Report 5 of the Research Committee for International Pharmaceutical Distribution
of the Federation of Japan Pharmaceutical Wholesalers Association

Report 5

International Comparison regarding Security and Quality Assurance for Pharmaceutical Distribution

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The Federation of
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CONTENTS

Executive Summary

Complication and globalization of pharmaceutical distribution is causing global issues in assuring security and quality of pharmaceuticals in the supply chain. Recently, with the cross-border distribution of pharmaceuticals becoming commonplace, it is necessary to make concerted efforts to harmonize domestic regulations with global demand while tackling the issue. The Research Committee has implemented surveys with the goal of obtaining suggestions for how Japan should proceed given the efforts of the EU and the US.

The distribution of pharmaceuticals in the EU, US, and Japan has structural differences and, of course, there are differing stances on regulation. In addition, regulations differ according to the member countries of the EU, and also according to the states of the US. In Japan, regulations are implemented uniformly nationwide, so it is necessary to keep in mind the differing social foundations for regulations.

In the EU, a prime cause of falsified products entering into the supply chain is parallel importing. The Falsified Medicines Directive（FMD）was formulated as a common rule for its member countries, in 2011. In this system, when handing pharmaceuticals to patients at a pharmacy, all pharmaceuticals are checked for authenticity using a barcode. Although it is difficult to establish a system that spans multiple countries, this can be considered a logical system for preventing the use of falsified medical products by patients without obstructing distribution within the EU.

In the US, the main cause of falsified medical products entering into the supply chain is the existence of repackaging vendors and online pharmacies. The *Drug Supply Chain Security Act*（DSCSA）formulated in 2013 is a system of managing the marketing records at each transfer of possession upstream and downstream, and aims to allow traceability at the dispensed package in a stepwise manner over the next 10 years. While the data and systems are enormous, the federal unification of the regulations that have been conventionally used and which differed by state is an efficient approach.

In Japan, regulations regarding traceability have been tightened following the distribution of falsified pill preparations of Harvoni in January 2017. In 2018, the Japanese Gook Distribution Practice（GDP）guidelines were published, and a draft revision of the *Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices* was submitted to the Diet.

Despite the assumption that the pharmaceutical distribution systems and regulatory backgrounds differ for each country; through this survey, given precedents in various other countries, it was found that Japan's single-layered system of pharmaceutical transactions and nationwide regulations function efficiently against the entering of substandard and falsified medical products into the supply chain. In addition, the survey suggested that the issue of returned goods is common to all countries, raised cautions for planning systems, and suggested how Internet-based pharmaceutical transactions should work.

Furthermore, concerning how Japan should proceed with regard to assuring the security and quality in distribution, the survey found the following points to be necessary.

- **It is necessary to share with a wide range of medical professionals the fact that the "single-layer" pharmaceutical distribution system of Japan contributes to the prevention of substandard and falsified medical products from entering into the supply chain, and it is required to maintain the distribution system in the future.**
- **Not only Japan, but also the EU and US have discussions in handling returned products. Since the return of products can lead to substandard and falsified medical products entering into the supply chain, there is desire for a solution to this issue.**
- **Current medically-related measures include both the tightening and easing of regulations; however, over-tightening and over-easing of regulations can both threaten the health of citizens, resulting in the increase of the social costs. It is necessary to establish policies while keeping this in mind.**
- **With the GDPs established in each country, the global regulations affecting multinational companies may not be suited to Japan's situation, so it is necessary to have safety measures that match the state of distribution in a region, rather than regulating distribution itself uniformly.**

Through this report, we hope for broader awareness of the importance of assuring security and quality in the distribution of pharmaceuticals, and further discussion among those in the field.

Chapter 1

Purpose

The proliferation of falsified medical products is a global issue. The difficulty for ordinary citizens to distinguish between real and fake pharmaceuticals and the high value and small amounts of pharmaceuticals make them an easy target for crime. With the increase in the demand for pharmaceuticals and proliferation of the Internet, organizations such as the World Health Organization（WHO）and the International Criminal Police Organization（Interpol）are implementing global-scale measures against falsified medical products. In the pharmaceutical supply chain, regulations regarding the security of pharmaceuticals in the distribution process have been getting more strict from the perspective of preventing the mixing of falsified medical products into distribution channels and of preventing lost treatment opportunities and harm to the health of citizens.

At the same time, pharmaceuticals that require detailed management of, for example, storage temperatures, are becoming more common, and the quality control in the distribution process is also a significant challenge for related parties. Recently, with the cross-border distribution of pharmaceuticals becoming commonplace, there is an urgent need to make concerted efforts to harmonize domestic regulations for security and quality management with global demand.

Against this backdrop, the Research Committee for International Pharmaceutical Distribution has implemented surveys with the goal of obtaining suggestions for how Japan should proceed given the state of security and quality assurance in the pharmaceutical distribution processes of the EU and the US. In addition, we have compiled proposals for future initiatives for Japan.

The survey was performed through questionnaires and interviews with the European Healthcare Distribution Association（GIRP）[1)], the Healthcare Distribution Association（HDA）[2)], and EU and US pharmaceutical wholesalers, as well as upon the literature and materials published on relevant websites and the like. The questionnaires and interviews were implemented in September and October of 2018, and literature and websites from 2018 were used.

1）GIRP: The European Healthcare Distribution Association
2）HDA: Healthcare Distribution Association

Chapter 2

International State of Substandard and Falsified Medical Products

1. Definition of Terms

Terms used to express "fake pharmaceutical products" have, until recently, included "counterfeit" and "fake medicines." However, there was no fixed, precise interpretation of what these represented. Consequently, from a public health stance, the WHO made the following definitions in 2017.

- **Substandard medical products: Products that fail to meet either their quality standards or their specifications**
- **Unregistered/unlicensed medical products: Products that have not undergone approval by the medicines regulatory authority of the country of distribution**
- **Falsified medical products: Products that deliberately and fraudulently misrepresent their identity, composition, or source (e.g., package inserts and packaging)**

Given that the WHO focuses its surveys and monitoring on "substandard and falsified medical products," this report shall also use these terms.

2. WHO Survey Results[3)]

(1) The Survey into Substandard and Falsified Medical Products

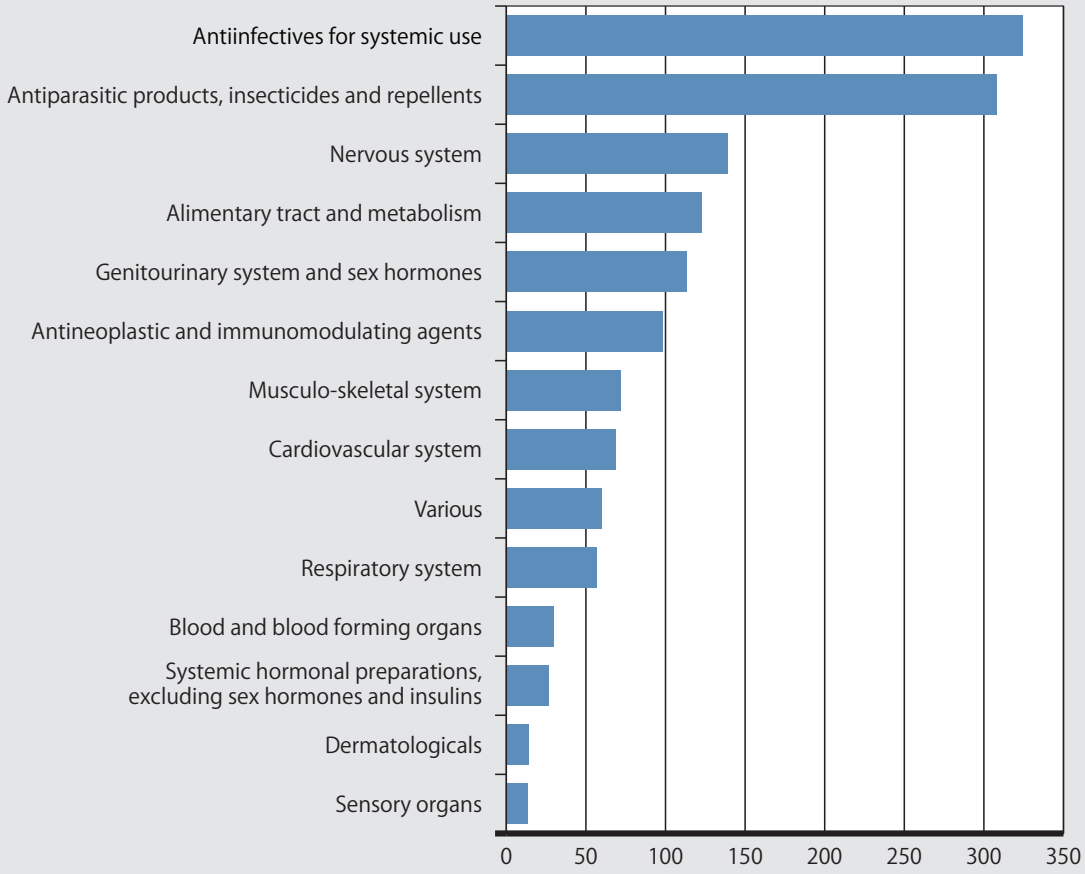
WHO's Global Surveillance and Monitoring System (GSMS) is an organization with the aim of raising the quality of survey reports regarding substandard and falsified medical products and preparing data that can be reflected in policies. There have been around 1500 reports in the four years between 2013 and 2017.

According to the analyses of these reports, the status of substandard and falsified medical products can be summarized as follows.

- **They exist in all regions of the world. As per the other advanced nations, there are reports of substandard and falsified medical products from West Europe and North America. It is impossible to escape the threat of substandard and falsified medical products in any country in the world.**
- **Incidents are discovered in proportion to the amount of surveys implemented (and number of trained surveyors). In other words, it can be postulated that current reports are the tip of the iceberg.**
- **Reports are widely distributed, not only among anti-obesity pharmaceuticals and erectile dysfunction (ED) pharmaceuticals, but also vaccines, general antibiotics, anti-malaria pharmaceuticals, and anti-cancer pharmaceuticals (Figure 1). The large number of reports on anti-malaria pharmaceuticals is due to the focus of surveys performed by the Global Fund to Fight AIDS, Tuberculosis and Malaria, which is estimated to have a large impact.**
- **Media reports are biased towards well-known patented products; however, both patented products and generics are the target of substandard and falsified medical products.**

3) Translation of the WHO Report, *WHO Global Surveillance and Monitoring System for substandard and falsified medical products.* Geneva: World Health Organization; 2017. The translation was not an official one by the WHO. The publication of an original English version is planned.

Figure 1: Reports to the WHO GSMS based on Anatomical Therapeutic Chemical (ATC) classification system (2013-2017)



(Source: WHO Global Surveillance and Monitoring System)

(2) Case Reports (Excerpt)

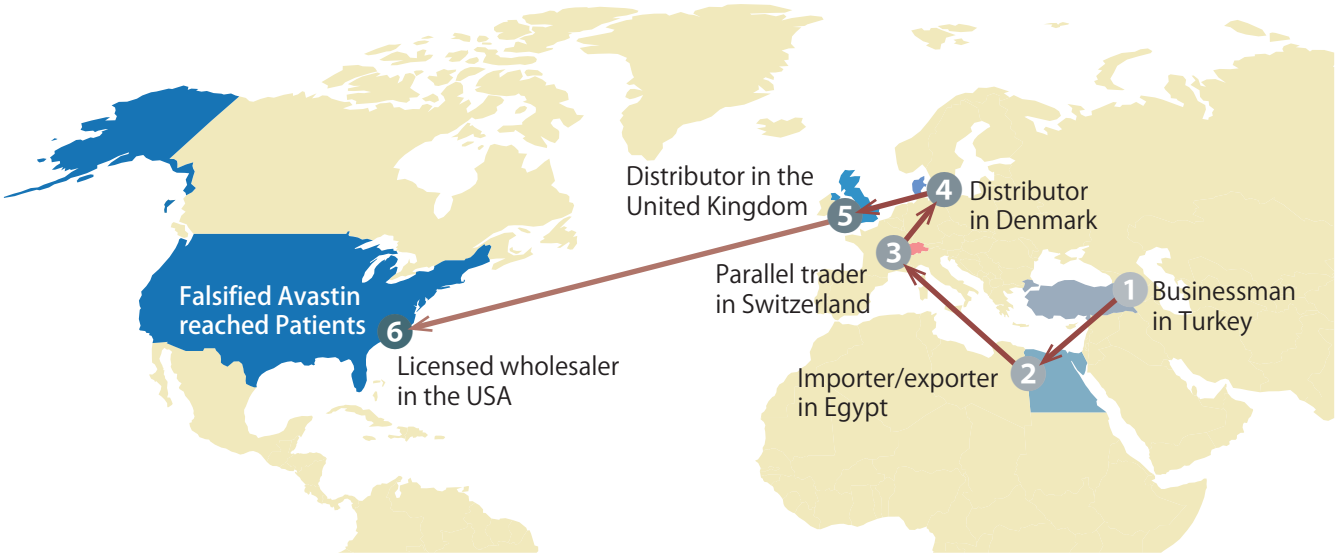
Cases of substandard and falsified medical products can be broadly classified into the three groups below.

1) Where access to high-quality, safe, effective pharmaceuticals is limited

Where a pharmaceutical is not covered by insurance, the price of the pharmaceutical is a crucial problem to the patient. In November 2011, the FDA of the US eliminated Avastin from the approval list for breast cancer patients, which resulted in loss of reimbursement for several types of insurance; however, the needs of the patients remained unchanged. Three months later, the FDA reported that 19 physicians in the US had obtained falsified Avastin pharmaceuticals. The distributors were official pharmaceutical wholesalers in the US and were providing the pharmaceutical 500 dollars cheaper than the official per administration price for the US. Upon testing, however, no Avastin components were detected in the vials at all. The distribution route for these falsified medical products is shown in Figure 2. The complication of the distribution routes and the involvement of many countries is evident.

The restriction to access of pharmaceuticals is not only due to price. There are also cases where lack of stock during natural disasters, and the like, as well as delays in manufacturing, have become causes of falsified medical products entering the market.

Figure 2: Mapping the Supply Chain of Falsified Avastin



(Source: WHO Global Surveillance and Monitoring System)

2) Where there are poor governance standards, such as poor ethics in hospitals and pharmaceutical dispensaries or corruption in the public sector

It is necessary for the buyer of a pharmaceutical to check the reliability of documentation; however, there are cases where such simple procedures are not being performed. When packaging states that manufacturing is performed in an advanced country, there is a tendency towards assuming security, but in West Africa in 2013, it was found that a French herbal company without a pharmaceutical license manufactured a low-efficacy anti-malarial pharmaceutical. Low-efficacy anti-malarials risk generating resistant microbes, which requires extreme caution. In addition, in Bangladesh in 2016, after purchasing vaccines for yellow fever from a man posing as a supplier of the Pasteur Institute, it was found that the vaccines had an expiry date that differed from vaccines of the same lot number. The supplier company did not exist, and the product was contaminated with bacteria.

3) Where techniques and ability to assure manufacturing and quality controls or distribution standards are limited

An issue in some regions is that, not only are manufacturing techniques poor, but the nation is unable to perform accurate testing or identify impurities. Even if a protocol is established, it will be ineffective if the budget is insufficient or the staff incapable of correctly adhering to it. In Pakistan in 2011, lax manufacturing standards lead to contamination of a cardiac pharmaceutical with an anti-malarial, leading to the death of 200 people and the hospitalization of 1000. In addition, large variations in the paracetamol content of pills and contamination with anti-epilepsy pharmaceuticals were found in the Democratic Republic of the Congo region in 2014, leading to reports of hypotension-related fatigue and nausea in many patients.

Chapter 3 Regulations and Market Initiatives regarding Traceability

The EU and the US formulated new regulations in 2011 and 2013, respectively, as a way of detecting substandard and falsified medical products entering into the supply chain and of preventing use of these by patients. Spurred by the distribution of falsified Harvoni combination tablets in January 2017, Japan implemented revisions to items of the ministerial ordinances to ensure immediate responses to such issues and prevent the recurrence of falsified products entering into the supply chain. A draft revision of the *Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices* (hereafter the "*Pharmaceuticals and Medical Devices Act*") was also presented to the Diet.

The records regarding the EU and US in this chapter are based on the interviews held during the survey (September to October, 2018).

1. EU

(1) Overview of the Falsified Medicines Directive (FMD)

1) Background

The EU grants the free distribution of pharmaceuticals between member countries by principle, so parallel importing[4] occurs frequently, leading to an increased risk of substandard and falsified medical products emerging. If a unique traceability system is implemented in each country to prevent substandard and falsified medical products from entering into the supply chain, this regulates distribution within the area, thereby increasing the cost of the supply chain.

Therefore, in 2011, the EU formulated rules unified across the 32 countries of Europe, called the FMD, and implementation by February 9, 2019 was made a requirement.

2) What is the FMD?

- **Overview**

  The FMD requires that pharmaceutical companies ensure the below steps for pharmaceuticals at the sales package.

  - **Two-dimensional barcodes (including product codes, lot numbers, expiry dates, and random numbers)**
  - **Anti-tempering device (that make it clear whether a package has been opened)**

  Pharmacies check for authenticity using a barcode when handing pharmaceuticals to patients.

- **Wholesaler barcode checks**

  Barcode checks are required in intermediate distribution stages for the following two cases.

  - **The product if not directly supplied from a manufacturing or Marketing Authorization Holders (MAH). This includes parallel importing.**
  - **The product is returned by another distributor or a pharmacy.**

  Transfer within the same wholesaler or between distribution centers of the same wholesaler does not require such checks (Figure 3).

4) Parallel importing: The importing of a foreign pharmaceutical by importer with an official contract where such importing is performed via a different route from the official route. In Europe, the pricing of pharmaceuticals varies by country, so there are cases where a pharmaceutical is imported from a country where the price is lower.

Figure3：Wholesaler's Responsibilities under FMD

(Source：GIRP)

- **Barcode checks and revocations**

  Barcode checks display unused genuine products as "active," allowing them to be dispensed.

  Dispensation is prohibited if any other message（"already been dispensed," "recalled," "withdrawn," "stolen," "locked," etc.）is displayed.

  By decommission of the product, data on that product is treated as "already been dispensed."

  Reversing a decommissioned code to the active state is possible if done by the same person at the same branch within 10 days of providing to the patient, if the product is within the expiry date and not recalled or stolen.

- **Data storage**

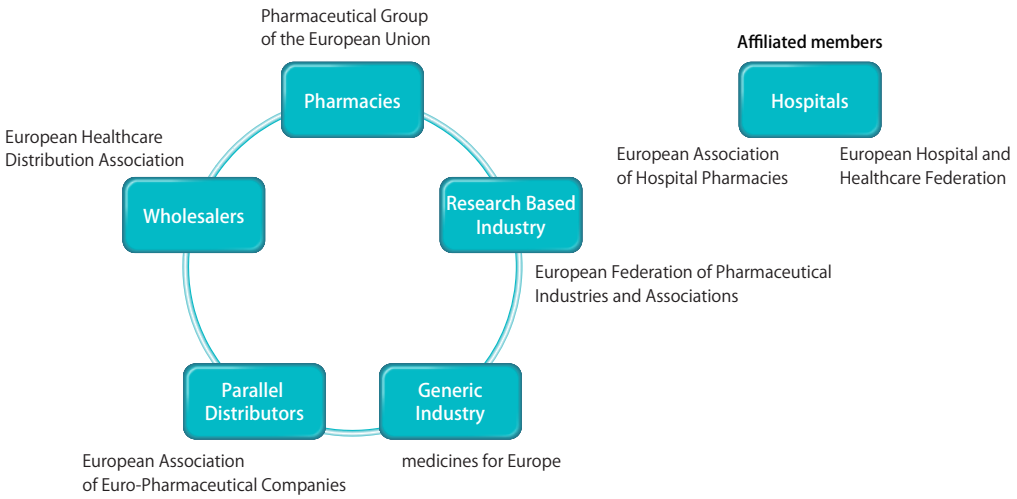
  Under the supervision of each member nation, the National Medicines Verification Organization（NMVO）stores key data and query[5] points.

  The European Medicines Verification Organization（EMVO）stores linked data on new and old lot numbers for parallel-imported products, and queries and information from when a unique identifier（UI）is checked or decommissioned across national borders.

- **Operating methods**

  A Stakeholder model is adopted, where management is operated by non-profit organizations of concerned parties, including pharmacy organizations, wholesaler organizations, and pharmaceutical company organizations, at either the country or EU level（**Figure4**）.

Figure4：Stakeholder model in FMD



5）Query: A request for processing by searching a database to extract information that meets specified conditions.

(Source：GIRP)

(2) Market Initiatives (Data from Interviews)

1) Current progress

At present (September 2018), preparations, such as changes to infrastructure and packaging, are progressing steadily and are already attaining results in some countries. However, despite having adopted the system of two-dimensional barcodes for pharmaceuticals, a six-year deferral for the actual checking of barcodes at pharmacies has been granted to Italy and Greece.

2) Merits for pharmaceutical wholesalers

The system aims to protect citizens and patients from falsified medical products and takes a practical, risk-based approach according to this goal. One of the merits of this from the perspective of the pharmaceutical wholesalers is that it lessens the burden of data checks on pharmaceutical wholesalers during the distribution process.

For wholesalers, data checks during the distribution process are not mandatory except for some cases, such as parallel importing and the return of products; however, the ability of obtaining lot number and expiry date information is a merit from a quality control standpoint.

3) Issues

- **Different progress between countries**

  Although all pharmacies must be aware of the system in February 2019, there are cases where training for related parties and pharmacies has fallen behind.

  While the management and operations are conducted by non-profit organizations, because the relationships and power of organizations differs in each country, there are differences in the progress of each country. Germany leads in the preparations. The need to assist slower countries has arisen.

- **Costs**

  The investments made by pharmaceutical companies are considerable. Pharmacies also each bear the burden of costs for connecting to the National Medicines Verification System (NMVS). Generally, financial assistance is poor.

- **Data ownership**

  From the perspective of recovering their investment costs, pharmaceutical companies have made moves towards capitalizing on the system for marketing. However, the FMD has, from the outset, prohibited use of the data beyond the prevention of falsified medical products, including at the inventory level.

- **Informing hospitals**

  The major players in the system are the pharmaceutical companies and pharmacies; however, given their handling of pharmaceuticals, hospitals must also use the system correctly. Despite this, there are issues with delays in informing hospitals of the system.

  Since hospitals purchase directly from pharmaceutical companies, their only responsibility is the decommissioning of the product. The decommissioning does not have to be at the time of use, but can be done anytime after acquisition. To simplify the procedures for hospitals, a review is underway to decommission the product at the crate level rather than the package.

4) Suggestions for Japan

The European traceability system only checks when there is a risk of falsified medical products, is of low cost to society, and is practical.

2. US

(1) Overview of the *Drug Supply Chain Security Act* (DSCSA)

1) Background

In the US, PTP packaging, and the like, is commonly performed by repackaging companies, and there also exist online pharmacies. These are both causes for substandard and falsified medical products entering into the supply chain.

While each state used to implement its own regulations, the DSCSA was established in November 2013 as a nationwide regulation.

2) What is the DSCSA?

- **Overview**

  Ethical pharmaceuticals should be affixed or imprinted a two-dimensional bar code that includes the product code, lot number, expiry date, and a random number to electronically manage the record of each transfer of ownership in the supply chain. The system is being established in a stepwise manner, to take 10 years since the act was established on November 27, 2013.

  In January 2015, as the act came into effect, the ePedigree laws[6], which had been formulated by each state, were nullified.

- **Data management across the whole supply chain**

  Since January 2015, the following data is provided to the next owner for each transfer of ownership accompanying the transfer of pharmaceuticals in the supply chain in the US. Data is stored for six years.

  - **Transaction Information (TI) : Product name, strength and dosage form, container size, product code, lot number, transaction date, and the names and addresses of both parties to the transaction, etc.**
  - **Transaction History (TH) : The transaction information for each prior transaction going back to the manufacturer of the product**
  - **Transaction Statement (TS): Records of businesses transferring ownership (either on paper or electronic media; records that the business is certified according to the law, that the product was received from a certified business, etc.)**

- **Role of each party involved**

  The deadline for conformance to the affix of two-dimensional barcodes (including the product code, lot number, expiry dates, and a random number) at the sales package by pharmaceutical companies was November 27, 2017 (with repackaging companies having a deadline one year later), and interoperable labeling on dispensing package unit (in the US, bottle preparations are common) will be mandatory by November 2023.

  The management of data at the lot level will be mandatory for pharmaceutical wholesalers and pharmacies from November 27, 2019 and November 27, 2020, respectively.

Through the above, traceability will be possible throughout the supply chain from November 2017 for the sales package, from November 2020 for the lot level, and from November 2023 for the dispensing package.

- **Pharmaceutical wholesaler and 3PL licenses**

  Until November 27, 2015, the FDA prepared federal standards for pharmaceutical wholesaler and 3PL[7] licenses.

(2) Market Initiatives (Data from Interviews)

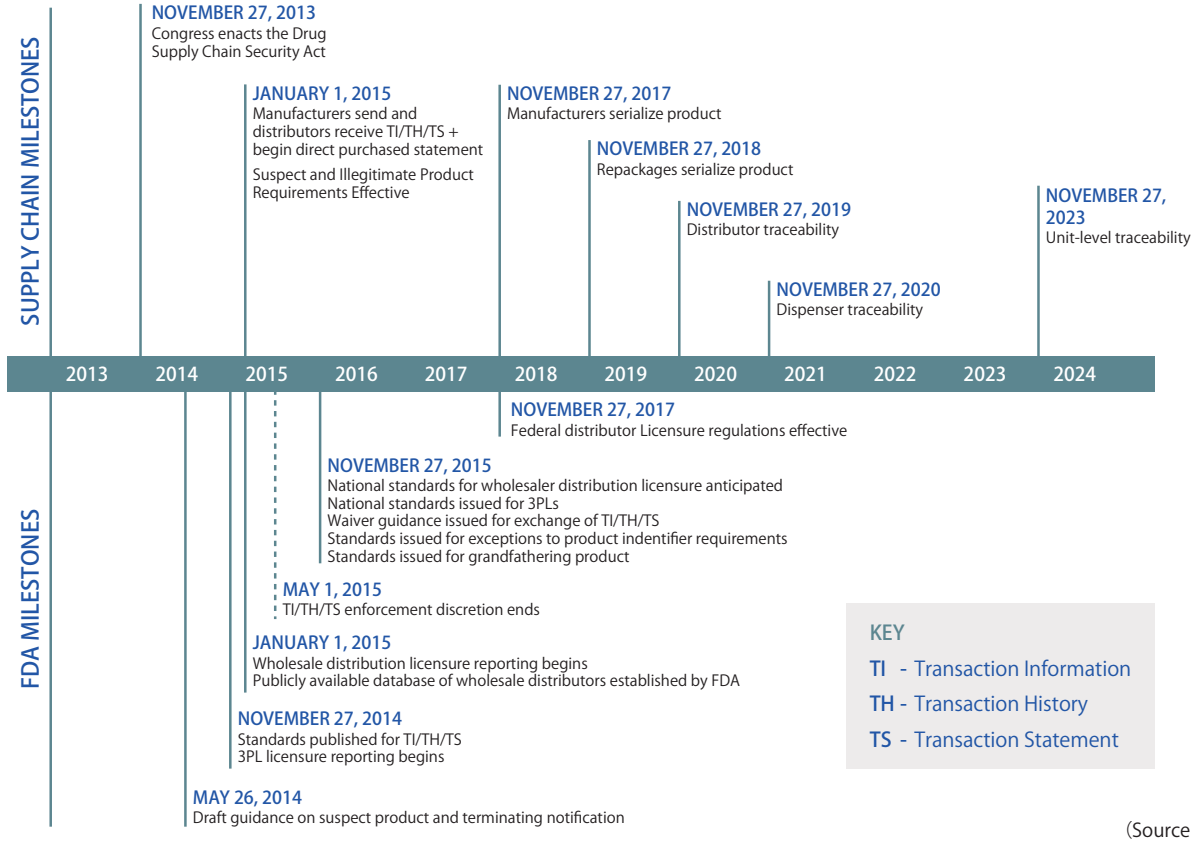
1) Current progress

The system is being established in a stepwise manner from the upstream to downstream systems until November 2023 (**Figure 5**). As of October 2018, pharmaceutical companies and repackaging companies were labeling the packaging of the smallest sales package with two-dimensional barcodes, and pharmaceutical wholesalers were updating their barcode reading hardware.

However, preparations of the guidelines by the federal government are lagging by one to two years. Consequently, companies are making decisions independently, with the HDA, an industry organization, having produced its own guidelines.

With regard to the downstream processes, generally little progress has been made in handling and educating pharmacies; however, large pharmacy chains, such as Walgreen, have already completed implementing platforms in accordance with the DSCSA.

Figure5: Federal Implementation timeline of DSCSA



(Source：HDA)

6) ePedigree Law: A law that required the traceability of all pharmaceuticals in the US, which was managed by each state.
7) 3PL (3rd Party Logistics): The outsourcing of all or part of logistics operations, or the vendors thereof.

2) Merits for pharmaceutical wholesalers

The differing, patchwork-like regulations of the 50 states have been unified by the new law, increasing the integrity of the US supply chain.

In addition, it is possible to give the data generated through the DSCSA practical applications. Proposed uses of this data include not only efficiency of handling of returned products using lot numbers, but, in the future, the pharmaceutical industry may use it to address the opioid crisis[8], reduce costs, and suppress fraud.

3) Issues

- **Delays in establishing guidelines**

  The process for realizing the system has not been stated explicitly, which has impeded progress.

  In particular, due to the delays in issuing guidelines for standardizing state licenses for wholesalers and 3PL, the states' regulations have partially taken precedence, lessening the intended impact.

- **The large amounts of data**

  TI, TH, and TS data must be stored for six years, necessitating that the pharmaceutical wholesalers store a large amount of upstream and downstream data.

- **Complicated systems**

  The interoperability of data, the handling of two-dimensional barcodes, and establishing the system for checking for saleable returns was more complicated than originally expected. Preparing guidelines regarding saleable returns is requiring considerable effort by the HDA.

- **Informing medical institutions and pharmacies**

  This is the biggest challenge for 2020 onwards, and it is foreseeable that there will be cases where the two-dimensional barcodes cannot be read. Issues in the actual implementation, such as a mismatch in the period for updating the master product, will need to be handled in a meticulous way.

- **Informing manufacturing outsourcers and repackaging companies**

  To avoid such incidents as data being carelessly overwritten, it is necessary that the significance of the system is sufficiently understood.

- **Communication between the federal government, state government, and pharmaceutical industry**

  For the system to be implemented in society, it is necessary for a dialog to be established on scenarios, expectations, and issues in actual implementation with relevant government bodies, particularly with the FDA. Those in state and regional medicines regulatory authorities must sufficiently understand the significance of the DSCSA.

4) Suggestions for Japan

When establishing systems related to pharmaceutical traceability, the following points require particular attention.

- **Ensuring a reasonable implementation timeline that clearly describes objectives and leverages**
- **The establishment of a forum for industry stakeholders to discuss implementation scenarios and explore the best way to use various standards**
- **That designs are made with an understanding of the diversity of the members of the supply chain**
- **The maintenance of close relationships among affected parties and with the regulatory agency**

3. Japan

(1) Results of the Survey by the Committee to Investigate Proper Measures Against Distribution of Counterfeit Prescription Drugs

In light of the 2017 case of the distribution of falsified Harvoni combination tablets, the Committee to Investigate Proper Measures Against Distribution of Counterfeit Prescription Drugs began reviewing countermeasures in March of the same year. Based on the interim summary by the committee (published in June 21, 2017), a revision to the ministerial ordinances was made for matters deemed to require an immediate response, and was officially declared on October 5, 2017 before being implemented on January 31, 2018.

Including the contents of the revisions to the ministerial ordinance, the main responses based on the interim summary are as shown below.

- **Elimination of "highly confidential" transactions (where strict confidentiality of the transferor is stipulated)**

Transaction partner's address, contact details, lot number, and expiry date were added to the items that must be entered in records when handing over or receiving pharmaceuticals. In addition, recording of the documents presented to confirm the name, address, and contact details of the transaction partner was also made a requirement. This aimed to make transaction records accurate and ensure traceability, prohibiting transactions that insist on "strict confidentiality." Moreover, pharmaceutical wholesalers must store these documents for three years from the date of their recording.

Furthermore, from the standpoint of ensuring the ability to follow up on transactions, the obligation to record and store, on a per-office basis, the movement of pharmaceuticals between offices of a single pharmacy company was added.

- **Clarification of rules on the marketing and conferring of opened pharmaceuticals**

Previously, there were no general rules for marketing and conferring of opened pharmaceuticals (divided selling); however, it was made an obligation to express the name, address, and other relevant information of the party that opened the pharmaceutical products.

Moreover, when dispensing to patients at the sales package, it was made necessary to establish measures to ensure that it was clear from external inspection that the product had been dispensed, in order to ensure that dispensed pharmaceuticals did not re-enter the supply chain.

- **Clarification of rules for cases where pharmaceuticals of dubious quality are identified**

It was determined that detailed procedures should be clearly explained in work manuals. Also, the requirement for appropriate management by managing pharmacists was clarified.

The committee focused discussions on issues left out of the interim summary and, in their final summary (published on December 28, 2017), presented a way to proceed from the perspective of preventing the recurrence of falsified products being distributed with regard to five items of examination (https://www.mhlw.go.jp/file/05-Shingikai-11121000-Iyakushokuhinkyoku-Soumuka/0000190025.pdf).

8) Opioid crisis: In the US, the overconsumption of prescription opioid analgesics is becoming a social problem.

(2) Discussions towards Revision of Systems including the *Pharmaceuticals and Medical Devices Act*

An examination into reviewing the *Pharmaceuticals and Medical Devices Act* was started in April 2018 from the perspective of furthering appropriate regulatory systems that include fully-fledged security measures founded in the state of globalization and advancing pharmaceutical and medical device technology. Details directly linked to pharmaceutical distribution included revisions to the methods of providing package insert information, improving traceability, and regulations regarding wholesale marketing vendors. The bill was submitted to the Diet in 2019.

(3) Barcode Labeling

Japanese traceability measures include expanding the scope of labeling as an effective step for pharmaceutical security, such as for the retrieval of pharmaceuticals and prevention of pharmaceutical mix-ups in hospitals. Recently, it has been reaffirmed that barcode labeling is an effective method for pharmaceutical companies, and the like, to appropriately fulfill their duties with regard to the security as the supply of generic medications increases.

A notification on August 30, 2016 increased the scope of the required labeling for new barcodes (product codes, expiry dates, manufacturing number or manufacturing symbol, and quantity [only for the bulk package]), making it necessary to express this on all ethical pharmaceuticals at the sales package and bulk package (specified biologically-derived products are of the dispensing unit). The implementation of this will be made mandatory by April 2021.

(4) Next-Generation Electronic Data Interchange (EDI) System: PEDIAS

The next-generation EDI system, PEDIAS, is a data exchange system specialized for ethical pharmaceuticals. It is useful not only for increasing the efficiency for pharmaceutical wholesalers and medical institutions in the future, but for ensuring security by consistently managing data from ordering to payment.

The Japan Pharmaceutical Wholesalers Association started demonstrations of PEDIAS in April 2017.

Features of the new data exchange system (Pharmaceutical Electronic Data Interchange Advanced System: PEDIAS)

1. It is possible to send and receive data that is unified among all dispensing pharmacies.
2. It is efficient due to being operated by a single systems company.
3. It is limited to only the data items required for transactions for ethical pharmaceuticals.

Chapter 4

Status of GDP

In general, good distribution practices（GDP）are policies that aim to maintain the quality of pharmaceuticals and the integrity of the supply chain through the pharmaceutical distribution process. International standards include the PIC/S GDP guidelines prepared in June 2014 by the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme（PIC/S[9]）, a global organization of pharmaceutical inspection authorities. The guidelines were created with the intent that they form the basis for pharmaceutical distributors and related vendors to prepare special rules that are matched to their various needs. As of July 2018, GDPs have been implemented by 41 countries around the world; however, their utilization differs between countries and regions.

1. EU

It was relatively early that GDPs appeared in the EU, with the *Guidelines on Good Distribution Practice of Medicinal Products for Human Use* being published in 1994. Through a large-scale revision in March 2013 and additional revisions in November of the same year, the document reached its current version, the *Guidelines of 5 November 2013 on Good Distribution Practice of Medicinal Products for Human Use*. The PICS/S GDP guidelines were produced upon the bases of the EU GDP.

This affects pharmaceutical wholesalers, with the following two items having a particularly large impact（as found in interviews）.

- **Since February 2019, it has been necessary for pharmaceutical wholesalers to print the lot number and expiry date on delivery documents sent to pharmacies（can be done electronically）.**
- **Temperature control has become mandatory for warehouses and delivery vehicles.**

2. US

The US has not produced independent guidance with regard to GDP. Standards for the storage, shipping, delivery, transport, and the like, of pharmaceuticals and raw materials for pharmaceuticals were listed under〈1079〉*Good Storage and Distribution Practice for Drug Products, 2015,* formulated by the United States Pharmacopeial Convention.

3. Japan

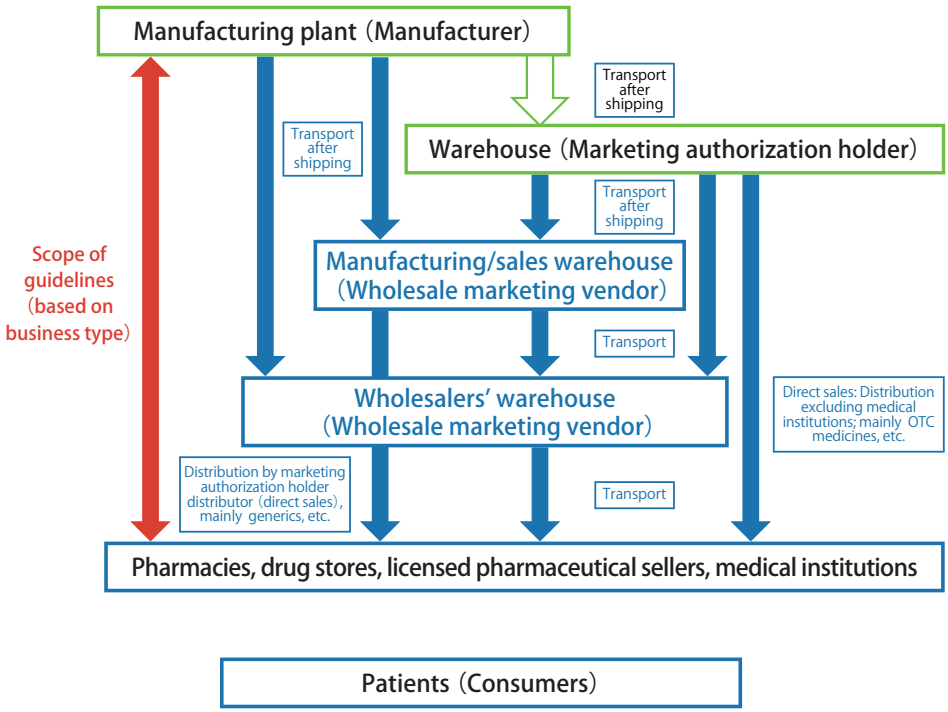
Members of the Japan Pharmaceutical Wholesalers Association have managed their operations according to the Japanese Good Supplying Practice（JGSP）, which was formulated by the association in 1975, as the policy for quality control and stable supply of pharmaceuticals. However, having officially joined the PIC/S in July 2014, guidelines on good distribution practice（GDP）of pharmaceuticals were published in December 2018 as initiatives to formulate Japanese GDPs that conformed to the PIC/S GDP.

9) PIC/S: An organization that prepares policies related to pharmaceutical GMPs and, as well as striving for global consistency, it continues to act to drive progress in mutual inspections between regulatory authorities. As of March 2019, 52 authorities（in 49 countries and regions）throughout Europe, America, Asia, Australia, and the like, were members and form a framework for global standards in the field of pharmaceutical GMPs.

The guidelines were intended to prompt autonomous efforts by wholesale marketing vendors and marketing authorization holders, and their scope includes duties related to the stocking of pharmaceuticals, their storage, and provision from shipping of a pharmaceutical in the marketplace until it reaches pharmacies, drug stores, and medical institutions（**Figure 6**）. Consequently, the "Imports and Exports" section of the PIC/S GDP guidelines are absent from the Japanese version.

Through its members, the Japan Pharmaceutical Wholesalers Association is currently facilitating the improvement of the JGSP according to the GDP guidelines.

Figure6：The Scope of Japanese GDP guidelines



（Source：MHLW）

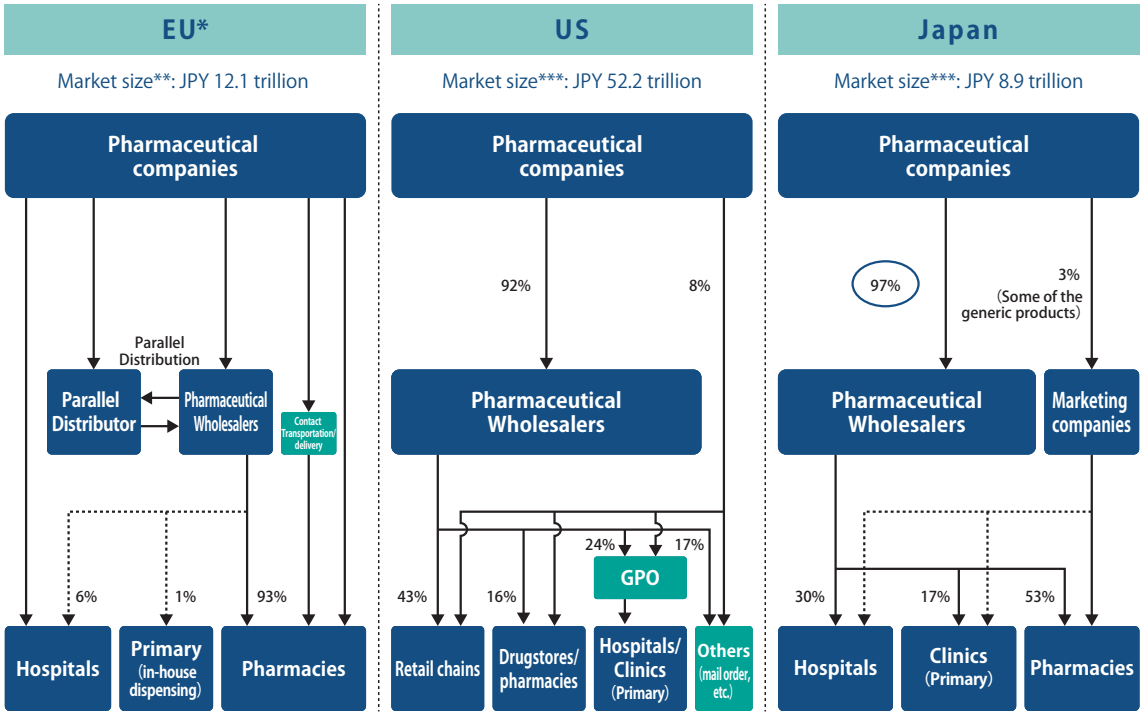
Chapter 5

Discussion

1. Evaluation of the Structure of Pharmaceutical Transactions

As shown in Figure 7, the distribution of EU, US, and Japanese pharmaceuticals has structural differences, and there are differing stances on regulation. It is difficult to produce a common system for traceability across the EU's member countries with differing medical systems and regulations, and the US is also a country where regulations differ by state. In Japan, regulations are implemented uniformly nationwide, so it is necessary to keep in mind the differing foundations for regulations.

Figure7：Distribution Flows of Pharmaceutical products in EU, US, and Japan



*UK, Germany, France, Italy, and Spain
**Total sales through pharmaceutical distributors in 2015
*** Total sales through pharmaceutical distributors in

(Source：JPWA, HDA Research Foundation, Institute for Pharma Economic Research)

Although a significant problem in the EU is that parallel importing leads to substandard and falsified medical products entering into the supply chain, parallel importing is not, of itself, considered in a negative light there. A public association for parallel importing (the European Association of Euro-Pharmaceutical Companies) participates in the management of the FMD as a member of the EMVO. In addition, EU pharmaceutical transactions are performed under the assumption of parallel importing occurring, and pharmacies in Germany and the UK are required to purchase over a certain amount of pharmaceuticals through parallel importing to reduce costs, which increases the complexity of substandard and falsified medical products entering into the supply chain in the EU.

In the US, there have been different regulations between the states. The interviews performed for this report found that considerable investment would be required to unify regulations across the country once they were established.

Conversely, Japan's official pharmaceutical transaction system is single-layered and operates under unified, nationwide regulations. In comparison with the EU and the US, it was reconfirmed that Japan's basic distribution structure was effective in preventing substandard and falsified medical products from entering into the distribution channels.

2. The Issue of Returned Products

The EU's FMD requires wholesalers to make data checks when products are returned. In the US, preparing guidelines for the return of products, particularly returned products that can be resold, is requiring time.
In other words, it was found that Japan is not the only country to have issues with handling returned products.

3. Precautions with Regard to Planning Systems

The US system started with a federal announcement based on lofty ideals; however, there was a considerable gap between this and the actual real-world situation. Moreover, it could be surmised that the delay of the government in publishing guidelines is causing considerable concern for those actually involved.

The end of the section on the US in Chapter 3 contains four suggestions for Japan from those in charge of the HDA: “formulation of a logical implementation plan,” “the necessity of public debate among stakeholders,” “understanding the diversity of the supply chain,” and “coordination between industry and the regulating authorities.” These are points that are well worth giving sufficient consideration when planning future systems for pharmaceutical distribution in Japan. In distributing the Japanese version of the GDP guidelines published in 2018 and establishing the next-generation EDI system, it is necessary to drive progress in each of the stages of discussion, planning, and implementation while making concerted efforts to share the purpose of these with those concerned.

4. Pharmaceutical Transactions Using the Internet

Illegal online pharmacies are becoming a global problem.
In the EU, there is an online pharmacy certification system, and patients can purchase pharmaceuticals online. The websites of registered pharmacies display a logo that is common throughout the EU（https://buysaferx.pharmacy/find-a-safe-online-pharmacy-eu/）.

The US also has online pharmacy registration and checking systems（LegitScript, .Pharmacy, etc.; https://buysaferx.pharmacy/find-a-safe-online-pharmacy/）.

However, unless the patients that buy the pharmaceuticals actually perceive the problem and select registered pharmacies, it will be impossible to eliminate the risk of falsified medical products falling into their hands. Another issue is that, on the Internet, even if the displayed language is Japanese, the site may actually be managed from overseas, making it impossible to control with regulations in a single country or region.

Chapter 6

Proposals

Despite the assumption that the ethical pharmaceutical distribution systems and backgrounds behind their regulation differ for each country, the state of security and quality assurance in the distribution processes for pharmaceuticals in the EU and US provides suggestions for appropriate distribution systems and regulations for Japan in the future and sheds light on the problems Japan will share with these regions. Based on the discussion given in Chapter 5 and the environment in which Japanese pharmaceutical distribution is being performed recently, we make the following proposals.

1. Maintenance of Japan's Highly-Reliable Distribution System

Japan has a "single-layer" distribution system for ethical pharmaceuticals, where pharmaceutical wholesalers directly provide pharmaceuticals to medical institutions and pharmacies from the marketing authorization holders. Given that this simple distribution system has contributed to the prevention of substandard and falsified medical products entering into the supply chain, it is necessary to maintain the distribution system in the future, in coordination with a wide range of medical professionals.

The cause of the distribution of falsified Harvoni combination tablets in 2017 was the existence of "multi-layer distribution" besides pharmaceutical wholesalers that acted as an intermediary between the marketing authorization holders and the medical institutions and pharmacies. Moreover, hotbeds for the distribution of substandard and falsified medical products are the re-labeling process during parallel importing in the EU and repackaging in the US. It is evident from both Japan's experiences and precedents overseas that the more intermediaries that exist between manufacturers and the medical institutions and pharmacies, the greater the risk of substandard and falsified medical products entering into the supply chain.

In addition, since the management of shipping information with lot numbers was made mandatory in 2018, the security of distribution via wholesalers has become even more reliable in Japan.

2. Enhancing Efforts to Deal with Returned Products

As was made clear by the examples of the EU and US, since the return of products can lead to substandard and falsified medical products entering into the supply chain, there is desire for a solution to this issue in Japan as well. One problem is that returned products that can be resold are not always returned to the pharmaceutical wholesalers in their original state.

With regard to pharmaceutical sealing methods, a notification by the Director General of the Pharmaceutical Safety and Environmental Health Bureau of the Ministry of Health, Labour and Welfare in August 2018 urged marketing authorization holders to take rapid measures to ensure that specifications prevent one from easily returning a product to its original state and prevent the insertion of foreign materials into the packaging through any openings; however, responses to this have as yet been insufficient.

The management of temperature during the pharmaceutical distribution process is also thoroughly covered in the Japanese GDP guidelines; however, storage at medical institutions and pharmacies is currently left up to the managers thereof. As for receiving returned products, it is necessary to enforce temperature management at medical institutions and pharmacies, and ensure thorough temperature records be made.

3. Balance between Tightening and Easing of Regulations

From the standpoint of reducing social security expenses, current medical measures focus on limiting public medical expenses and improving productivity through ICT utilization; in other words, there are two trends of tightening and easing of regulations. Over-tightening and over-easing of regulations can both threaten the health of citizens, resulting in the increase of the social costs. It is necessary to establish policies while keeping this in mind. Currently, Japan has built a society where ethical pharmaceuticals can be used with the peace of mind that they are safe. As well as the contribution of the single-layered distribution system to this, it can also be said to be the effect of appropriate public regulation. It is important to learn from precedents from overseas that, when such security is lost, restoring it comes at considerable social cost.

In Japan's current universal health insurance program, there are no cases where access to pharmaceuticals listed in insurance is restricted depending upon the type of medical institution or medical insurance. However, overseas, there have been reports of cases where changes to the reimbursement system has made access to some pharmaceuticals difficult, thus triggering the entry of substandard and falsified medical products into the supply chain.

Moreover, the implementation of online advice for taking medicine is currently limited to national strategic special zones; however, non-face-to-face pharmaceutical transactions may increase due to future easing of regulations that will increase the prevalence of online advice for taking medicines. It is not necessary to wait for overseas precedents regarding online pharmacies to see that this will become a hotbed for substandard and falsified medical products, rather it is clear from the results of Japanese surveys of ED pharmaceuticals[10] and the like. In this respect, there is a need to further promote attention among the populace.

4. Balance between Globalization and Localization

It is necessary to have safety measures that match the structure of distribution in a region, rather than regulating distribution uniformly. The existence of publicly available documentation to explain the Japanese distribution environment is important for the future handling of global companies. This is a role that the Japanese GDP guidelines and JGSP can be expected to fulfill.

With the establishment of GDPs in each country, not only pharmaceutical wholesalers but pharmaceutical companies are also preparing their own internal GDPs. The global regulation of multi-national companies, however, may not conform to the circumstances of Japan.

For example, in the case of pharmaceutical companies headquartered in the US, regulations on responding to disasters focus on fires, such as wildfires, and require the installation of water sprinklers in warehouses. However, Japanese regulations focus on seismic vibration isolation, and it would be difficult to install water

sprinklers that are activated as soon as a disaster occurs. There will be cases where such environmental differences will require that time be taken to obtain understanding from multi-national companies.

Through this report, we hope for broader awareness of the importance of assuring security and quality in the distribution of pharmaceuticals, and further discussion among those in the field.

10) A combined survey with four companies into falsified ED pharmaceuticals in 2016 found that, of those pharmaceuticals imported via the Internet (importing by individuals), the proportion of falsified ED pharmaceuticals was 40%.

International Comparison regarding Security and Quality Assurance for Pharmaceutical Distribution

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