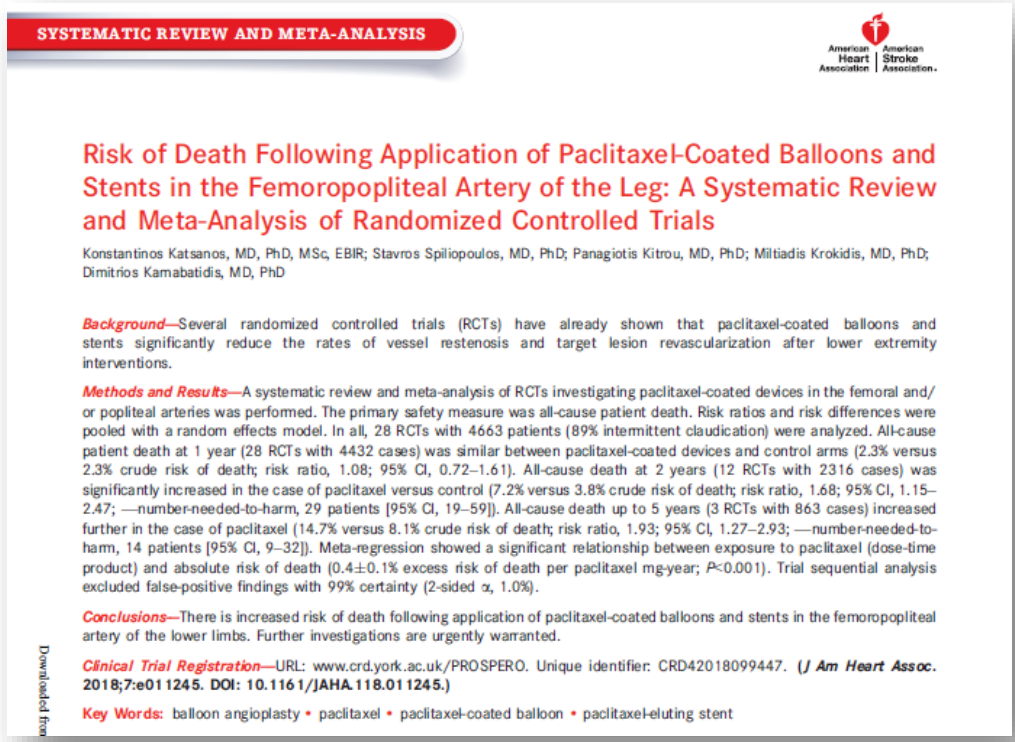


Drug eluting stent (DES)

https://www.cookmedical.co.jp/products/zilver-ptx%E8%96%AC%E5%89%A4%E6%BA%B6%E5%87%BA%E5%9E%8B%E6%9C%AB%E6%A2%A2%E8%A1%80%E7%AE%A1%E7%94%A8%E3%82%B9%E3%83%86%E3%83%B3%E3%83%88/

# Does paclitaxel increase long-term mortality?

- In December 2018, a systematic review and meta-analysis was published on paclitaxel-coated balloons and stents in the femoropopliteal artery
- All-cause mortality in paclitaxel-coated device group  was significantly increased at 2 years and 5 years , which suggests increased risk of death following application of paclitaxel-coated devices.



SYSTEMATIC REVIEW AND META-ANALYSIS

American Heart Association | American Stroke Association.

## Risk of Death Following Application of Paclitaxel-Coated Balloons and Stents in the Femoropopliteal Artery of the Leg: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Konstantinos Katsanos, MD, PhD, MSc, EBIR; Stavros Spiliopoulos, MD, PhD; Panagiotis Kitrou, MD, PhD; Miltiadis Krokidis, MD, PhD; Dimitrios Karnabatidis, MD, PhD

***Background***—Several randomized controlled trials (RCTs) have already shown that paclitaxel-coated balloons and stents significantly reduce the rates of vessel restenosis and target lesion revascularization after lower extremity interventions.

***Methods and Results***—A systematic review and meta-analysis of RCTs investigating paclitaxel-coated devices in the femoral and/or popliteal arteries was performed. The primary safety measure was all-cause patient death. Risk ratios and risk differences were pooled with a random effects model. In all, 28 RCTs with 4663 patients (89% intermittent claudication) were analyzed. All-cause patient death at 1 year (28 RCTs with 4432 cases) was similar between paclitaxel-coated devices and control arms (2.3% versus 2.3% crude risk of death; risk ratio, 1.08; 95% CI, 0.72–1.61). All-cause death at 2 years (12 RCTs with 2316 cases) was significantly increased in the case of paclitaxel versus control (7.2% versus 3.8% crude risk of death; risk ratio, 1.68; 95% CI, 1.15–2.47; —number-needed-to-harm, 29 patients [95% CI, 19–59]). All-cause death up to 5 years (3 RCTs with 863 cases) increased further in the case of paclitaxel (14.7% versus 8.1% crude risk of death; risk ratio, 1.93; 95% CI, 1.27–2.93; —number-needed-to-harm, 14 patients [95% CI, 9–32]). Meta-regression showed a significant relationship between exposure to paclitaxel (dose-time product) and absolute risk of death (0.4±0.1% excess risk of death per paclitaxel mg-year; $P<0.001$). Trial sequential analysis excluded false-positive findings with 99% certainty (2-sided $\alpha$, 1.0%).

***Conclusions***—There is increased risk of death following application of paclitaxel-coated balloons and stents in the femoropopliteal artery of the lower limbs. Further investigations are urgently warranted.

***Clinical Trial Registration***—URL: www.crd.york.ac.uk/PROSPERO. Unique identifier: CRD42018099447. (***J Am Heart Assoc.* 2018;7:e011245. DOI: 10.1161/JAHA.118.011245.)**

**Key Words:** balloon angioplasty • paclitaxel • paclitaxel-coated balloon • paclitaxel-eluting stent



J Am Heart Assoc. 2018 ; 7 : e011245

# Examples of Regulatory Actions regarding PTX

| Date | Region | Action |
|---|---|---|
| 2019 Jan. | USA | Letters to Health Care Providers: Treatment of Peripheral Arterial Disease with Paclitaxel-Coated Balloons and Paclitaxel-Eluting Stents Potentially Associated with Increased Mortality |
| 2019 Feb.~ Mar. | EU | First notice on this issue |
| 2019 May | France | Recommendations for healthcare professionals.<br>• **Preferably use alternative treatment options to paclitaxel-coated balloons and paclitaxel-eluting stents.** |
| 2019 Jun. | UK | Recommendations from the independent Expert Advisory Group<br>• The EAG recommended that **these devices are not used to treat patients with intermittent claudication (a pain in the leg caused by the lack of blood flow).** |
| 2019 Aug. | USA | (Update based on 2019 June panel meeting of the Advisory Committee) Letters to Health Care Providers<br>Recommendation for health care providers<br>• Diligent patient monitoring<br>• Discussion about the risk and benefits of all options with patient (***"For many patients, alternative treatment options to paclitaxel-coated balloons and paclitaxel-eluting stents provide a more favorable benefit-risk profile"***)<br>• Report any adverse events or suspected adverse events |
| 2020 Jun. | EU | Field Safety Notice from relevant manufacturers about the **revision of IFU**<br>• Warning: Discuss the results of the Katsanos meta-analysis and the benefits and risk of available treatment options with patient.<br>• Summary of the meta-analysis: Katsanos meta-nalysis, FDA Data Analysis, and information regarding clinical data for the specific product. |

# Initial information from PMDA On April 2019

2019 年 4 月 19 日
独立行政法人医薬品医療機器総合機構（PMDA）
医療機器品質管理・安全対策部
医療機器安全課

大腿膝窩動脈におけるパクリタキセルコーティングバルーン及びステントについて

2018 年 12 月、Katsanos らは、大腿膝窩動脈におけるパクリタキセルコーティングバルーン及びステント（以下「当該機器」という。）に関するメタアナリシスの結果を公表しました（J Am Heart Assoc. 2018；7：e011245）。当該論文では、非コーティング機器を用いた対照群と比較して、当該機器を用いて治療を受けた患者群の全死亡率は、1 年次は差を認めないものの、2 年次及び 5 年次では高く、死亡のリスクの増加の可能性が示唆されるとされております。なお、解析結果の詳細については、原著論文を確認ください。

当該論文の公表以降、アメリカ食品医薬品局（FDA）[1),2)]、イギリス医薬品・医療製品規制庁（MHRA）[3)]、及びフランス医薬品・保健製品安全庁（ANSM）[4)]では、当該機器を使用する医療従事者に対して、当該論文内容、及び各国にてリスク評価を実施中である旨を情報提供しております。また、FDA は、市販前の臨床試験に関するフォローアップ成績を解析した結果を踏まえて、リスク評価が完了するまでは当該機器以外の治療選択肢を推奨する旨の 2 回目の情報提供を、2019 年 3 月 15 日に実施しております。

April 19, 2019
Division for Safety of Medical Devices
Office of Manufacturing Quality and Vigilance for Medical Devices
Pharmaceuticals and Medical Devices Agency (PMDA)

Paclitaxel-coated Balloons and Stents in the Femoropopliteal Artery

In December 2018, Katsanos et al. published the results of a meta-analysis for paclitaxel-coated balloons and stents in the femoropopliteal artery (hereinafter referred to as "paclitaxel-coated devices") (J Am Heart Assoc. 2018 ; 7 : e011245). According to this article, although all-cause mortality in patients treated with paclitaxel-coated devices did not differ from the control arms using uncoated devices at 1 year, it was higher at 2 years and 5 years, suggesting a possible increased mortality rate associated with paclitaxel-coated devices. Please confirm the details of analysis results in the original article.

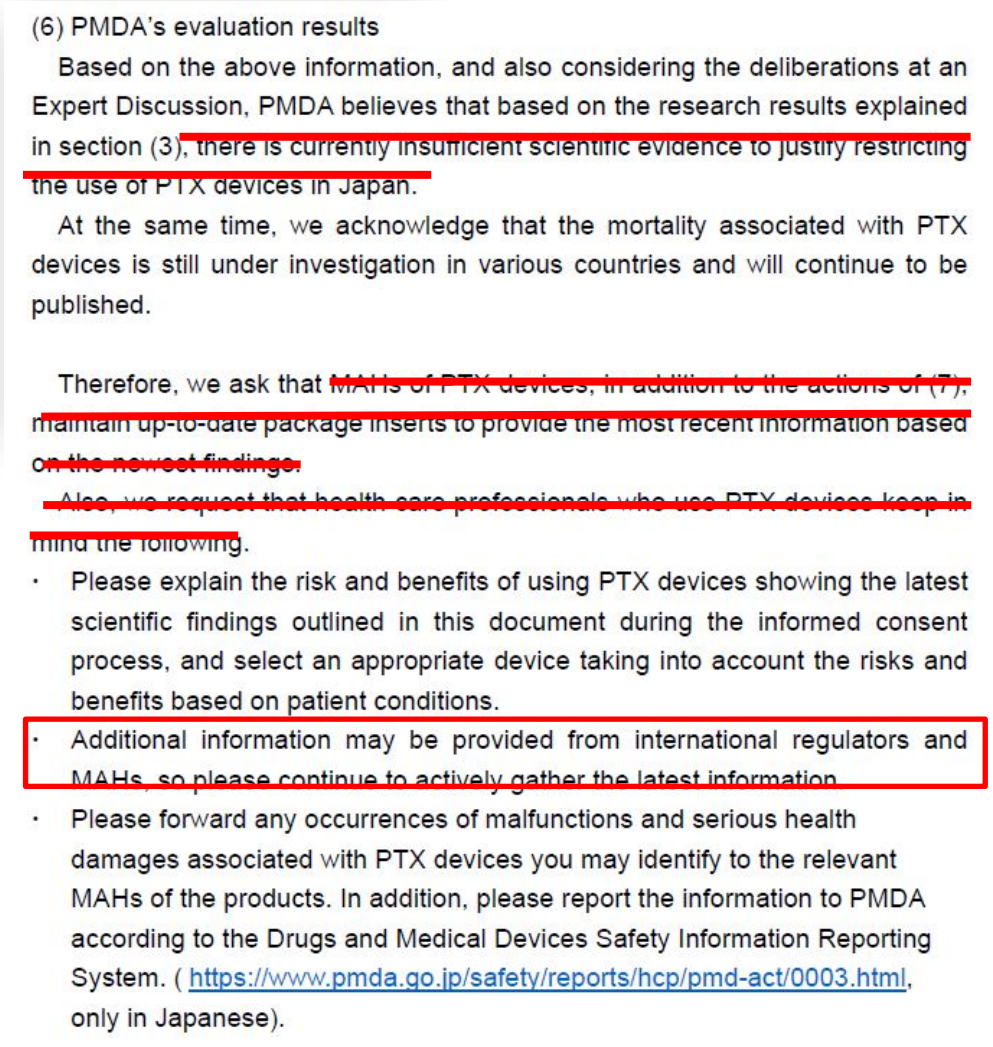
Since the publication of this article, the US Food and Drug Administration (FDA)[1)2)], the UK Medicines and Healthcare Products Regulatory Agency (MHRA)[3)], and the French Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM)[4)] have been providing health care professionals using paclitaxel-coated devices with information on the content of this article and the fact that risk evaluations are being conducted in various countries. In addition, FDA communicated its second information on March 15, 2019 that the agency encourages treatment options other than paclitaxel-coated devices until completion of its risk evaluation based on the analysis of follow-up results of the pre-marketing clinical trials for the devices.

# PMDA’s action

- Initially only "risk information of ongoing evaluation “ was published
  - PTX-coated devices have shown some clinical benefits for treatment in the Femoropopliteal Artery.
  - Causal relationship between paclitaxel and mortality was unclear
  - To evaluate the risks put forward in recent research, it is necessary to consider ethnic differences in pharmacokinetics, life-style, etc.
- To perform a risk analysis of a Japanese population, **a group of experts evaluated the data collected by manufacturers under a Health and Labour Sciences Research Grant**.

# Additional information based on Japanese data

- There was **no significant difference in 5-year life prognosis between PTX device group and non-PTX group**
- Based on this information, PMDA announced that **there is currently insufficient scientific evidence to justify restricting the use of PTX devices in Japan.**



(6) PMDA's evaluation results

Based on the above information, and also considering the deliberations at an Expert Discussion, PMDA believes that based on the research results explained in section (3), there is currently insufficient scientific evidence to justify restricting the use of PTX devices in Japan.

At the same time, we acknowledge that the mortality associated with PTX devices is still under investigation in various countries and will continue to be published.

Therefore, we ask that MAHs of PTX devices, in addition to the actions of (7), maintain up-to-date package inserts to provide the most recent information based on the newest findings.

Also, we request that health care professionals who use PTX devices keep in mind the following.

- Please explain the risk and benefits of using PTX devices showing the latest scientific findings outlined in this document during the informed consent process, and select an appropriate device taking into account the risks and benefits based on patient conditions.
- Additional information may be provided from international regulators and MAHs, so please continue to actively gather the latest information.
- Please forward any occurrences of malfunctions and serious health damages associated with PTX devices you may identify to the relevant MAHs of the products. In addition, please report the information to PMDA according to the Drugs and Medical Devices Safety Information Reporting System. ( https://www.pmda.go.jp/safety/reports/hcp/pmd-act/0003.html, only in Japanese).

# 【Notification】 Self-inspection of Package Insert

- [Important Precautions] of [Precautions]
  **・This device should be used in consideration of risks and benefits in light of the patient's conditions.**
  **・Informed consent should be obtained based on the representative results in Japan (see [REFERENCES AND REFERENCE REQUEST]) in addition to overseas information.**
- [REFERENCES AND REFERENCE REQUEST]
  **・Dr. Katsanos's systematic review and meta-analysis**
  **・Dr. Nakamura's HL Sciences Research**
  **・Statement from Japanese society for Vascular Surgery, Japanese Association of Interventional Radiology, Japanese Association of Cardiovascular Intervention and Therapeutics)**
  **・Nordanstig J, et al., "Mortality with Paclitaxel-Coated Devices in Peripheral Artery Disease", N Engl J Med, 2020; 383:2538-2546**

- The measures of FSCA is to be decided appropriately **based on the risk-level of the issues and condition of each country.**

Thank you for your kind attention!