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# Introducing Research Collaboration and GMP Human Resource Development at Three Universities with GMP Laboratories in Japan

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# Introducing Research Collaboration and GMP Human Resource Development at Three Universities with GMP Laboratories in Japan

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## Abstract

This paper summarises initiatives presented on June 1st 2023 at a seminar during a visit to Technological University Dublin. The authors travelled from 3 universities in Japan to share some of the collaborative research, education and training initiatives developed by them. Figure 1, presents an illustration of the university locations, together with the authors and their individual university locations.


Figure 1: Illustration representation of the authors and their affiliated universities

In their presentation the authors gave an overview of the current situation of Knowledge Management and Quality Culture in Japan, highlighting some recent issues and challenges, and presented some initiatives under development to specifically address these challenges.

## 1. Pharmaceutical Manufacturing Regulation in Japan

The manufacture of pharmaceuticals in Japan is regulated by Ministry of Health, Labour and Welfare and the Pharmaceuticals and Medical Devices Agency (PMDA). In 2021, the GMP Ministerial Ordinance that manufacturing facilities must comply with was revised. This revision embedded the concept of the Pharmaceutical Quality System (PQS), introduced in 2010 by ICH in Q10, and incorporated into the PIC/S guidelines in 2017, resulting in harmonization of international regulation requirement across the ICH regions.

However, despite the great strides towards international harmonization of regulation, unfortunate incidents of improper manufacturing leading to defective products on the market occurred. One of these incidents, the 'Kobayashi-Kako case' led to 245 adverse event reports including 2 deaths. As a result, Kobayashi-Kako was ordered to suspend its manufacturing and marketing operations for 116 days.

*The Kobayashi-Kako Case*
Cross-contamination of Itraconazole tablets (antifungal generic) by Rilmazofone Hydrochloride Hydrate (API sleeping drug) occurred in December 2020. The contamination was directly caused by an operator who introduced the wrong API in a process step which was not described in the manufacturing and marketing authorization document. Moreover, according to the procedure manual, the process required a two-person operation, but due to the busy production schedule, it became a one-person operation, resulting in a simple confirmation error. Management knew that this was the situation at the site and that illegal manufacturing operations were being carried out, yet they continued to conceal the fraud by presenting falsified manufacturing records even during administrative audits.

Since this major incident, several illegal conditions have been found in the manufacture of pharmaceutical products, especially in generic drug companies, leading to problems in the supply of drugs, the problem of which will be addressed later in this paper.

But for now, focusing on ways to prevent this happening again, several themes have emerged as follows:

- With the revised Japanese GMP ministerial ordinance of 2021, the *effectives of the PQS* should now be considered during inspections
- Maturity of *quality culture* is a foundation for the effectiveness of the PQS and quality culture in the company that serves as a foundation for the data Integrity

- The importance of understanding *knowledge management throughout the product lifecycle,* thus ensuring appropriate transfer of knowledge from the development department to the manufacturing department

- The need for research on resolving *drug shortages* caused by the increasing number of manufacturing issues (specifically in generic manufactures) triggered by the Kobayashi-Kako incident.

- A review of the GQP system which is unique to Japan and consideration of whether a *QP system* like the EU may be more appropriate going forward.

- Development of Human Resources for GMP activities by provide education and training for everyone involved in manufacturing, from the workers to the management level.

These themes will be explored further in this paper.

## 2. Quality Culture Development

The Parenteral Drug Association (PDA) and International Society for Pharmaceutical Engineering (ISPE) have published a guide to improving quality culture in pharmaceutical manufacturing facilities (ref) and based on this, a quality culture evaluation index has been created with the five categories identified by the guide and a total of 28 questions for each, as illustrated in Figure 2.


Figure 2: Illustration of Evaluation index

This quality culture evaluation index was developed by TUS and the Japanese Generic Manufactures Association (JGA) and a survey of 37 affiliated generic companies was conducted. This research is currently being published, so cannot be shared here in detail.

However, two specific challenges emerged from the research as follows:

- Employees have very few opportunities to listen to the voices of patients and patient support groups. This results in a lack of awareness that the medicines they manufacture are connected to patients.

- There is a lack of proper allocation of resources required for management reviews, as well as the need for appropriate personnel allocation and recruitment.

Interviews with companies that have successfully solved this issues are planned to be conducted to get insights into possible solutions that could be published.

The development of a quality culture is a situation where there are no tools to measure or evaluate. Therefore, in this research study, terms to define items for evaluating the degree of development of a quality culture have been identified and a tool to visually evaluate the degree of development has been created. By the creation of such an evaluation tool, it is anticipated that the degree of development of the quality culture of each company can be evaluated, and this information will be useful for understanding points to be improved, thus contribute to the stable supply of high-quality pharmaceutical products.

## 3. Knowledge Management Development

In 2021, a survey on Knowledge Management understanding and deployment was conducted in conjunction with the Japan Federation of Pharmaceutical Manufacturers' Associations, and responses from 395 companies were obtained.

The insights revealed from this survey are summarised as follows:

- The concept and purpose of knowledge management itself are well understood.

- However, when implementing knowledge management there were challenges in understanding what knowledge management should be and how to put it into practice.

- Many companies experienced challenges in transferring their know-how to another company, or experienced cases of poor reproducibility of manufacturing or testing due to insufficient information.

- Electronic storage of knowledge is a lagging issue.

The effectiveness of knowledge management through the use of the knowledge creation spiral proposed by Dr. Nonaka in 1994 and the RKI cycle proposed by Lipa and O'Donnell in 2020 is being researched. A recent investigation into the problem of fraudulent manufacturing of generic drugs in Japan has led to the conclusion that information sharing among development, manufacturing, and regulatory affairs departments is insufficient, and the authors propose that '*knowledge communication*' is a new concept that should be considered for inter-departmental knowledge sharing. Knowledge communication serves to enable or augment cross-departmental combinations.

**Knowledge Communication**
(© 2021 Sakurai & Takarada):
**Explicit knowledge sharing between organisations that are segregated by business lines and/or confidentiality obligations and difficult to incorporate into a single knowledge creation spiral. It can be an enabler/enhancer of "Combination" across the organisations.**

## 4. Drug Shortage challenges in Japan

Japan is currently experiencing a serious drug shortage, especially generic drugs.

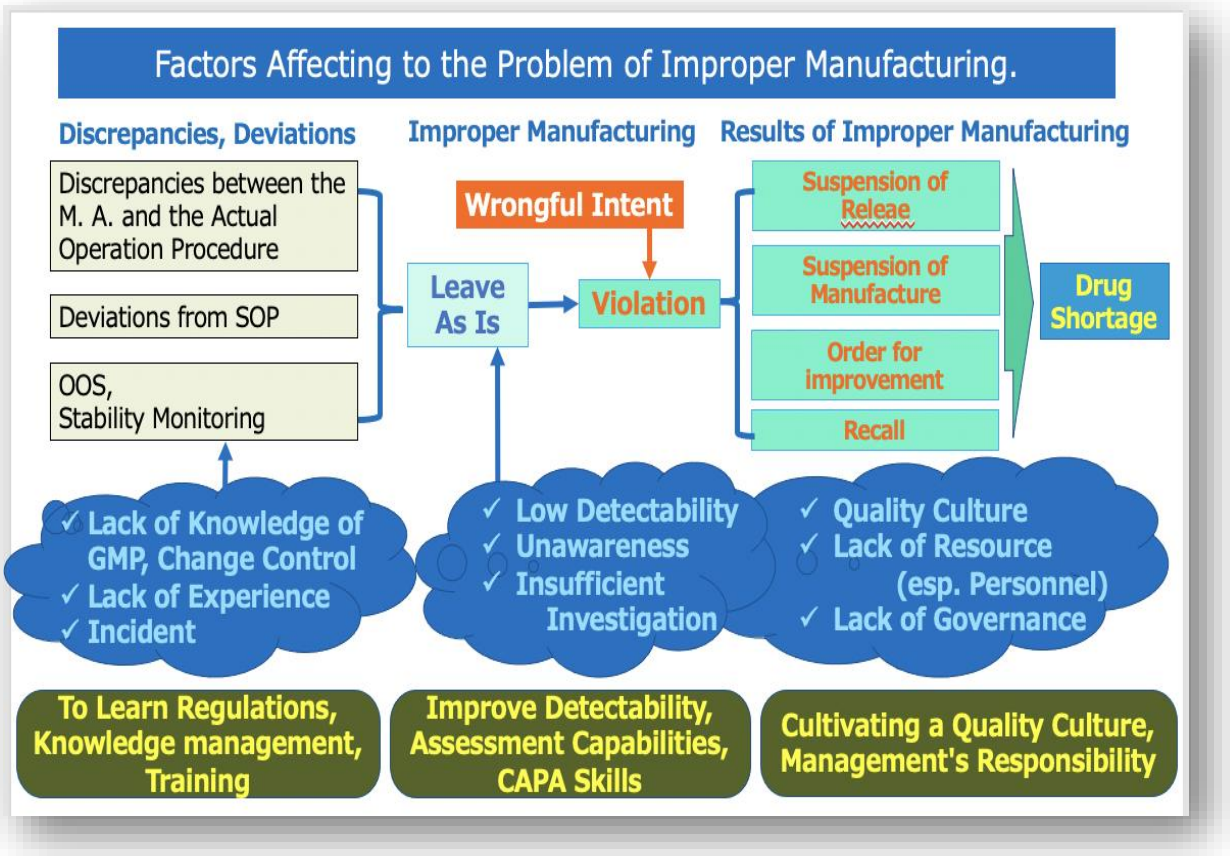
There are four main reasons suggested for these drug shortages:

- The procurement of APIs for antibiotics
- The problem of improper manufacturing. (For example, Kobayashi-Kako's case)
- The influence of Covid-19.
- The situation in Ukraine.

This paper explores in more details the challenge of improper manufacturing of pharmaceuticals as a field related to regulatory science.

***The challenge of improper manufacturing of pharmaceuticals***

Factors leading to the problem of improper manufacturing of pharmaceuticals are summarized in Figure 3 below.




Looking first at the challenge of discrepancies between the marketing authorization and the actual manufacturing procedure, or deviations from the SOP. This can be attributed to the lack of knowledge of GMP or change control procedures, inexperience, or perhaps an incident or deviation occurring. If handled immediately, these deviations and discrepancies are mere deviations and discrepancies, But, if not dealt with in the correct manner, or if ignored completely, they most likely will lead to a situation of improper manufacturing.

Another challenge, although not neglect, is when repeated deviations occur due to inadequate investigation, failure to identify root causes, and inability to implement effective CAPA. Furthermore, there may be cases where a quality culture is not sufficiently fostered,

resources are insufficient to take appropriate action, or poor governance leads to neglect and improper manufacturing.

On the other hand, improper manufacturing could be done intentionally.

***Addressing these challenges***

To address the problem of the lack of knowledge and experience, education and training on GMP and various regulations should be implemented. In addition, issues that lead to improper production require improved problem detectability, root cause investigation, and appropriate CAPA promotion. It is also necessary to foster a quality culture and resolve issues related to management responsibility.

These issues of quality culture and knowledge management a new research team was launched in 2023 year to explore a research project entitled *"Research and Investigation into The Prevention of Quality Problems and the Continuous Improvement of Quality at Pharmaceutical Manufacturers"* funded by on MHLW Health Labour sciences research grant.

This research project has 5 study themes as follows:

- A Study on Improving the Problem Detection and Improvement Skills of Manufacturers
- A Study on the State of Quality Risk Information Communication between Public and Private Sectors
- A Study on Business-to-Business Outsourcing
- A Survey of the Actual Situation of Pharmaceutical Manufacturers with the intention to propose corrective measures to address challenges identified
- A student to identify Efficient and Effective Quality Control Methods Using Digitalized Systems.

Details of the outputs of this research study will be presented once completed.

## 5. Development of a GMP Audit Manual

In order to improve the effectiveness of GMP audits of MAHs in Japan, an GMP audit manual was developed as part of the Health and Labor Science Research Group. Training activities for

industry on the use of the manuals are being conducted in collaboration with the 3 universities presenting this paper.

There are five elements in the GMP training Manual as follows:

- The pre-audit phase which reviews the organizational structure
- The audit planning phase
- The conduct of the audit phase
- The phase where manufacturing improvements are evaluated
- The post-audit phase which explores improvement suggestions to the manufacturing facility and the evaluation of the manufacturing facility, and a review of the audit confidence to improve the quality of the audit.

Figure 4 below illustrates the GMP training Manual

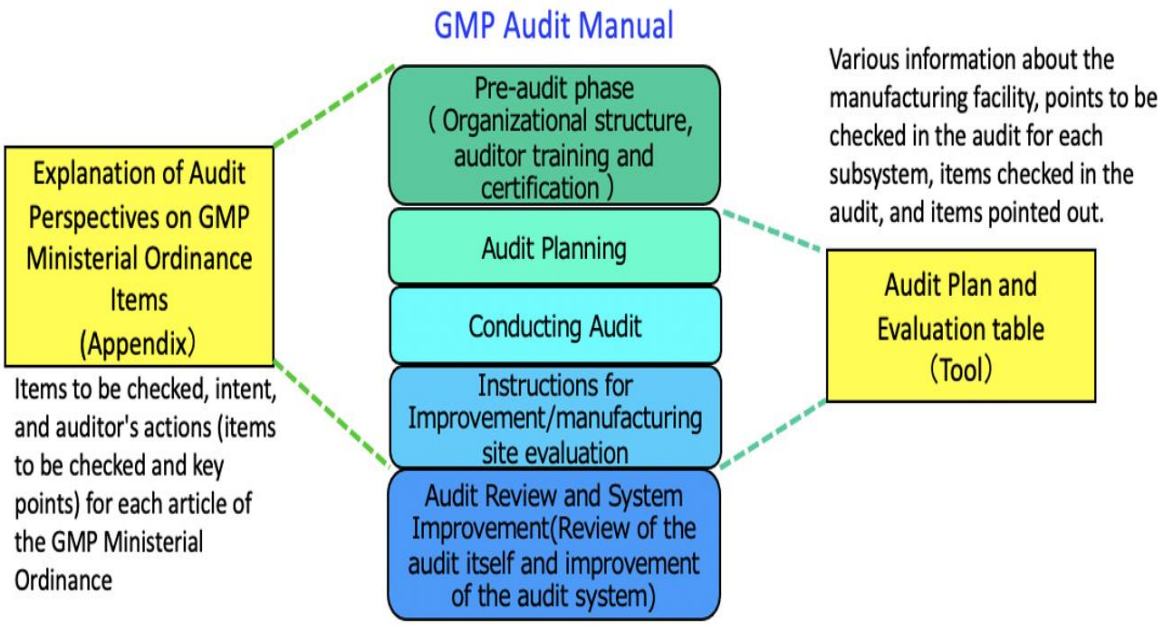



Figure 4

An appendix to the GMP manual was created that explains the significance required by each article of the Japanese GMP ordinance, what should be done, and what the auditor should check from what perspective during the audit. This table is presented in Figure 5 below.

| GMP Ministerial Ordinance Items | Items to be checked | intention | Auditor Actions |
|---|---|---|---|
| Article.4 | ・・・・ | ・・・・ | ＊＊＊＊ |
| Article.5 | ・・・・ | ・・・・ | ＊＊＊＊ |

Figure 5

In addition, a table was created to guide the inspections process by considering the pre-audit planning and post-audit evaluation in a subsystem. This table shown in Figure 6, is an integral sheet which records the checkpoints considered during planning, the items confirmed during the audit, the items identified for improvement, the level of these items and the level of the subsystem and the manufacturing site.

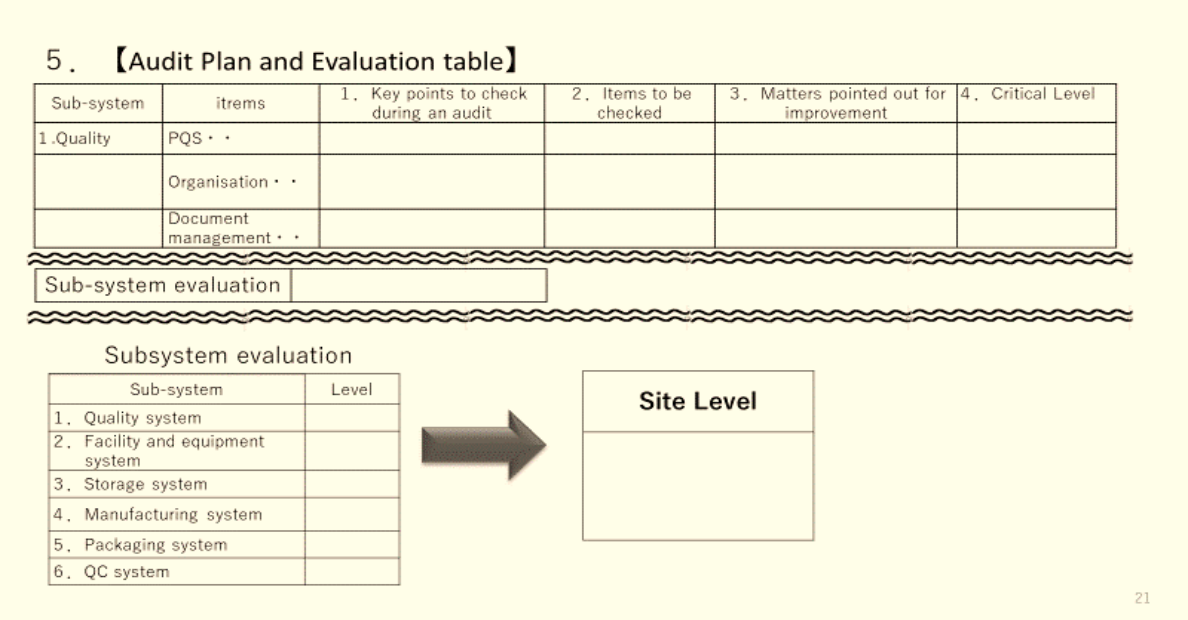



Figure 6

## 6. Issues related to the responsible person for the product batch release in Japan

MAHs are responsible for the proper management and supervision of manufacturing facilities to ensure product quality, and to do this, they must make full use of their "knowledge" of manufacturing and quality management to conduct GMP audits and provide appropriate guidance. In order to do this, they need to properly understand and judge the information

obtained from the audits and to share and pass it on as knowledge within the organisation. They need to use this knowledge to ensure appropriate communication methods regarding deviations, changes, and quality information with the manufacturing facility occur in a timely manner, on a daily basis.

The audit manual presented in section 5 is one example of a tool that can be used to enhance knowledge flow during auditing thus aiding Knowledge Management.

However, the audit manual alone with not be enough to solve the problem in Japan.
More important is the need to have a trained workforce that can properly understand and make decisions regarding GMP in the first place. Currently in Japan, securing such human resources with this experience, training and knowledge is a problem, especially in the area of Quality Assurance.

Specifically, there problems with Japan's quality assurance system as the position of the responsible person who determines the release of the finished product batch oversees the implementation of GMP is not clear.  Nor are the skills required for this role understood
For example, for a facility that produces drug substances (Site A), drug products (Site B) and finished packages (Site c), each site has a Manufacturing Manager who oversees the GMP operations, and the MAH must have one responsible person to make a decision to release the finish product batch to market, who is legally registered. This scenario is depicted in Figure 7.

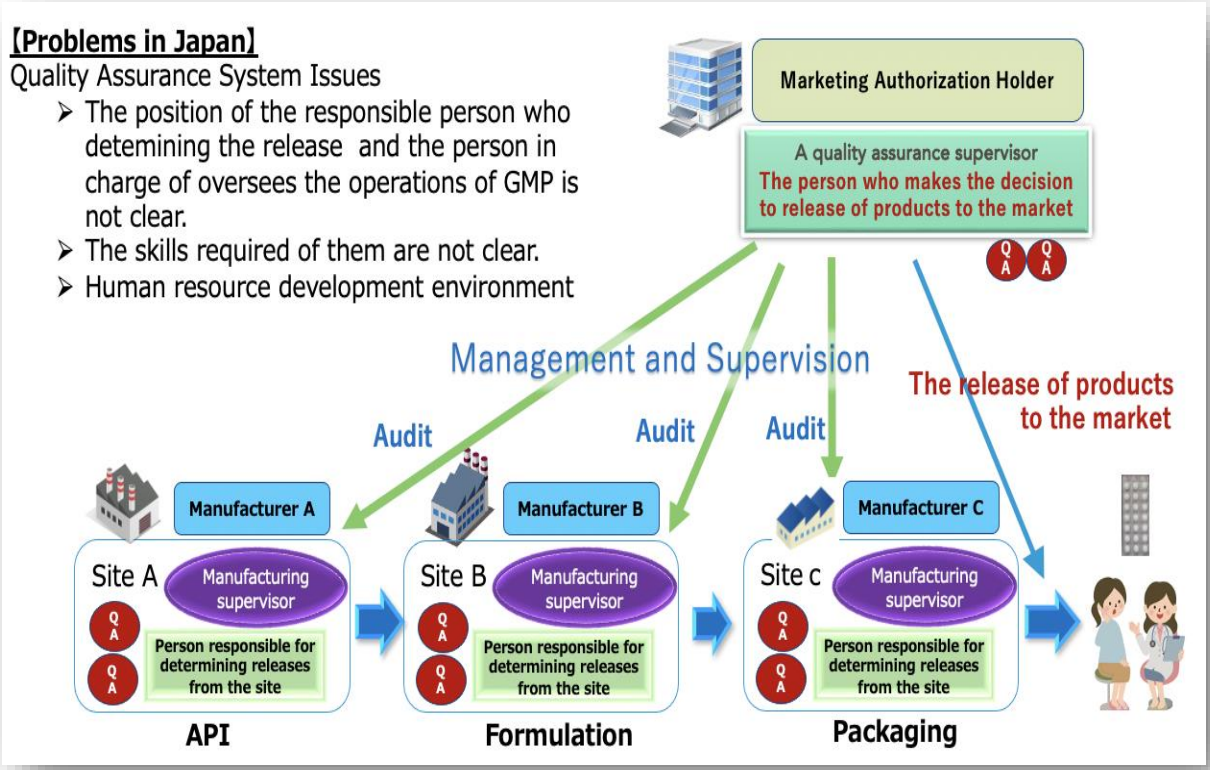



Figure 7

This scenario results in a situation where:

- The person who makes the decision to release of products to the market is not stationed at the manufacturing facility, thus it is difficult to grasp the status of GMP operations, although periodic audits are conducted at the manufacturing sites.

- MAH has only one person responsible for making decisions on market release, while the manufacturing site has only one "Manufacturing supervisor of pharmaceuticals" who oversees the operations of GMP, thus it is necessary to assign QA personnel to perform quality assurance tasks and audits, but the level of training of these QA personnel varies

- 'Manufacturing supervisor of pharmaceuticals' need to be qualified as pharmacists, but there is no GMP in pharmacy education.

- There is no certification or training course like QP.

The research discussed in this paper is exploring recommendations for an effective quality assurance system, qualification, and human resource development system and one solution identified is the development of GMP education training for industry.

## 7. Developing a GMP education/training course for industry and student

The 3 universities are collaborating to develop an education and training course for people involved in pharmaceutical manufacturing in Japan, especially for QA personnel who play a key role in quality assurance of pharmaceutical products at manufacturing plants. Work is ongoing on this and Figure 8 summaries the extent and status of each program.

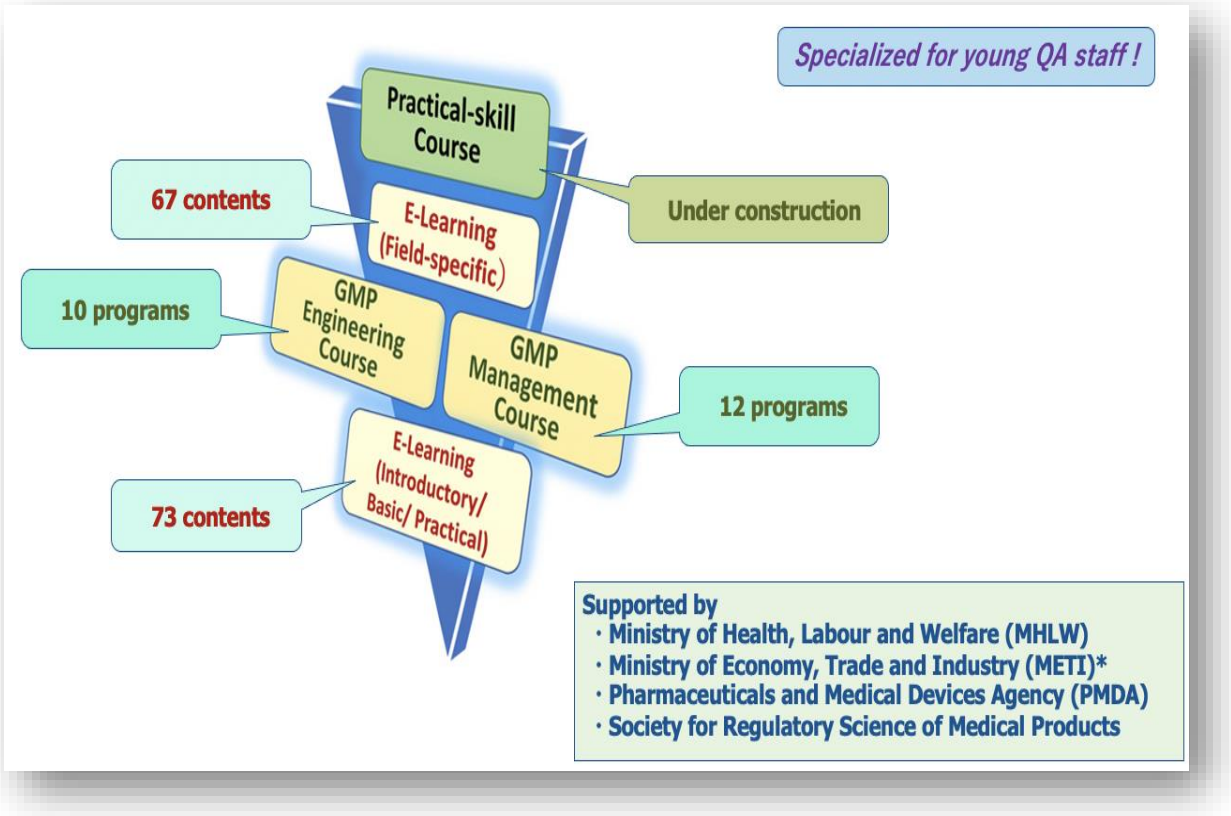



Figure 8

These are planned to be increased further and in the future, it is planned to create a practical skills course with a pharmaceutical support company that has a training lab in Japan.

## 8. Conclusion, presenting 2 slides from PMDA.

We conclude with 2 slides provided by PMDA illustrating their work in the Asian Region, Figures 9 and 10.

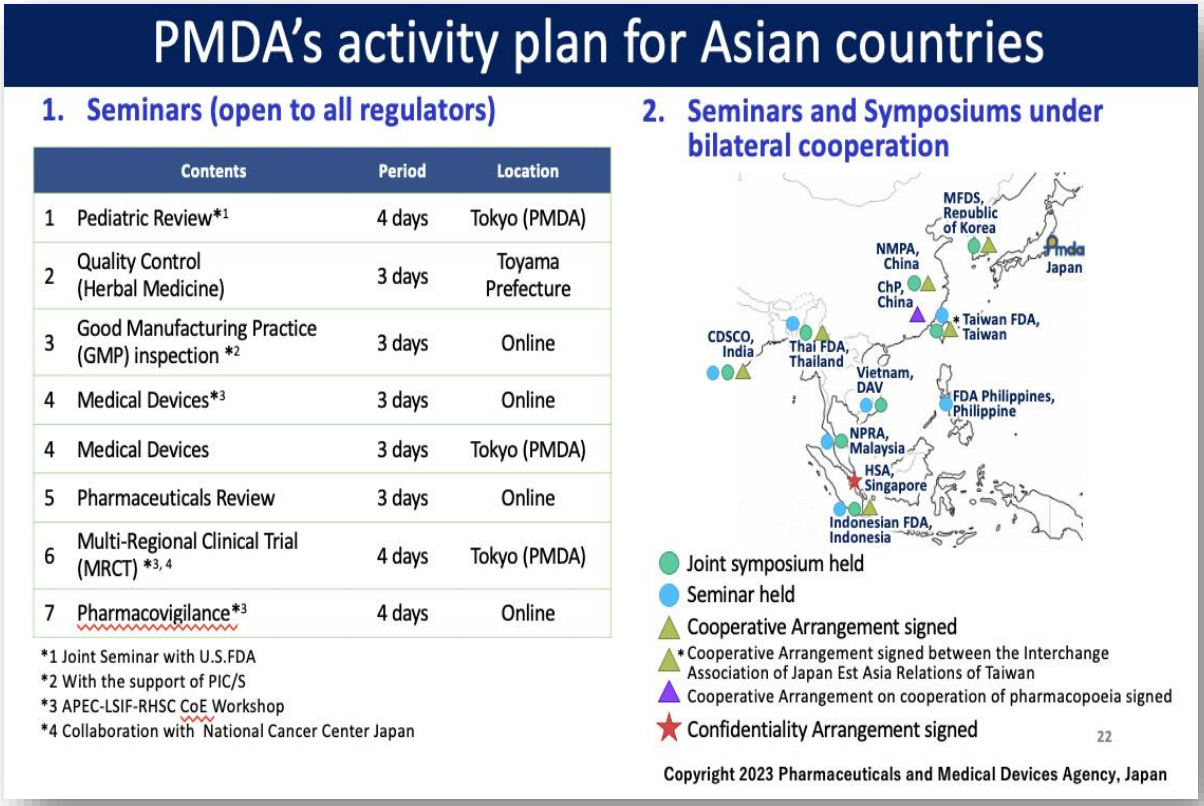



Figure 9

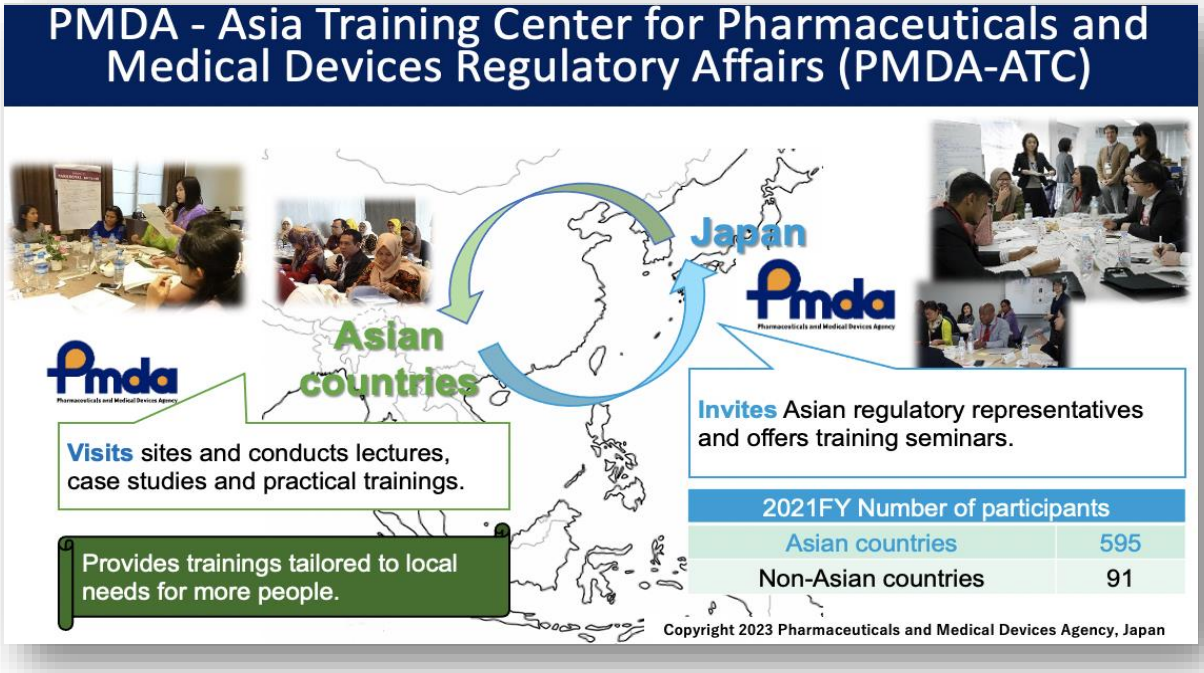



Figure 10