Voluntary Recall

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GMP Sub-Committee

JPMA Quality & Technology Committee

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From Japanese Characteristic point of view …

- Japanese customer is extremely sensitive about foreign matters (FM), discoloration, appearance… on not only product itself but the package.

- J-Pharmaceutical companies pay strong attention to materials, process, gowning, visual inspection …

- In Japan, there are several recalls due to FM contamination every year, which makes huge cost loss and suffers serious damage to a corporate image.

➡ **Consumer's safety awareness has been escalating.**
➡ **Corporate governance and compliance becomes vital.**

Background for recall in Japanese Industry

1994-1995	Foreign matter issue in Mineral Water (PET bottle)
1995 Apr.	Revised GMP Obligation of report for recall
1995 July	Introduction of PL Law
1995-2000	Many recall incidents due to foreign matter (glass) in drugs
2000 Mar.	Guidelines for monitoring recall of drugs MHW
2000 July	Micro. contamination crisis on milk products in Food Industry
2002	Scam of disguising imported beef in Food industry
2005-2009	Deceptive labeling of origins in Food industry
	Import defective goods from China in Food industry
2010	Defect of Gas pedal in Car Industry
2011	Recall of the soap including hydrolyzed wheat in cosmetic industry
	East Japan Earthquake – Radiation Contamination issue
2013	Skin lotion issue due to vitiligo (white spot) in cosmetic industry

Recall related Regulatory Law

1. Pharmaceutical Affairs Law, Article 77 & 80 (1960)

   薬事法（昭和35年法律１４５号） 第７７・８０条

2. Order for Enforcement of the Pharmaceutical Affairs, Article 80 (1961)

   薬事法施行令（昭和３６年政令１１号） 第８０条

3. MHLW Ministerial Ordinance No.136, 2004 =GQP Ordinance

   厚生労働省令１３６号（平成１６年９月２２日）

4. MHLW Notification No. 237 March 8, 2000

   'Guidelines for Monitoring Recalls of Drugs, etc.'*

   厚生労働省医薬安全局長通知２３７号（平成１２年３月８日）

   『医薬品等の回収に関する監視指導要領』 －後述

* *This guideline was published on the basis of study 'Recall of drugs and medical devices' via Health and Labor Sciences Research.*

   (revised: March 22, 2011)

   厚生労働省医薬食発0322号第3号（平成23年3月22日）

   『医薬品等の回収について』の一部改正について

MHLW Ministerial Ordinance No.136
Article 12: Handling Recall

Article12 The marketing authorization holder of drugs shall, in case where he/she conducts recall of drugs, have, in accordance with the quality assurance duty procedure documents, etc., the quality assurance manager conduct the following duties.

製造販売業者は、品質保証責任者に次の業務を実施させなければならない。

(1) To segregate the drugs recalled, and to dispose of them properly after storing for a certain period, and

回収品を区分して保管し、適正に廃棄すること。

(2) To establish records describing the details of the recall, and to report in writing them to the general marketing manager.

回収記録を作成し、総責に報告すること。

MHLW Notification No.237

'Guidelines for Monitoring Recalls of Drugs, etc.'

- Issued on March 8, 2000, Revised on March 31, 2005

1. Definition of Recall, Basic Concept of Recall 回収の定義・基本的考え方
   (1) Definition of Recall
   (2) Basic Concept of Recall

A. Any doubt in Effectiveness of product /Safety of patient

有効性及び安全性の観点からの判断

B. Expansion of same complaints 不良範囲の特定に関する判断

C. Judgment based on the property of the foreign matter found and the type of product 混入した異物の種類と製品の性質からの判断

2. Handling after starting recall of the drugs 回収着手報告の取り扱い
3. Report of completion of recall 回収終了報告
4. Others (Confirmation of improvement, disposal of recalled products, etc.) その他（改善策と回収医薬品の処分の確認）

MHLW Notification No.237

'Guidelines for Monitoring Recalls of Drugs, etc.'

2. Basic Concept of Recall

- C. Judgment based on the property of the foreign matter found and the type of product:

  < Textual quotation >

  - In the case of drugs, make a judgment based on the type of product (sterile or non-sterile) and the property of foreign matter found in the product (inherent foreign matter like glass fragments, exogenous foreign matter like wood chips, or biological foreign matter like hair or insect). For a sterile product, the important judgment criterion is whether or not sterility is reliably guaranteed. Recall the product, if exogenous or biological foreign matter is present.
  - In the case of a non-sterile product, recall the product, when biological foreign matter is found.

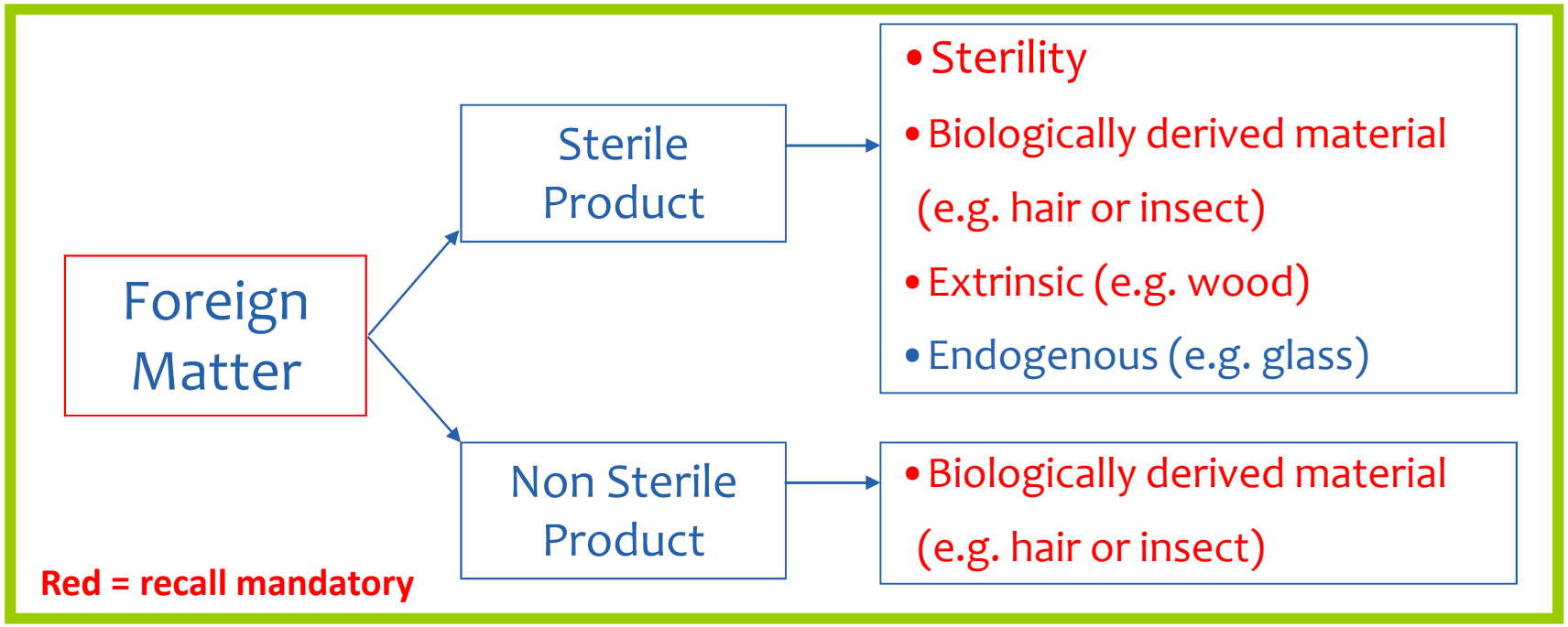
MHLW Notification No.237

'Guidelines for Monitoring Recalls of Drugs, etc.'

2. Basic Concept of Recall

C. Judgment based on the property of the foreign matter found and the type of product

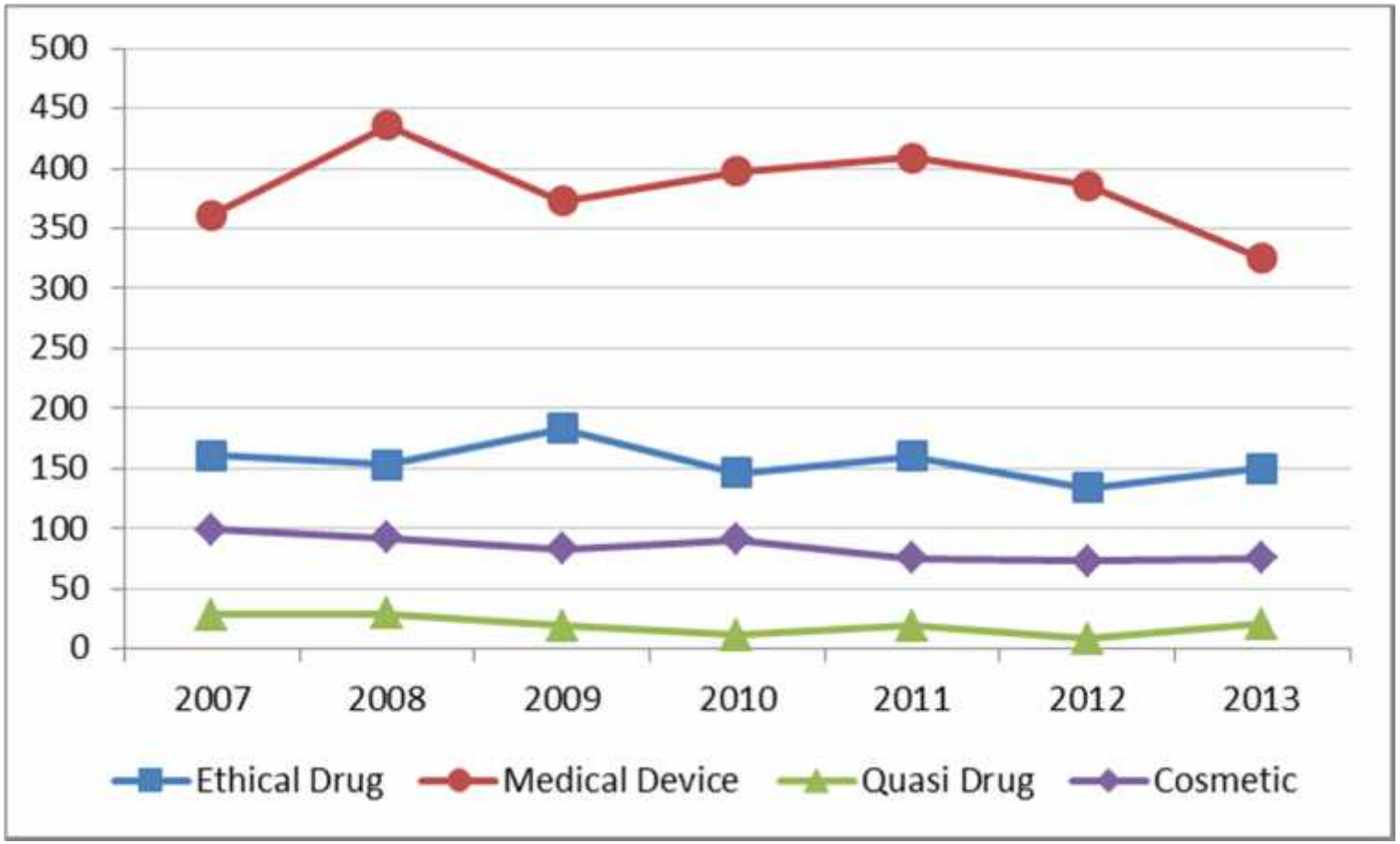
< Summary >



How to Make a decision about 'Voluntary Recall'

- ✓ **Conflict with pharmaceuticals affaires law / discrepancy between regulatory commitment?**
- ✓ **Any doubt in effectiveness of product / safety of patients ?**
  - ** occurrence of concerned product / lot related adverse event,*
  - ** health hazard risk…*
- ✓ **Multiple events (expansion of same complaints) OR completely isolated / limited on a concerned incident / lot?**
  - ** All marketed lots have to be recalled if there is no scientific / reasonable / logical reasons to ensure the isolated / limited incident.*
- ✓ **Judgment based on the property of the foreign matter found and the type of product**
  - ** Biological foreign matter (hair, insect) has a possibility to bring about degradation of product itself due to microbial contamination.*

Recall Trend in Japan 2007-2013 / Total

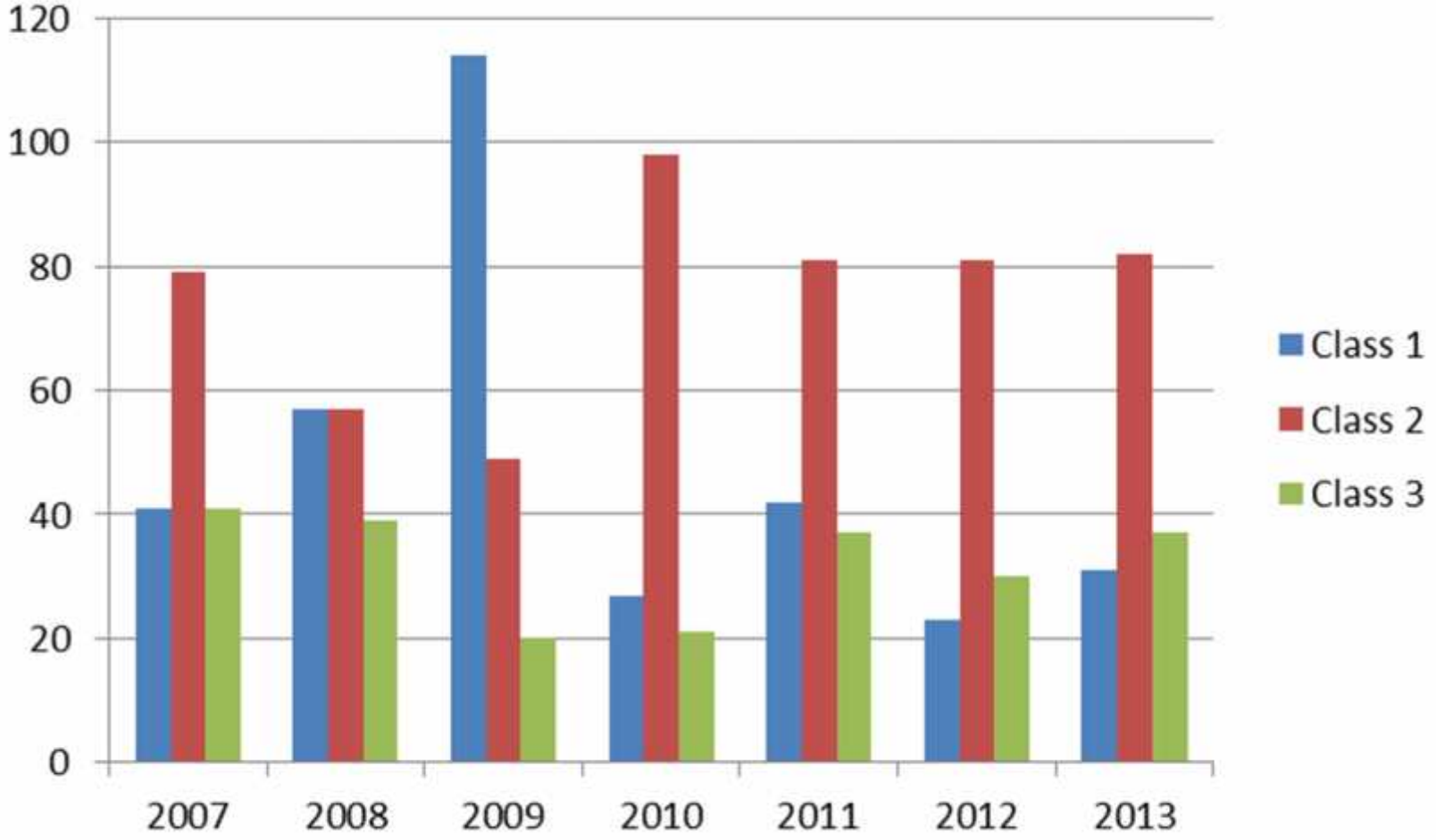


* extracted from PMDA Web site

Classification of Recall

- Class I
  - A situation in which there is a reasonable probability that the use of a product will cause serious adverse health consequences or death
  - その製品の使用等が、重篤な健康被害又は死亡の原因となり得る状況をいう。
- Class II
  - A situation in which use of a product may cause temporary or medically reversible adverse health consequences or where the probability of serious adverse health consequences is remote
  - その製品の使用等が、一時的な若しくは医学的に治癒可能な健康被害の原因となる可能性があるか又は重篤な健康被害のおそれはまず考えられない状況をいう。
- Class III
  - A situation in which use of a product is not likely to cause adverse health consequences
  - その製品の使用等が、健康被害の原因となるとはまず考えられない状況をいう。

Recall Trend for Ethical Drugs in Japan 2007-2013



Focus on Class I
Ethical Drug in the past 3 years

	2011	2012	2013
Blood Products	42	23	31
Others	0	0	0
Total	42	23	31

- All Class I recalled were blood products supplied from Japanese Red Cross Society in the past 3 years.
- Recall was made on the basis of declaration / information from blood donors after donation.
  - ✓ Positive result on HIV, HBc antibody test
  - ✓ Influenza infection
  - ✓ The donor had been living in the specific country

Special note: except Blood Products, in 2008, some heparin products were recalled due to contamination of over sulfated chondroitin sulfate.

Focus on Class II (1)
Ethical Drug in the past 3 years

	2011	2012	2013	Total
Product Defect	40	28	29	97
Labeling Error	8	2	2	12
Mix-up	3	7	5	15
Contamination	7	9	5	21
Stability OOS	10	16	31	57
Others	13	19	10	42
Total	81	81	82	244

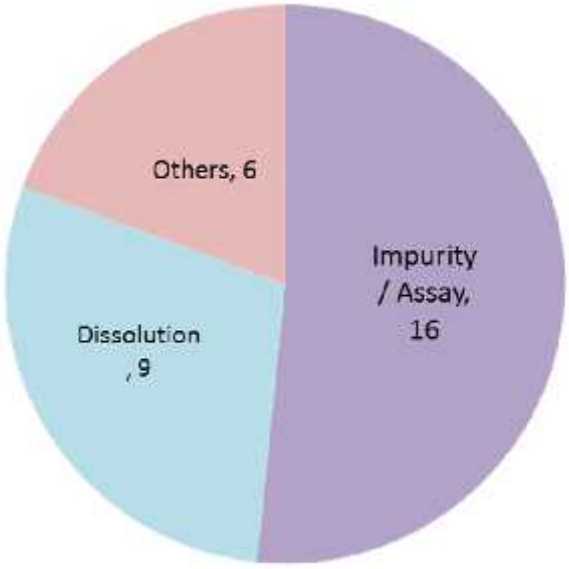
- No significant change on total number was seen.
- Half of product defect was from diagnostic products.
  - ✓ False-positive result
  - ✓ Reduced or no response, wrong result
- 2nd. Major of product defect was that excipients not listed in approved dossiers had been used, or the process not approved had been applied.

Focus on Class II (2)
Ethical Drug in the past 3 years

Recall due to contamination

	2011	2012	2013	Total
Hair	4	4	2	10
Insect	1	0	0	1
Blood	1	0	0	1
Glass	0	1	1	2
Metal	0	0	2	2
Plastic	0	2	0	2
Mold	0	1	0	1
By-proudct	1	1	0	2
Total	7	9	5	21

Details of Stability OOS in 2013



- Hair contamination has been seen every year even though pharmaceutical companies pay very strong attention to it.
- As the current trend, voluntary recall due to dissolution failure on non-sterile products (solid dosage form) is getting increase.

Focus on Class III
Ethical Drug in the past 3 years

	2011	2012	2013	Total
Product Defect	6	1	8	15
Labeling Error	24	19	16	59
Mix-up	3	1	2	6
Contamination	0	0	7	7
Stability OOS	0	0	0	0
Others	4	9	4	17
Total	37	30	37	104

- Major in Class III was due to Labeling Error.
  - ✓ No print of lot number / shelf life including illegible prints
  - ✓ Error in shelf life, no print of "Powerful Drug", "Poisonous Drug"
- "Mix-up" in Class III was to find packaging insert or label of other products

Recall Case (Others)

- 101 tablets were found in the bottle labeled “100 tabs containing”
  Class III
- Tablets having split line were released (The original has no split line).
  Class III
- The product had been distributed to wholesalers before QA release.
  Class III
- The manufacturer forgot the manufacturing license renewal.
  Class II
- The manufacturer forgot the analysis of “Identification test”.
  Class II
- The recalled product was released.
  Class II

How should we prevent a recall? (1)

- **Learn about the period**
  - ***Change of earning structure, Tough competition…***
    - ***Have to pursuit further efficiency…***
      - ✓ *Shift to cheaper materials / new suppliers*
      - ✓ *Omission of analysis, Process change, organization downsizing*

    Risk increase, lose / decrease an opportunity to detect…

  - ***A rise in awareness of product safety, effectiveness and compliance, information disclosure…***
    - ✓ *Customer's severe perspective in product quality*
    - ✓ *Require further user-friendly dosage-forms, devices, new technology*

    Fast-track development / launch, Heavily involved in works

    Unknown / unexpected risks…

How should we prevent any recall? (2)

- **Implement ICH Q quartet as practical & sustainable operations**

  (Consistent Quality Management from law materials to finished products)

  - ***Pharmaceutical Development***
    - ✓ *Apply Quality by Design over the product life cycle*
  - ***Quality Risk Management***
    - ✓ *How to manage "Risk" systematically within the limited resources*
  - ***Pharmaceutical Quality System***
    - ✓ *Annual Product Review, continuous improvements (monitoring & CAPAs)*
  - ***Development and Manufacture of Drug Substances***
    - ✓ *Definition & Control of true CQAs*

- **Preventive actions of any contaminations**
- **100% visual inspection**
  - ✓ *But, visual inspection is consistently the final measure. Daily preventive actions in process are very effective and sustained way.*

Think of nothing better than "Back to GMP original premise"

Thank you for your kind attention !

Terima kasih

JPMA

Contributing society with new pharmaceuticals

About 'JAPAN QUALITY'

- As experienced by suppliers who have Japanese customers, they must have been embarrassing or uncomfortable to complaints about cosmetic defects.

- There is sometimes no impact on drug effectiveness and safety. Leaving aside the question of Japanese persistence, this matter can't be avoided as far as doing business in Japan.

- Cosmetic quality is one of significant key factors in 'JAPAN QUALITY'.

- European Compliance Academy held a conference as titled 'JAPAN QUALITY' on 14-15 May.
  Thus, Especially in pharmaceutical industry,
  'JAPAN QUALITY' is becoming known to the world.