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INFORMATION SYSTEM FOR TRACEABILITY TO PROTECT PATIENT SAFETY: SOUTH KOREAN SERIALIZATION REGULATION PERSPECTIVE

Jaejong Han and Hyunsoo Kim

Department of Industrial and Management Engineering
Kyonggi University
San 94-6, Iui-dong, Yeongtong-gu, Suwon, Gyeonggi-do 16227, Korea
jayjay.han@gmail.com; hskim@kyonggi.ac.kr

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Abstract. *The pharmaceutical industry plays a significant role in the human life and well-being all over the world and the importance of protecting patient safety cannot be overemphasized. With this purpose in mind, many countries have adopted serialization regulations to ensure traceability and visibility in the pharmaceutical supply chain. While the South Korean government also adopted this regulation in 2011, some very innovative South Korean pharmaceutical companies had already successfully built RFID-based serialization systems. However, patient safety cannot be easily guaranteed without a tight collaboration between government and industry. This study reviews the South Korean serialization regulation and then compares it with the US and EU regulations to verify the feasibility of its original purpose. In a nutshell, despite the application of advanced technologies compared to other countries, the current South Korean regulation is not sufficient to safely prevent patients from bad medicines. The specific system functions regarding this problem are also analyzed and a direction for improvement is suggested.*
Keywords: Pharmaceutical serialization, Traceability, Patient safety, Track and trace

1. **Introduction.** The pharmaceutical industry plays a significant role in the human life and well-being all over the world; due to the increase in the ageing patient population, its market size has enlarged and the environment has become more complex in recent years [1]. The rapid expansion of the global market has led pharmaceutical companies to an exponential complexity increase accompanied by a decreased visibility within the supply chain [2]. In addition, due to the availability of information technologies for online pharmaceutical sales, this phenomenon has allowed criminal activities to thrive in this field [2,3]. Furthermore, by government order or internal quality issues, recall and return managements have become an important part of the supply chain in this industry [4,5]. Because of these complexities, the grey market has emerged and the amount of fake drugs is now growing much faster. The World Health Organization (WHO) has published a report indicating that 10.5% of the medicines in low- and middle-income countries are identified as substandard or falsified (SF) [6-8]. SF medicines can be dangerous and even lethal to patients. Despite the opinion that South Korea is relatively safe in these concerns, even the few cases reported between 2005 and 2018 cannot be ignored [9-12]. To solve the patient safety issue, several countries around the world have started the serialization regulations to ensure traceability of the drug supply chain. Serialization indicates the holistic process and technical system assigning a unique number to each product for its tracking and tracing through the whole supply chain to verify its authenticity. So far, there have been many studies on serialization regulations amongst the US and EU, but studies regarding South Korean regulations have been hard to find [2-6,13-18].

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In this paper, we review the status of the South Korean serialization regulation in the pharmaceutical industry to reach the goals for patient safety. This article is organized as follows. Chapter 1 describes the paper background. Chapter 2 explains the US, EU and South Korean serialization regulations and Chapter 3 analyzes their serialization regulation statuses. Chapter 4 compares and analyzes the status of four major functions of the serialization system between US, EU and South Korea. Chapter 5 summarizes the conclusion of this paper.

2. **Global Serialization Regulations.** Majority of the key pharmaceutical markets around the world, such as US, EU, Turkey, Russia, South Korea, China, India, Pakistan, Jordan, Saudi Arabia, Ukraine, Brazil, and Argentina, are already regulating serialization and implementing this system to secure local supply chains [13,14]. Specifically, multiple regulations and transaction data collections are coming into effect in the big market within the next couple of years, as mandated by US and EU laws.

2.1. **US serialization regulation.** Along with the 2004 Combating Counterfeiting Drugs report, the US Food and Drug Administration (FDA) highly recommended new technologies such as radio frequency identification (RFID) and electronic Pedigree (e-Pedigree) as tools to improve the safety of the drug supply chain [5,15,16]. By 2007, California decided e-Pedigree would be in use within the state and has been pushed several times until 2015 [5]. California's e-Pedigree law was preempted by the Drug Quality and Security Act (DQSA) which was signed into law by former US President Obama on November 27, 2013 [13]. Title II of the DQSA is referred to as the Drug Supply Chain Security Act (DSCSA) and it establishes new federal requirements for drug serialization, transaction documentation and verification. It aims to develop an interoperable electronic system by 2023 for identifying and tracing certain prescription drugs through the US supply chain and to establish national licensure standards for wholesale distributors and third-party logistics providers [17]. The DSCSA mandates a 10-year long series of milestones for each major echelon of the US drug supply chain. With the start of the first milestone on January 1, 2015, all supply chain participants were required to be licensed, and to quarantine and conduct investigations into any suspect product. On that same date, manufacturers, wholesale distributors, and re-packagers began passing specific sets of transaction documents in paper or electronic form along with their shipments every time the ownership changed. By July 1, 2015, the dispensers were told to begin saving the transaction documents they received. The trading documents, also known as 3T (Transaction Information, Transaction History and Transaction Statement), are currently lot-level, but will be turned into package-level electronically by 2023 [14,17]. For the manufacturers, the deadline for placing a unique product identifier on certain prescription drug packages in human- and machine-readable format is November 27, 2017, while the deadline for re-packagers is November 27, 2018. Even though RFID was preferred by the FDA in the early stages, the GS1-based data matrix barcode has been selected as the data carrier due to cost efficiency, several technical issues, and the conflict of interest amongst the stakeholders [5,15,16].

2.2. **EU serialization regulation.** In 2013, the EU Commission enacted the Directive 2011/62/EU, also referred to as the EU Falsified Medicines Directive (EU FMD). The Delegated Act on Safety features was published on February 9, 2016. This part of the EU FMD outlines how the EU shall track and trace medicines via serialization, government reporting, and product verification. Pharmaceutical companies, parallel importers, wholesalers, and pharmacies should comply with this by February 2019 [3,14,18]. In EU, the serialized identification must be printed or attached at the secondary or saleable-unit level. This identification includes product identifier, serial number, lot or batch number, and an expiration date (the same elements in the US). However, an additional element,

the reimbursement number, can be optionally added based on the specific state requirements [14,18]. With the serialization, the marketing authorization holder must submit the product and its market information, including product code, lot or batch number, expiration date, doses per pack, target markets, and serial number, to the European Medicines Verification System (EMVS) [18].

Moreover, point-of-dispensation verification is required by law. In other words, the pharmacy dispensers must verify the product identity prior to dispensation. Although the wholesale distributors in EU do not need to report to the EMVS directly, they must support the end-to-end serialization and compliance reporting by performing risk-based product verification through the supply chain; to do this, they must interrogate the safety features of the product prior to resale when receiving medicines from a supplier or saleable returned products from a pharmacy or wholesaler [18]. The EU FMD also requires anti-tampering technologies to determine whether product packages have been compromised [14,18].

2.3. **South Korean serialization regulation.** In the Republic of Korea, by the Pharmaceutical Affairs Act and the Regulation on Safety of Drug, etc., all finished drugs are given a barcode or RFID and the supply record is submitted to the Korea Pharmaceutical Information Service (KPIS) [19,20]. The Notification on the Use and Management of Drug Barcodes and RFID tags in 2011, amended once again on April 18, 2013, has established new regulations for drug traceability. It specifies their use and management details to achieve cost reduction and efficient history management by building the foundation for the information-based distribution of drugs [20]. By the notification, designated drugs were mandated to expose the expiration date and lot numbers starting in 2012. The same was expected for prescription drugs from 2013. The application of an additional serial number with the GS1-128 barcode on prescription drugs started in 2015. From 2013, the companies employing RFID had to implement the serialization system and the near-real-time supply reporting [19,20]. The South Korean government has been actively encouraging the use of RFID because of its efficient distribution management, resulting in 16 companies (3.5% of 458 companies) using RFID as of 2017 [21]. Starting July 2016, all pharmaceutical manufacturers were required to report item-level supply records daily at the point of shipping, and likewise for the wholesale distributors from July 2017.

3. **Analysis of Three Countries' Serialization Systems Status.** Table 1 analyzes the status of the serialization systems of the US, EU, and South Korea. The US covers the entire supply chain, requires each participant to exchange the product data, and manages the change of ownership to verify so that the bad medicine can be filtered out at each point. On the other hand, the end-to-end verification is adopted in EU, which means that pharmacy verifies the product based on the data provided by the manufacturer

Table 1. Status of three countries' serialization systems

Items	**US**	**EU**	**South Korea**
Coverage	Whole supply chain	End-to-End	Manufacturer and wholesaler
Data carrier for AIDC	Barcode	Barcode	Barcode, RFID
Electronic report to central DB	No central DB, Industry supported	European Hub	KPIS
Data exchange between partners	T3 Documents, Industry used	Not required, but Industry used	KPIS provided, Industry not used
Change of ownership management	Required, Industry used	Not required, but Industry used	Not required, and Industry not used

at the point of dispense, stopping the bad medicine at least from reaching the patient. Even though the EU regulation does not require the wholesalers to report to the central database, they exchange the transaction data with the trading partners to support the pharmacy and perform the risk-based verification.

However, the South Korean regulation is targeting only to the manufacturers and wholesalers. Therefore, pharmacies or hospitals are out of bound and no verification of bad products within the supply chain is required under the current regulation.

Exact data capture and real-time connection to the cyber system are very important factors to gain visibility of the physical products. Therefore, it was advantageous of South Korea to have commercialized the use of RFID and applied it to its system. While most of the wholesalers have already implemented the RFID readers and the barcode scanners in South Korea, we believe that the South Korean government would benefit more if it promoted the use of RFID as planned in the early stage [19]. Moreover, the near-real-time electronic report system also has the merit to track and trace items at the right time. South Korea, however, does not provide any method to check for bad medicine.

In addition, the serialization system is also a very powerful tool for companies to efficiently manage their supply chain as reported in many studies already [3,13,14,18,19]. The companies in the US and EU share their supply chain data in accordance with industry standards supporting serialization regulation and their own work efficiency. South Korean manufacturers and wholesalers should change their minds on the regulation in a positive manner by collaborating more with each other and taking advantage of the internal and shared data. Instead of depending on the current government system, trading partners should exchange data, such as Advanced Shipment Notices, with the help of industry solutions. This way wholesalers can utilize the data at receipt to inspect the products and manage their inventory. Moreover, strengthening the communication between industry and government would give a chance to filter out the hazardous medicines.

4. **Comparing the Four Functions of the Serialization Systems from Three Countries.** The South Korean Ministry of Food and Drug Safety recently ordered a recall of 59 hypertension drugs containing Valsartan. The KPIS provided the information about their locations to the manufacturers but the incomplete and obsolete data hindered their track and recall [23]. In 2013, a similar situation occurred and the rate of unavailable recall for the nonconforming drug was 97.3%. The information shared did not match the actual status of the drug, which led to the failure in tracking them properly [24]. According to KBS, SBS, and other Korean news stations, falsified hypertension medicines were indeed confiscated and there were no ways to blocking them from the supply chain. Unfortunately, a more serious problem occurred when the drugs were taken by a patient [9-11].

In order to prevent these cases from happening, the serialization system is regarded as an important solution and its working mechanism is described in Figure 1 [3-6]. There are four major functions in the serialization system to protect the patient from the bad drugs. ① Track and Trace: all drugs should be monitored while its distribution is in the supply chain. ② Recall Order: Government should order to recall nonconforming drugs. ③ Stop Bad Drug: Bad drugs must not be propagated to the next step of the supply chain as soon as its status is known. ④ Verification or Authentication: all stakeholders including patients, can access the drug data and check if it is not fake, falsified, and illegally distributed.

Table 2 shows how these four functions are implemented in the US, EU, and South Korean serialization systems.

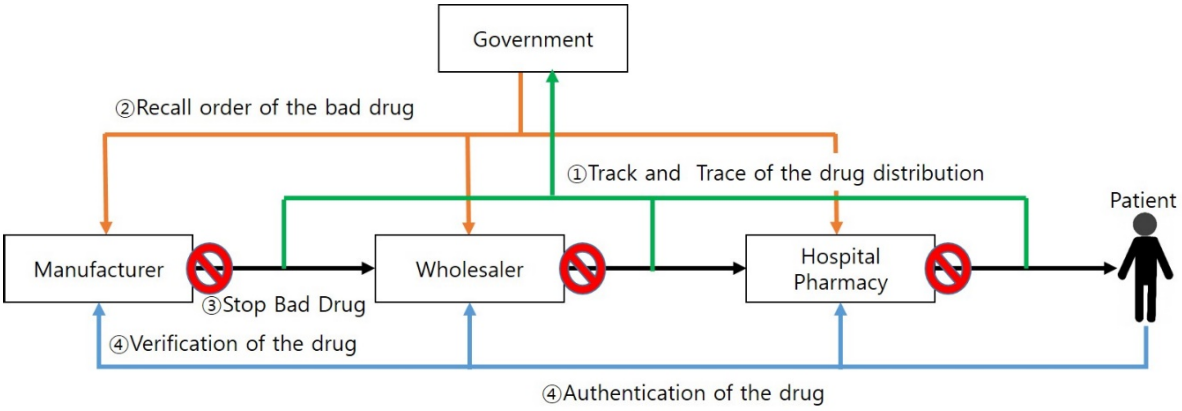

FIGURE 1. Serialization system functions for the patient safety

TABLE 2. Implementation of the serialization system functions in the US, EU, and South Korea

Function	US	EU	South Korea
Track and Trace	By regulation and Industry	Not by regulation, but by Industry	By regulation, but only manufacturer and wholesaler
Recall Order	Transaction Document	Update central DB	Track data provided to manufacturer, if needed
Stop Bad Drug	Transaction validation on change of ownership	Before dispensation	Out of scope
Verification or Authentication	Whole supply chain verification	End-to-End Risk-based	Not yet

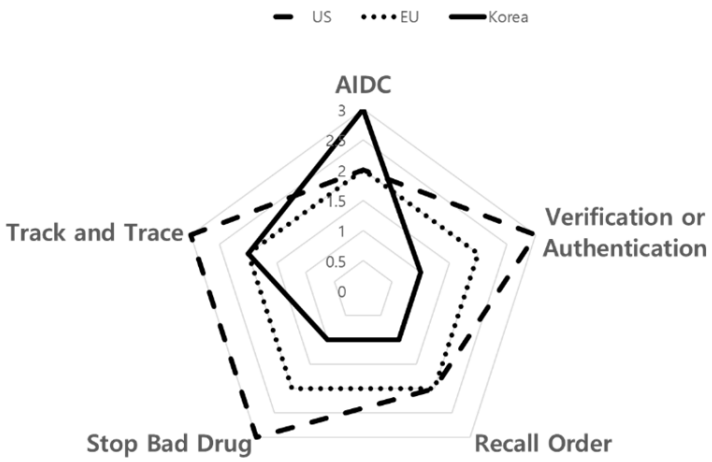

FIGURE 2. Comparison of functions for the patient safety of three countries

Figure 2 summarizes the levels of these four functions along with the automatic identification and data capture (AIDC) technology to compare South Korea's situation to the US and EU. We subjectively defined the rating point of each function according to the criterion of levels in Table 3. South Korea was given three points (satisfied level) in the AIDC category, but only one or two points (dissatisfied or average level) in other categories. This was because the most important stakeholders, the patients, were missing from the scope and there was no method to check or control the supply of nonconforming drugs in

TABLE 3. Rating criterion of levels of four major functions with AIDC of serialization system

Functions	**Satisfied level (Three points)**	**Average level (Two points)**	**Dissatisfied level (One point)**
Track and Trace	Covers whole supply chains	Not whole, but includes important echelon	No T&T
Recall Order	Real-time recall order system	Not real-time, but direct order system exists	No direct order system
Stop Bad Drug	Bad drug check on receipt or shipment by regulation	Bad drug check on receipt or shipment by Industry	No bad drug check
Verification or Authentication	Whole supply chain	At least before dispensation	No Verification
AIDC	1D, 2D barcode, RFID	1D, 2D barcode	1D barcode

the serialization regulation itself. The current South Korean regulation aims towards cost reduction and efficient history management as its goals. This can be accomplished with the current regulation, but in order to achieve the most significant objective in patient safety management, institutional supplementation and industrial efforts will be required together.

Although there are other ways such as Drug Utilization Review (DUR) and recall orders through the websites and public notifications to stop bad drug propagation in the South Korea, the lack of interconnection between the systems and the asynchronous information hinders the possibility of achieving the original mission at the right time. Since the individual interests are different amongst the deputed authorities, the information architecture within the government should be redesigned to integrate all existing systems as well as updated for new missions in the future.

5. **Conclusions.** The importance of public patient safety in the pharmaceutical industry cannot be overemphasized. Several efforts have been made worldwide by pharmaceutical industries and the regulatory authorities for a long time. Many of them agreed that serialization regulation would have been the best option to secure traceability by identifying each product and sharing and managing the exact moving data through the supply chain among all the stakeholders and patients. In this paper we reviewed the major serialization regulations of US and EU and compared them to the South Korean regulation. We also simultaneously examined the issues about patient safety based on actual cases to verify the feasibility of it with the current South Korean serialization regulation.

Despite the many efforts and the application of advanced technologies compared to other countries, the current South Korean regulation is not sufficient to safely prevent patients from bad medicines. This is because the main purpose of the Korean serialization regulation is to manage the distribution performance. Therefore, it fails to establish detailed scenarios for patient safety management. The system for patient safety management is an incompatible system operated by other authorities prior to the serialization system. In addition, the pharmaceutical industry itself is unable to adapt to environmental changes and wants to stay in accordance with outdated practices.

In future works, a deep observation will be conducted into the results of actual RFID usage in implementing the serialization system in South Korea. Big data analysis of accumulated serialized supply chain information will also be performed. A more advanced communication method for collaboration must be studied to block the bad medicines in the market by seamlessly connecting with legacy systems.

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