EVALUATING THE IMPACT OF A SHARED PHARMACEUTICAL SUPPLY CHAIN MODEL TO MINIMIZE COUNTERFEIT DRUGS, DIVERTED DRUGS, AND DRUG SHORTAGES

by

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Abstract

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The pharmaceutical supply chain in the United States of America (USA) is getting complicated and is often not controllable due to a globally open market, increasing online market, and many illegal activities. Consumers who cannot afford to buy high priced genuine products are tempted by easily accessible counterfeit drugs on illegal web site pharmacies in or out of the USA. Many corrupt participants, such as wholesalers or pharmacies in the supply chain, take advantage of weak enforcement and a flawed drug supply chain for financial gain. The public health system and numerous patients are in, or could be in, painful situations caused from pharmaceutical supply chain problems including counterfeit drugs, diverted drugs, and drug shortage. In order to secure the drug supply chain, several solutions have been discussed, including a unit level serialized trace and tracking system, ePedigiree, and more. In this research, current problems and their causes will be discussed, and current solutions with their limitations will be presented. The proposed model, third party centralized integrated system (TPCIS) is presented, which overcomes some of barriers of existing solutions and several simulation models including ePedgiree, drug shortage, and recall models which have been

developed for comparison. The simulation models show how the proposed model may help improve the current problems with public health systems.

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Chapter 1

Introduction

1.1 Background and motivation

When it comes to the security of the pharmaceutical supply chain in the USA, there could be mainly three issues being considered seriously. They are counterfeit drugs, drug diversion, and drug shortage. As the number of those cases has been increasing every year and public health systems and patients' health have been threatened directly by those problems, law enforcement and related industries are concerned and moving forward to secure pharmaceutical supply chain. However, although there have been efforts from all stakeholders, it seems that much more work from the public and industry sectors is needed to reach a consensus. Any partial approaches from private or public sector could increase costs later to be integrated into federal level standards. Related laws passed previously, including Drug Quality and Security Act and California ePedigree law, do not guarantee solving all the problems. In the past, the laws were delayed several times because of the resistance from industrial areas including wholesalers, and it could happen again. Any other but progressive, innovative and systematic approaches to develop and implement alternative solutions should be considered to cope with not only counterfeit and diverted drugs but also the drug shortage problem.

1.1.1 Counterfeit drugs

The World Health Organization (WHO) defines a counterfeit drug as: "A medicine which is deliberately and fraudulently mislabeled with respect to identity and/or source. Counterfeiting can apply to both branded and generic products and counterfeit products may include products with the correct ingredients or with the wrong ingredients, without

active ingredients, with insufficient active ingredients or with fake packaging" (WHO 2008). Counterfeit drugs can hurt patients' health because the fake medication often has no or insufficient active ingredients. Even a breach of confidence of a medication could cause mistrust, not only of other medications, but also in the whole public health system. Based on the WHO Drug Information 2008, 30% of medication in some areas including Latin America, Southeast Asia and Sub-Saharan Africa are counterfeited.

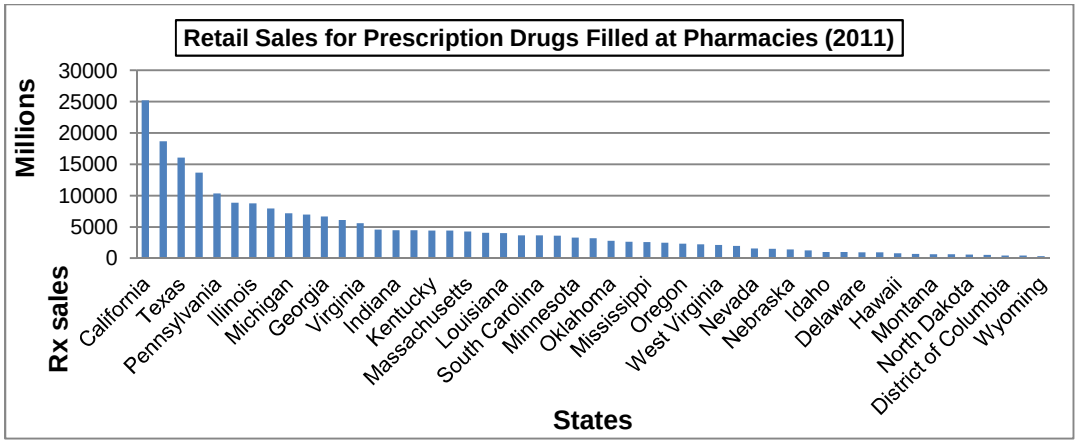


Figure 1-1 Prescription drug market in USA

Even in a developed country, including the USA, almost 1% of market value of medication is counterfeit. In 2011 total retail sales of prescription drugs in pharmacies in the USA was almost 228 billion dollars (Kaiser Family Foundation 2012). Even 1% of the market values could easily reach 2.3 billion dollars. Figure 1-2 shows that the counterfeit cases increased every year almost 35% in average (FDA 2012). Unless a number of factors around the counterfeit drug can be changed soon, this increased trend is likely to continue. Figure 1-3 shows how difficult it is to tell between genuine and counterfeit drugs. Applying new and advanced technologies with manufacturing and packing to cope with counterfeit drugs might not be enough because the technologies would be subsequently used by counterfeiters very soon.

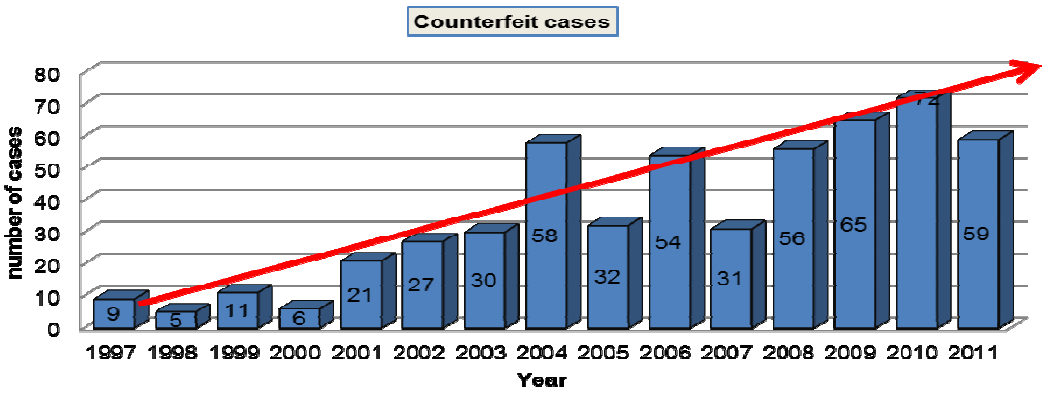


Figure 1-2 Counterfeit cases in USA

Figure 1-3 Examples of counterfeit drugs (FDA)

However, there is no doubt that these technologies can help prevent the counterfeit drug from coming into the drug supply chain in the USA.

1.1.2 Drug Diversion

"Drug diversion, broadly defined, is when the legal supply chain of prescription analgesic drugs is broken, and drugs are transferred from a licit to an illicit channel of distribution or use" (Laura A. Stokow ski 2008). Based on the definition, stolen drugs are one type of diverted drugs. Stolen drugs from manufacturers' warehouses or delivery trucks could go out of the legal supply chain, in which medications are controlled under regulations to assure their best quality for patients. This quality issue of the diverted drug is a main reason for the existence of the Food and Drug Administration (FDA) and WHO. These diverted drugs are considered as counterfeit drugs. The second type of diverted drugs occurs when drugs already used by consumers re-enter the supply chain through pharmacies and wholesalers. Some consumers take advantage of insurance benefits so that they may buy many high-priced drugs, including HIV medications, with low prices or free without intention of using them and resell those bought medications to pharmacies or wholesalers. In this case, the legal, safe temperature-controlled supply line might be broken, and those drugs stored in unsafe conditions could hurt patients' health. The final case is selling sample drugs to consumers by pharmacies. Sample medications are free and not supposed to be sold. However, pharmacies can collect these sample prescription drugs from numerous physicians' offices, repackage, and sell them to consumers (FDA 2011). Just like counterfeit drugs, the quality of diverted drugs is not guaranteed, and the innocent consumers have to be charged for all the costs resulting from these problems.

1.1.3 Drug Shortage

The Center for Drug Evaluation and Research (CDER) defines a drug shortage as: "A situation in which the total supply of all clinically interchangeable versions of an FDA-regulated drug is inadequate to meet the current or projected demand at the user

level" (CDER 2012). The Food and Drug Administration Safety and Innovation Act (FDASIA) define drug shortages as follows: "a period of time when the demand or projected demand for a drug within the United States exceeds the supply of the drug" (FDA 2013). In the worst cases of drug shortages, patients who are not getting proper treatments with the right medication could die. In one study, 43 percent of hospitals with cancer patients had delays in treatment due to drug shortage problems. In looking for an alternative drug, there might not be enough data on that alternative drug (Alexandra Olgin 2014). More than 99% of hospitals reported experiencing drug shortages, and many human resources are being used to handle drug shortage-related operations. There is an average of 8 or 9 hours per a week spent for this job by pharmacies. Related national labor cost for drug shortages could be $216 million (Julie Golembiewski 2012).

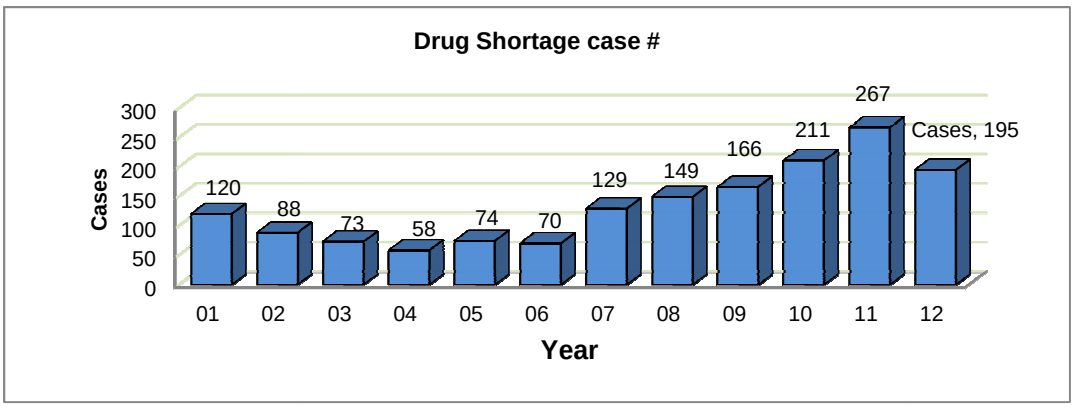


Figure 1-4 Number of drug shortage cases

Figure 1-4 also shows that the number of drug shortages has increased in recent years (Rob Stein 2012).

1.2 Research Objectives

All stakeholders in the pharmaceutical supply chain including government agencies, manufacturers, and distributors are cooperating to develop solutions against

the problems mentioned above. Many companies including wholesalers and distributors are developing new technologies or tools, and manufacturers are applying them into their production to cope with counterfeit or diverted drugs. Federal and state governments are making efforts to develop industrial standards, strong legal enforcement, and regulations for securing public health systems. In many cases, public and private sectors are working together for the same objectives. Implementation of unit level of trace and tracking systems is one big subject being discussed. Mass serialization for the unit level product might be the core of trace and tracking systems. The ePedigree systems based on the Serialized Global Trade Item Number (SGTIN) are being developed and implemented by many companies. A centralized data sharing system has been proposed to improve drug shortage problems. It could be obvious that the ePedigree system would help drug authentication and an efficient drug process benefited from the traceability and visibility systems. Traceable items' logistics data sharing between some integrated trading partners could support the products' visibility so that finally it helps improve drug shortage problems. However, there still are limitations with the solutions. This limitation will be discussed in later chapters. For developing a solution that overcomes the limitations of current solutions, more systematic and integrative approaches are needed. One of the objectives in this research is to develop and propose an alternative model that could be a solution for the prevention of counterfeit drugs, diverted drugs and drug shortage problems. The other objective is to develop a simulation model to prove that the proposed model might be better than the other models for securing the pharmaceutical supply chain.

Chapter 2

Identification of Problems and Causes

Criminal organizations produce counterfeit drugs for money. In their network of sales, corrupt wholesalers or distributors are collaborating by introducing the counterfeit drugs into the legal supply chain. They take big advantages of the unsecured pharmaceutical supply chain. Law enforcement including government agencies could not reach all the way into each individual participant's illegal activities. Online markets and a complicated supply chain require greater and stronger law enforcements than ever before, otherwise it is creating more opportunities of counterfeit and diverted drugs.

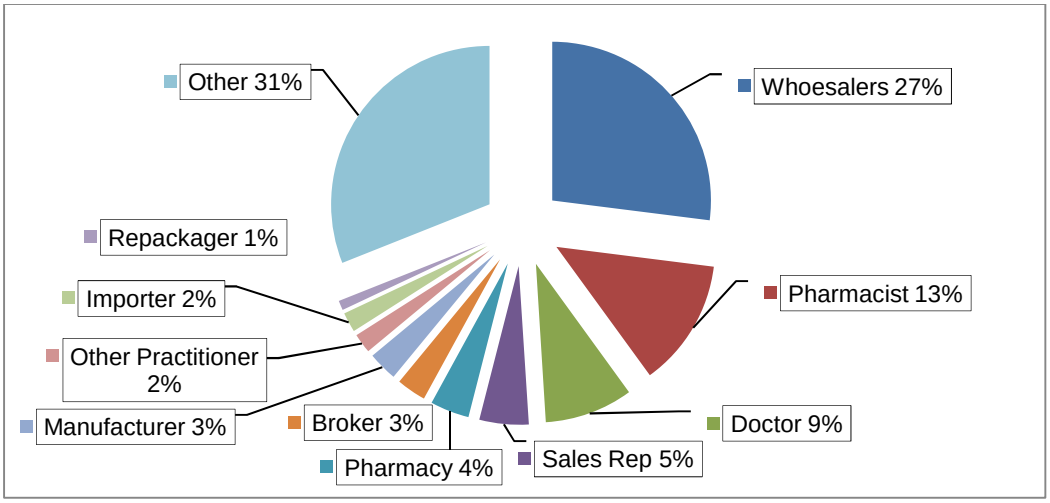


Figure 2-1 Percentage of all suspected groups by type of trade

The FDA did a survey of all the cases of counterfeit or diverted drug investigated by FDA-OCI from 2003 to 2008 in 2011. Figure 2-1 shows that what types of companies did how much of illegal activities in pharmaceutical supply chain (FDA 2011). It indicates that wholesalers and pharmacists are major participants that are playing an irresponsible role making the pharmaceutical supply chain vulnerable, and putting the public health system

and patients' health in danger. Studies in detail for each case of counterfeit, diverted drug, and drug shortages help to better understand the problems and their causes.

2.1 Counterfeit Drug

An example case study involves a corrupt wholesaler. In 2003, a wholesaler named Albers Medical Distributors in Kansas City, Missouri, imported illegal counterfeit drugs, which were 'Lipitor', a cholesterol reducing drug, from Costa Rica in Central America. There were a total of 11 individuals, 2 wholesalers, and 1 repackager, who were involved in this case. FDA said that $20 million of counterfeit drugs distributed in the USA market (FDA 2005). Based on the case study from the manufacturer, Pfizer, Inc., 18 million counterfeit tablets were recalled from 15 states as shown Figure 2-3, 600,000 USA residents might have received counterfeit 'Lipitor'. The distributors used a false pedigree to distribute into the legitimate supply chain (Pfizer 2007).

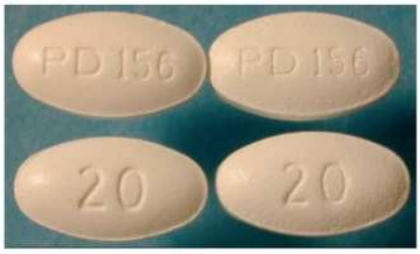


Figure 2-2 Counterfeit vs original Lipitor (www.pfizer.com)

Figure 2-3 States with counterfeit 'Lipitor' (www.pfizer.com)

It is very important to know that the false pedigree was a very powerful tool to make one of the biggest counterfeit drug distributions and recall cases ever happened to the US pharmaceutical market. Distributors use pedigree for transaction of pharmaceutical products. Unlike ePedigree (electronic document based), a paper pedigree could be easily falsified by corrupt distributors. The more shell companies, that do not hold products use the falsified pedigree for sale transactions, the more difficult to regulate the legitimate supply chain and for law enforcement to control illegal activities. A pedigree has all the historic information about the products' sales, e.g., previous sellers' or buyers' information, and product manufacturing information. The pedigree is the document or electronic file that authenticates that the drugs are genuine when business transactions are conducted. Details of a pedigree will be discussed in later chapters.

The second case was an illegal import by a pharmacy. San Jacinto, who was owner of Lifeway Pharmacy, imported 1,000 Cialis counterfeited tablets and 4,500 Viagra tablets. The average wholesale price of each tablet was $13.55 and $9.55 respectively, but he bought them for 30 cents per tablet. He ordered the fake drugs from China through an online market and the Immigration and Customs Enforcement (ICE) inspectors found the counterfeit drugs at the DFW (Dallas Fort Worth) airport (Donald J. DeGabrielle , Jr. 2006).

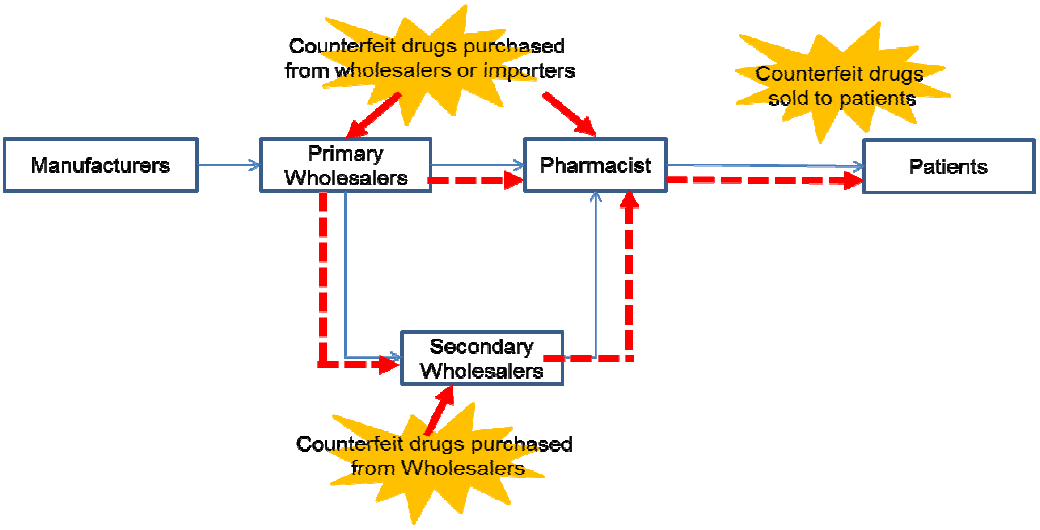


Figure 2-4 Vulnerable pharmaceutical supply chain for counterfeit drugs

This is the case that shows global markets and growing online market is helping increase the supply of counterfeit drugs from all around the world into USA markets. The limitation of law enforcement for so many online and offline illegal activities allows more opportunities for the counterfeiters.

The final case is related to illegal import of counterfeit drugs by health care solutions, which is one type of participant in the pharmaceutical supply chain in the USA. In 2012 FDA Office of Criminal Investigation (FDA-OCI) started investigation for Montana Health Care Solutions (MHCS) in Montana. MHCS imported counterfeited Avastin® from a distributor, Volunteer Distribution, in Tennessee. Volunteer Distribution bought that counterfeit drug from River East Supplies, a wholesaler in the United Kingdom which bought that drug from a manufacturer in the European Union. After investigation, no active ingredient was found in the drug. Based on the report from FDA-OCI, MHCS charged $1,700 per vial for Avastin® which was priced normally $2,300 per vial. Furthermore some physicians who bought the counterfeit drugs knew that Avastin® was foreign and an unapproved version of Avastin® but they still charged the price for original

Avastin® to their consumers (FDA OCI 2013). Figure 2-4, simplifies the supply chain that includes the main entrances for wholesalers and pharmacies. Vulnerable and not sophisticated distribution systems are providing opportunities to a group of greedy participants to conduct illegal business with counterfeit drugs. Since falsified pedigrees are being used for better looks like legal business activities, there would be no doubt that the solution to counterfeit drugs should be focused on pedigree systems. From these case studies, it is clear that there were no effective drug authentication processes through the entire supply chain. Even though companies have their owns solutions such as smart codes, special inks and forensic materials in the products or packages, it might not be valid authentication systems when those partial solutions are not shared and integrated with other partners (Jim Kerper 2013). Many organizations and studies have proposed that unit-level serialization and track and trace systems will provide for proactive solutions of the current counterfeit drug problems. State and Federal governments are also moving toward an ePedigree system which has key data sharing with upstream and downstream suppliers and unit level tracking and tracing capability throughout the whole supply chain.

2.2 Drug Diversion

For the same reasons, diverted drugs hurt individual patient's health and public health systems as a whole. However, the physical flow of diverted drugs is different from the counterfeit drugs' flow, as it was mentioned before. In 2006, eight individuals and six companies were charged in $70 million related diverted prescription drugs. Corrupt wholesalers and pharmacists worked together on an illegal supply of diverted drugs. They bought stolen drugs or unused prescription drugs and resold them to wholesalers or pharmacies (Spitzer 2006). Strong law enforcement seems to be the only solution for

grey illegal business activities. However, when it comes to connection between grey markets and a legitimate supply chain, other solutions than simply stronger law enforcements should be used. Again, unit level of visibility and traceability throughout the whole pharmaceutical supply chain should be developed and implemented. Figure 2-5 describes that mainly corrupt secondary wholesalers and pharmacists are the bad actors in the diversion activities found in the pharmaceutical supply chain in USA (FDA 2011).

2.3 Drug Shortage

Figure 2-6 describes that the main causes of drug shortages are related to manufacturing processes (FDA 2013). Lots of manufacturing issues are related to quality problems. CGMP (Current Good Manufacturing Practice) and other quality control tools can help improve those quality issues.

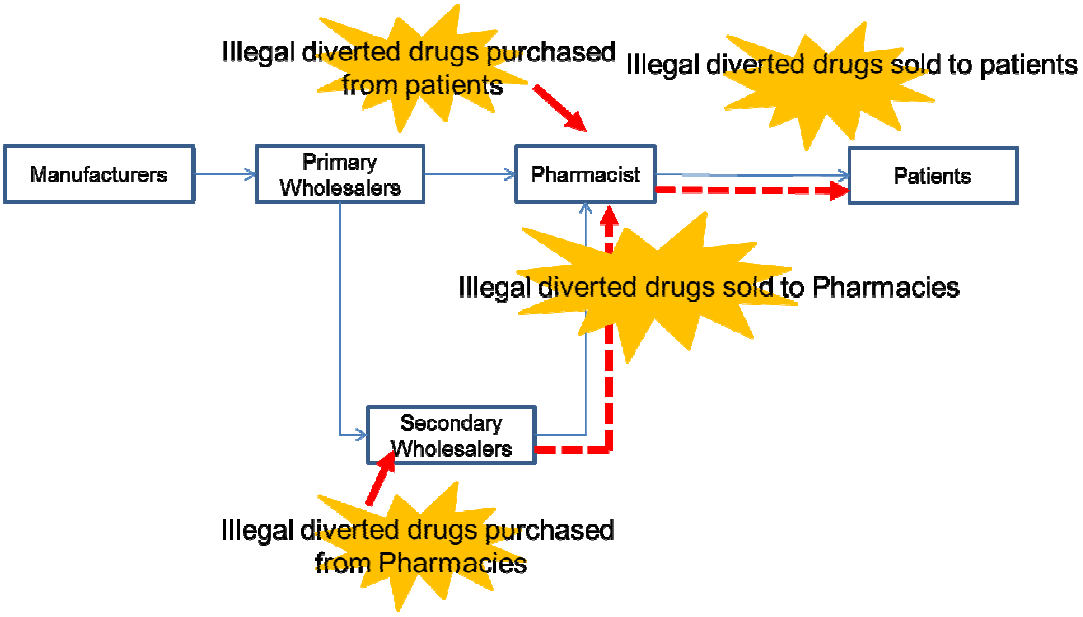


Figure 2-5 Vulnerable pharmaceutical supply chain for drug diversion

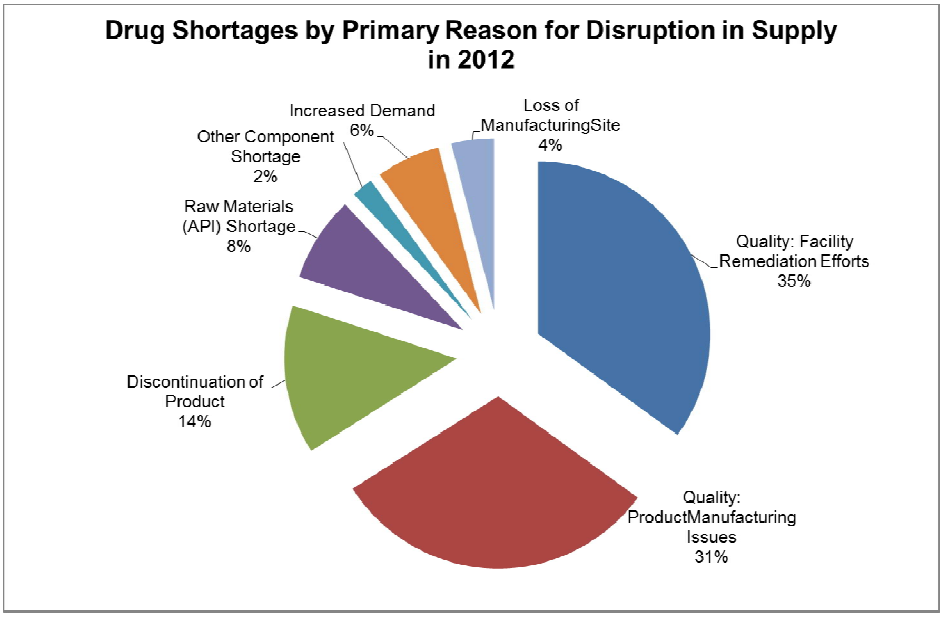


Figure 2-6 Drug shortage primary reasons

Discontinuation of the products due to low profit, facility modification, and quality issues could also be the cause of drugs shortages. However, other than these, other manufacturing issues were also discussed, e.g., poor inventory practices, no FDA inventory control power on supply chain and natural disaster (Susan F. Pararella 2012). Little or no inventory cushion to handle short term drug shortages, variability in procurement capabilities between small and big healthcare facilities, and grey market could be reasons for drug shortages (IMS 2013). For instance, just-in-time inventory management policy minimizing inventory to reduce inventory cost could make little or no inventory buffers, and that could be a cause of short-term drug shortage (Bethesda 2013).

Chapter 3

Current efforts and solutions

3.1 Counterfeit drug, drug diversion

For a secure pharmaceutical supply chain, new approaches and stronger leadership are necessary (NABP 2013). On a tactical level, many companies are applying partial solutions for their own needs. Federal government enforces related regulations and pharmaceutical related organization such as NABP (National Association of Boards Pharmacy) proposed new or upgraded regulation solutions. There are mainly three sorts of approaches for counterfeit and diverted drug issues. Firstly, it is a regulation approach. Many individuals and studies are mentioning that heavy penalties and improved oversight should be imposed (Paul Chilcutt et al 2004). Since many corrupt wholesalers and pharmacies are playing critical roles with distributing counterfeit and diverted drugs, more valid and effective regulation for distributors should be considered. NABP' VAWD® program is one of them. Wholesalers have to pass through a criteria compliance review, e.g., review of wholesalers operating policy, on-site survey of facility and operations, and background checks to be VAWD-accredited wholesaler distributors (NABP 2013). What this program is trying to do is to keep watch on distributors' business and operational activities and to proactively prevent any illegal business activities including buying and selling counterfeit and diverted drugs. The other program is a VIPPS (Verified Internet Pharmacy Practice Sites) program that was also proposed by NABP. Based on the WHO reports, illegal internet based pharmacies sold counterfeit drugs without prescriptions, and 50% of cases of drugs purchased from internet pharmacies which had no physical address were counterfeit drugs (WHO 2006). Still currently many consumers who cannot afford to buy high-priced genuine products are likely to visit internet based pharmacies. Last year the state of Maine allowed

consumers to buy prescription drugs by mail from other countries such as Canada, because many seniors could not otherwise afford their medications (Julie Rovner 2013). There are many consumers who are more sensitive to medications' prices than to the products' qualities. If the online pharmacies supply good quality for a better price, then that will be good for customers and public health systems. The key point of VIPPS is that the NABP can guarantee the online pharmacies that pass certain conditions just like the wholesalers do for getting VAWD®, and the online pharmacies put the VIPPS logo on web sites telling consumers that they are not selling counterfeit or diverted drugs.

Figure 3-1 Sample of online pharmacy using VIPPS logo

Considering that VIPPS logo could be easily used for any online pharmacies, it is obvious that there should be more tools than VAPPS for even on-line pharmacy issues. Unlike regulation approaches from government agencies, private companies' approaches are more technology based. Since counterfeit drug problems hurt not only public health systems, but also manufacturers' reputations and theirs sales, manufacturers are developing their own solutions against counterfeit drugs. Use of a hologram is one example of the technologies being explored. The point of this technology is to make holograms to be recognized easily and difficult to copy. Unique numbers could be printed as hologram form and centralized data based systems could verify the products'

authentication (Lan Lancaster 2008). This technology could be valid and effective for a drug's authentication unless counterfeit manufacturers could copy the authentication. In African or India, authentication solutions based cloud computing including HP 'mPedigree Network' and 'Sprozxil' are being used. Those solutions allow consumers to check that the products are genuine or not, at any time and any place by putting or scanning unique numbers printed on the products. These solutions are focused on the simple authentication for end user customers and do not support real time verification of drugs through the whole supply chain. One of the core conditions for a solution securing pharmaceutical supply chain is real time authentication with products' moving though the whole supply chain (David 2006). Government's regulation approaches and private companies' technology approaches were discussed. Each approach against counterfeit or diverted drugs could make very powerful solutions in certain conditions. There appears to be no one-step-solution which can solve all issues caused by an insecure pharmaceutical supply chain. Progressive and innovative approaches for integrated, collaborative and systematic solutions should be discussed. And these approaches must allow all stakeholders including governments, private companies and all experts in these issues to work together to secure the pharmaceutical supply chain. The ePedigree is a good example for the approaches. Since ePedigree is a so big and important topic in this research, it will be better to be discussed in separate sub chapters.

3.2 Drug shortage

Since discontinuation of manufacturing has the biggest impact on drug shortages, the solution also should be focused on what causes the discontinuation of producing. More than 50% of causes that led injectable drug shortages were from products' quality issues, which made production sudden stop. Some production problems seem to be

unavoidable and do not lead to big drug shortages. However, there are numerous events that lead to discontinuation of production which may lead to long and large drug shortage problems. Some of them could be expected and controllable, e.g., facility changes. If FDA or manufacturers are able to anticipant a certain drug shortage, then they could work together to prevent that drug shortage from occurring or mitigate the impact on public health even in unavoidable situations. That is the reason FDA has an early notification program. After the president of the USA signed Food and Drug Administration Safety and Innovation Act (FDASIA), all manufacturers are required to notify to FDA of any issues that lead to potential drug shortage or disruption of the supply of a product (FDASIA 2012). FDA prevented roughly 200 drug shortages in 2011 and 280 in 2012. FDASIA gave FDA better opportunities to prevent drugs shortages. It also asks FDA not only to have a capability to handle issues from drug shortage but also to develop long term strategies and prevent drugs shortage from occurring (FDA 2013). It might be necessary to discuss how FDA copes with drug shortages from manufacturers' notification to closing of the cases for finding any process that should be improved. It has mainly three steps from beginning to end. Firstly, FDA gets notifications from manufacturers. Secondly, after FDA gets notification implying drug shortages from manufacturers, it assesses the risk of drug shortages. It also verifies that drug shortage is going to really occur or not. FDA uses resources and tools such as its databases, market research databases, and networks with participants in the supply chain to collect initial information and evaluate the product inventory in the whole supply chain. Finally, when FDA determines that the drug shortages are really expected, it works to mitigate impact from the drug shortages on the overall market. It could help manufacturers any way for the drugs' production or import alternative products when it is necessary. FDA figures out the root cause of drug shortages, and it develops short or long term solutions for the

problems (FDA 2013). However, FDA's capability of coping with drug shortages could be very narrow and limited if manufacturers do not notify their production issues to FDA in advance. FDA also does not currently have authority to control participants' inventory in the supply chain. The Generic Pharmaceutical Association proposed the "Accelerated Recovery Initiative" and FTC (Federal Trade Commission) approved that in September 2012. It was proposed to improve drug shortages of generic injectable medications by sharing real time inventory and production information between the participants. The third independent corporation collects and analyzes the data collected from the participant, and help stakeholders in dealing with drug shortage issues (Bethesda 2013).

3.3 ePedigree

Since a paper based pedigree could be easily falsified, more secure type of pedigree was needed. The ePedigree was from the motivation that pedigree system could be used for e-commerce, and not be easily falsified for drug authentication. The main objective of pedigree was to prevent counterfeit and diverted drugs from occurring by verification of transaction information including sellers' name, physical address, and details in products. The ePedigree system has various unique characteristics that support integrated and systematic solutions for securing the pharmaceutical supply chain in the USA. Some features and basic concepts of ePedigree system are very important to be discussed in this research.

3.3.1 History of ePedigree

The USA Congress passed the PDMA (Prescription Drug Marketing Act) in 1987, which required a statement known pedigree for selling a drug. The pedigree was supposed to have information about sales including date of transaction, names, and

address and more. However, even after FDA published final rules to implement the pedigree in 1999, it was not in effect until 2006 due to strong opposition to pedigree law. One of the reasons the FDA delayed the effective date of PDMA was ePedigree. Industry promised that it would implement an electronic track and trace system by 2007, which obviously could meet pedigree requirements. However, since it was also obvious that industry could not do that by 2007, FDA published a notice mentioning no more delay of PDMA in June 2006. It published also PDMA CPG (Compliance Policy Guide) in December 2006 (FDA 2006). Each state government also passed its own laws against counterfeit and diverted drugs. Florida passed the Florida Prescription Drug Protection Act in 2003 after several big serious counterfeit and diverted drug cases. This law required every wholesaler to supply a pedigree to each customer which is stronger than PDMA, which required certain wholesalers were required to do that. It also required that each wholesaler must authenticate that the drugs were original or counterfeit. This law was amended to include electronic pedigree in 2005 (Sandra, R. Stovall 2006). California allows participants in pharmaceutical the supply chain to observe ePedigree law that will take effect from Jan 2015 by stages. Based on the California board of pharmacy website, this California ePedigree law requires that 50% of a manufacturers' product must have a unique serialization number and be managed by electronic track and trace system, which is the ePedigree system. The other 50% of the products should be included by 2016. The 50% rules are based on the unit volume, product package (SKU) type, and drug product family (Virginia Herold 2014). Wholesalers and repackagers must apply ePedigree with their products by July 1, 2016. Pharmacies and their warehouses must implement ePedigree by July 1, 2017 (www.pharmacy.ca.gov). Allowing each individual state to develop its own approach to the counterfeit and diverted drug problem has brought some issues related to standards. For instance, if 50 states in the US have their own

regulations, and they are not on the standard format with pedigree law, it might give overwhelming burdens to small and mid-sized companies by increasing cost and operation difficulties (Gregory Conko 2013). Finally, the US president, Barack Obama signed Drug Quality and Security Act (DQSA) in November 2013. It required FDA to provide implementation guidance within 12 months and develop a national track and trace system to secure the pharmaceutical supply chain. It also required that all drug packages carry a serial number within 4 years (Phil Taylor 2013).

3.3.2 Basic concepts of ePedigree

One of two main concepts of ePedigree is the implementation of traceability and visibility for the pharmaceutical products. Based on the federal pedigree law, each product unit must have a globally unique serialized number and ePedigree system can track and trace the unit level of any product by inquiring its serialized number (Phil Taylor 2013). This unit level serialization enables not only wholesalers but also end users to authenticate the products that they buy, and it could support better secured PSC against counterfeit and diverted drugs. The other main concept of ePedigree is the authentication process. Based on pedigree law, it generally requires wholesalers or other participants pass the documented pedigree, which has product, trading partners' information, and their signature for authentication to the recipients. However, when it comes to ePedigree, the authentication algorithm could be different based on what standard the companies have integrated into their ePedigree systems. For example, Drug Pedigree Messaging Standard (DPMS) ratified by Global Standard One (GS1, http://www.gs1.org) in 2007 creates and passes pedigrees to the buyers, and the buyers add their information to the pedigree and so on. It seems similar to the way of document based pedigree systems but the only difference is the electronic document type and digital signatures. Since some

states do require only paper based pedigree currently, ePedigree needs to support a document based pedigree feature by allowing the attachment of files and manual authentication (EPCglobal 2007). However, Electronic Product Code Information Services (EPCIS) does the authentication in different ways. Since Drug Pedigree Messaging Standard (DPMS) has its weakness in several aspects, GS1 proposed EPC network with EPCIS for ePedigree. The participant in EPC Network with EPCIS can exchange data when they need, which improves the data storage space needed with DPMS. The trading partners inquire the concerning data from other trading partners for ePedigree or traceability information. Each participant can have either local EPCIS repository or store the data in the centralized databases. Still there are lots of things to be discussed for this standard, e.g., how the trading partners pass or share the data to other partners, how much data the participant needs to share, who initiates ePedigree at first and many more.

3.3.3 Standards and issues

There are many regulations from each state making at least 50 different state level regulations and various companies that have their own system for exchange or sharing information with their partners through the supply chain, which makes the federal level of standard for data communication critically important. For instance, one small wholesaler could not afford to have more than two software and operating systems to meet two different states' regulations in economic or operational manner. The economic and operational issues have causes state or federal government delay at pushing the industry implementation of the pedigree or ePedigree systems. Furthermore, the standard of the ePedigree in the USA would be the standard in global environment, and this makes its completion even difficult. Since cost of implementation and operation of

the ePedigree system would be dependent on what standards the companies are using, when it comes to a development of standard for ePedigree system, cost and interoperability are the key aspects needed to be considered. As it was mentioned before, there are two standards for ePedigree currently. One of them is Drug Pedigree Messaging Standard (PDMS).

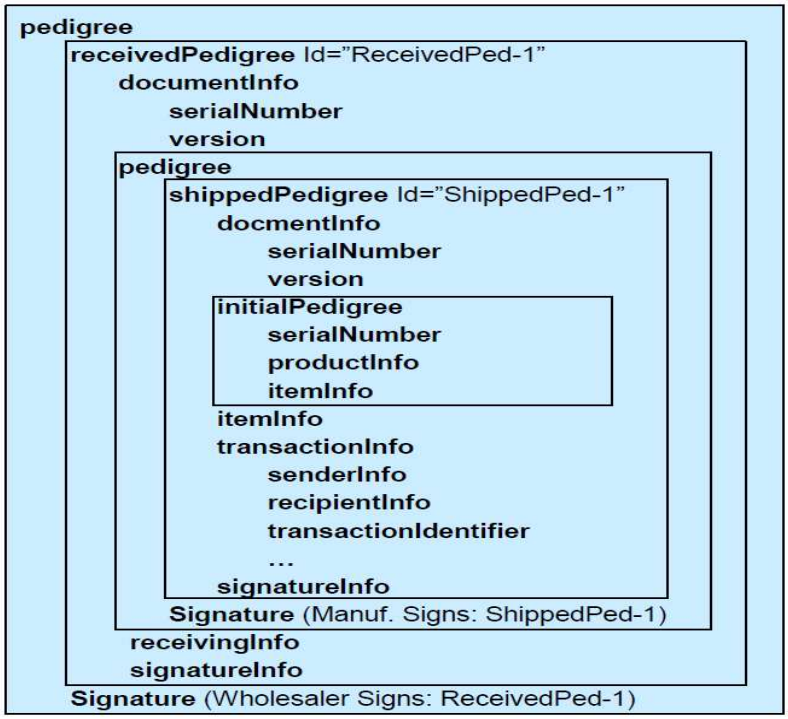


Figure 3-2 Example of ePedigree with PDMS

Based on DPMS, after ePedigree was created and as it moves to downstream trading partners, it adds ePedigree information to the old epedigree. Figure 3-2 shows that how pedigrees are nested within other pedigree (EPCglobal 2007). This way of data exchange may bring some concerns. Firstly, since more pedigree information would be added as it goes farther downstream to trading partners on the supply chain, some wholesalers and pharmacies need to store more data and need to have more storage spaces. This could be big burden to small size participants. Secondly, it supports a good

trace ability solution because each trading partner can have ePedigree that include its previous pedigree, but this does not support good tracking function to downstream trading partners. Thirdly, it requires every trading partner to have duplicate pedigree on each partner's local system, which requires large storage spaces again. Finally, since every trading partner needs to pass pedigree to their recipients, the more supply chain complicated, the more communication channel would be needed (Dirk Rodgers 2010). In addition, since DPMS was not designed based on unit level serialization, when the trading partners need to store or handle Serialized Global Trade Number (SGTIN) and related data, DPMS could not efficiently supply its original objectives (SupplyScape 2008). This large data and storage space may lead to slowing data access speed to certain trading partners. So GS1 proposed EPCglobal network with EPCIS.

3.3.4 ePedigree with EPCIS

Federal or state governments require very basic traceability and visibility features from ePedigree to minimize economic or operational cost and reduce implementation time for the pharmaceutical industry. One of the basic features is unit level traceability and visibility. Figure 3-3 explains basic traceability concept between trading partners (GS1 2012). Firstly, if the traceability data is private, which is shared only between two trading partners, then the traceability data is exchanged only between previous partner and subsequent partner. Secondly, if the data is in public, which is shared with all trading partners, then the traceability data is in certain database and certain location, which allows participants to access the data at any time and place within its network. Finally, if the data is a key for the identification, then the identification carrier including RFID, barcode, and 2D barcode has the data (GS1 2012).

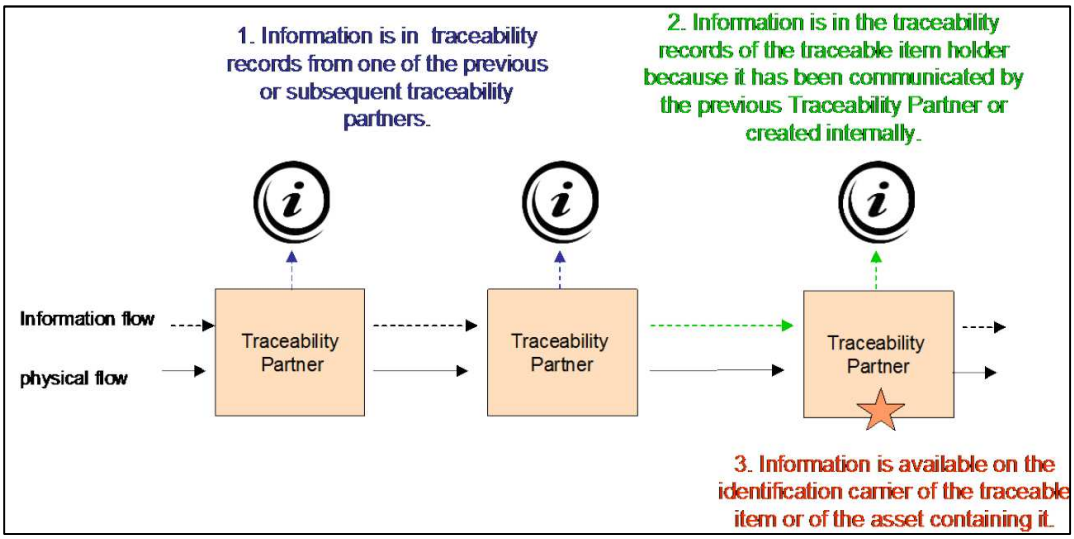


Figure 3-3 Where is the traceability data?

Based on GS1 traceability standard, traceability data includes trading partners, location, date or time of the event, traceable item, and finally what happened, which is process or event. Figure 3-3 also describes how data is transferred to other trading partners. It shows that as the products move to the downstream trading partners, the information of the product comes along with its products. For a trace request, which is looking for some information of the certain products because of the authorities' or consumers' needs, the trace request initiator needs to refer back to previous trading partners all the way up to manufacturers in a repetitive way (GS1 2012). However, EPCIS support a more flexible way of doing this with EPCIS, and each participant is able to inquiry data to the any trading partners' EPCIS repository or centralized database. EPCIS was designed originally based on Electronic Product Code (EPC). The EPC is "designed as a universal identifier that provides a unique identity for every physical object anywhere in the world, for all time" (www.wikipedia.org). GS1 defines this code as a high precision identification.

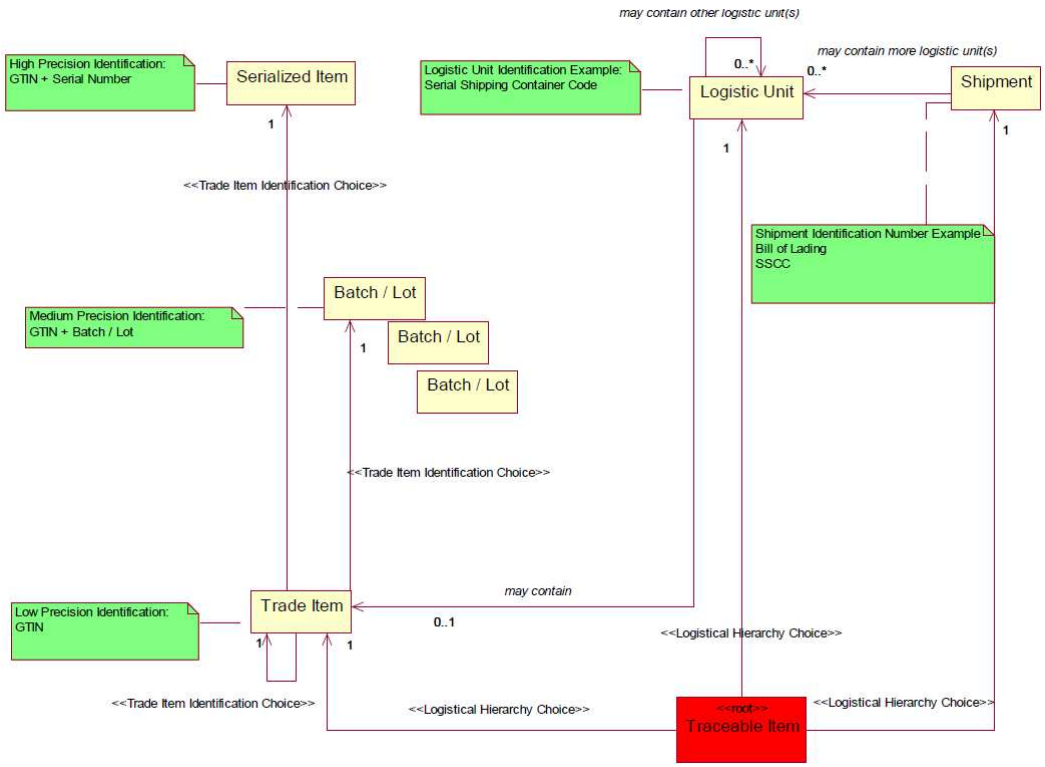


Figure 3-4 Traceable item hierarchy (source from GS1)

GS1 defines EPC as GTIN (Global Trade Item Number), which is unique on SKU level with a serial number, which makes the code unique in a unit level globally.

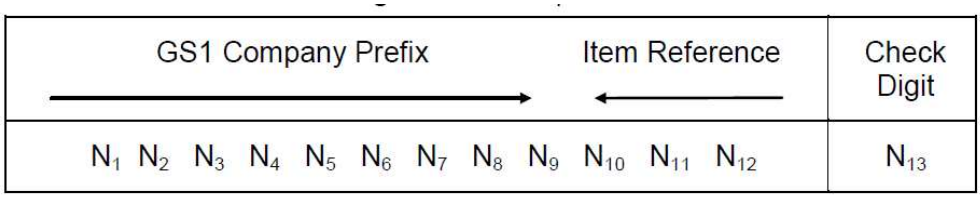


Figure 3-5 Example of gtin-13 (source from GS1)

If EPC is linked other standard codes including GTIN, Serial Shipping Container Code (SSCC), and Global Location Number (GLN), then the system can supply almost every level of traceability, e.g., boxes, pallets, containers and even location of the unit passed through the supply chain. Figure 3-5 shows that how company code and item

code assign into GSTIN. The carriers of EPC could be RFID or 2D barcodes as long as it carries SGTIN on itself.

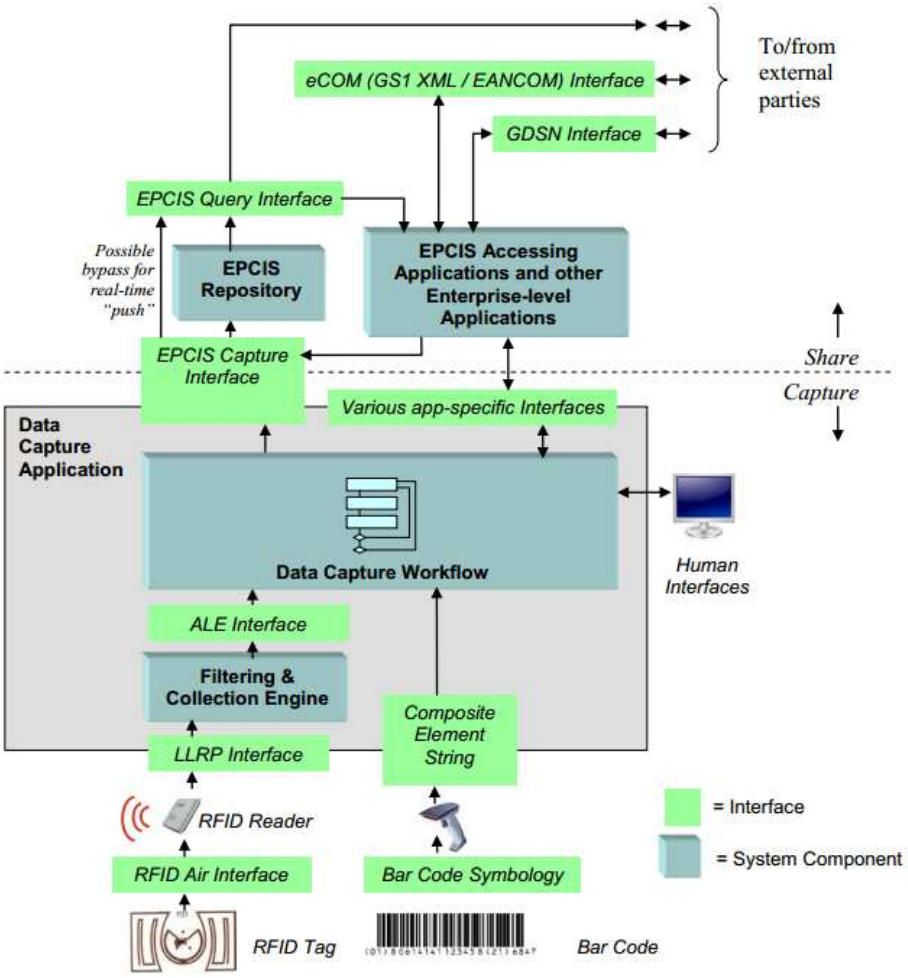


Figure 3-6 EPCIS architecture frame (source from GS1)

Figure 3-6 describes how EPCIS standard captures traceability data and interface with middleware and applications. Companies can share not only the traceable Item's event data including what, when, where and why about physical observations but also additional information including the time, data, temperature and location of the events. EPCIS database or repository enable each trading partner's applications access such

additional data (GS white paper). Unlike that drug authentication process is based on the digital signature in pedigrees with DPMS, the drug authentication with EPCIS could be based on event exchanges between trading partners. Figure 3-7 describes how SGTIN and related information could be shared with all other trading partners in the supply chain.

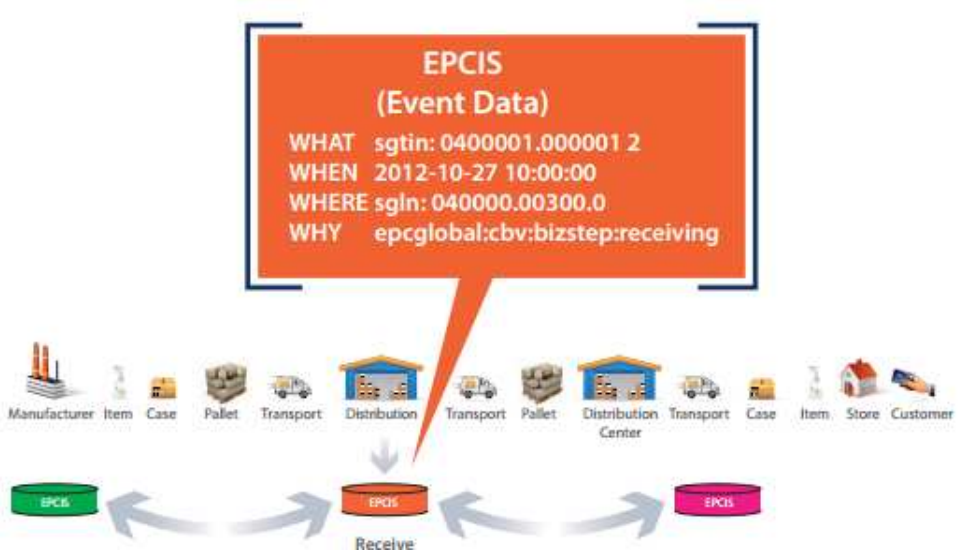


Figure 3-7 Even data with GS1 EPCIS (source from GS1)

3.3.5 Current ePedigree ssolutions

Companies within a pharmaceutical supply chain are moving forward to comply with the regulations and standards, and they have no extra time for that. ePedigree solution providers are supplying different types of ePedigree systems, e.g., 'Axway Track & Trace' supports either centralized database system or distributed database system. In centralized database systems, the companies put their traceable time information in the solution providers' systems. The providers supply ePedigree and related services including product authentication, serial number management and expiration data or lot number management. In distributed database systems, the solution providers may supply

only initial implementation of the EPCIS and related systems, and maintenance services. The trading partners exchange data and manage the data or system based on their agreement. For small or medium size companies, which could not afford to have local EPCIS Repository Service or full service of Centralized database ePedigree, the cloud based solution could be solutions for their ePedigree systems because the cloud based systems, including 'ePedigree' from TraceLink, could supply lower prices to small companies which use small time or less resources. In cloud based systems the solution providers charge the user based on their utilization of the systems. It is obvious that small companies use less time and resources so that they could pay less. Table 3-1 shows some of solutions' key features and standards.

3.3.6 Limitations of ePedigree with EPCIS

For one goal, securing pharmaceutical supply chain in the US, stage and federal governments and industries have been working together from Prescription Drug Marketing Act (PDMA) in 1987 to Drug Quality and Security Act (DQSA) in Nov 2013 in regulations and from DPMS to EPCIS in standards. EPCIS was designed based on mass serialization in contrast to PDMS which was designed based on documented pedigree. Still there are several obstacles with implementation of ePedigree complying with federal and states level regulations. Firstly, costs could be big challenges for small or medium size companies. Each unit need to have RFID or 2D barcode having Serialized Global Trade Number (SGTIN), which makes additional costs from product design, manufacturing and even operation processes. Every participant also has to have related software and hardware. The pharmaceutical industry estimated that $3.5 billion could be spent to comply with California pedigree law (Gregory Conko 2013). Secondly, operation could be more complicated. Some companies need to have more operation burdens

because of managing of serialized products or duplication of the same process, e.g., data capturing process with RFID, 2D barcode or manual key input. Thirdly, there could be technical issues with RFID or communication with other trading partners. Still there is limitation of application of RFID with liquid products and biologics. Finally, standardization is a huge issues needed to be overcome. Since DPMS has some concerns including handling big size of data with serialized products, requirements of vast storage spaces for small or medium size wholesalers or pharmacies, GS1 proposed an EPCglobal event driven model and EPCIS for ePedigree systems (K. NamGung et al 2012).

Table 3-1 e-Pedigree solutions

Solution Name	Company	Standard/Database	Key Features	References (Projects)
Axway Track & Trace	Axway (www.Axway.com)	EPCIS, PDMS /Centralized, stand alone	GS1 EPCglobal-certified event repository with built-in master data, Global Compliance including DSCSA, Product ID verification, Serial number management, Integrate any internal or external application (EPCIS and non-EPCIS)	AstraZeneca, Genzyme
Oracle Pedigree and Serialization Manager (OPSM)	Oracle (www.oracle.com)	EPCIS, PDMS	Serial Generation, Electronic Pedigree with Digital Signature, EPCIS Capture and Query services, EPCIS Repository for data exchange with supply chain partners	
E-Pedigree	TraceLink	EPCIS, PDMS /SaaS (Software as a Service, Cloud)	Supply partner interoperability via Pedigree Portals, Support both paper and electronic pedigrees	
Active ePedigree Management™	rfxcel corporation (http://www.rfxcel.com/)	EPCIS, PDMS/Cloud	Secure Web Browser Access, SAP Certified Integration, Barcode and RFID Technology Integration	LLC Wholesale Supply (Tempe, AZ)

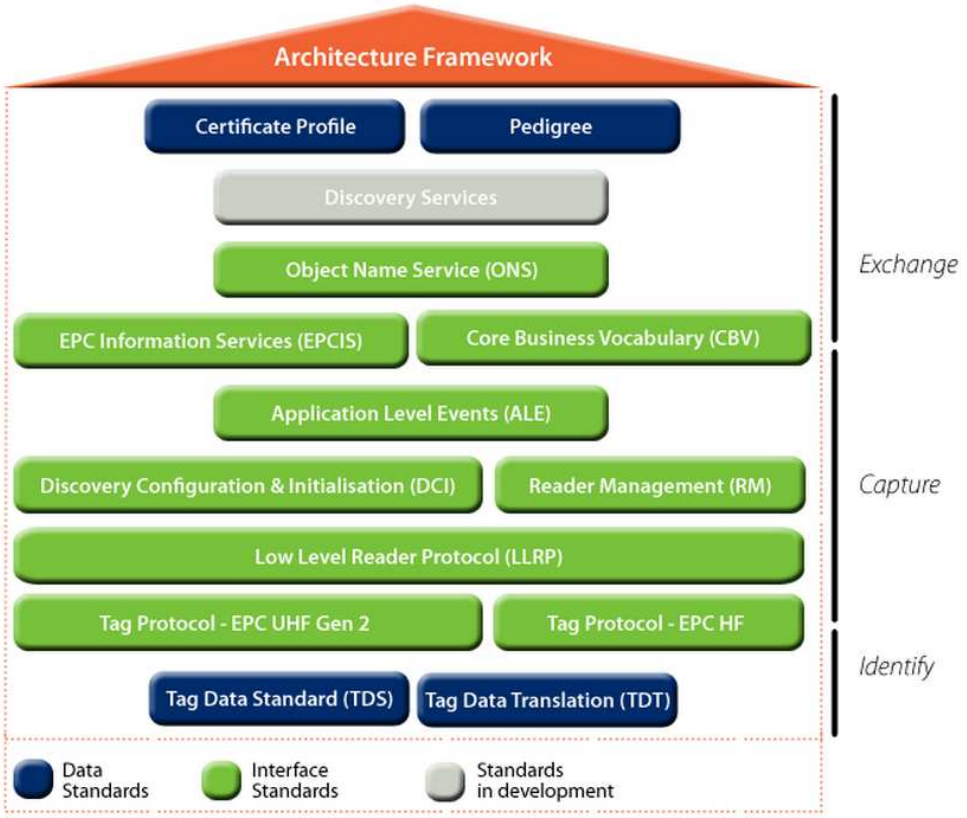


Figure 3-8 EPCglobal architecture framework (source GS1)

However, since basically GS1 required minimum data sharing between trading partners, each trading partners needs to inquire pedigree information when needed. Of course EPCIS allows trading partner to have centralized database at any place or any type. It would totally depend on what agreements the trading partners reach. EPCIS supports data sharing standards within trading partners in the network, which limits data sharing with the companies that are not in the same EPCIS Network. Discovery Service could help trading partners' inquiry data from the companies that are out of their EPCIS Network. Figure 3-8 describes what standards are used for extending data sharing with trading partners within network and companies out of network. However, based on information from www.gs1.org, this Discovery Services standard is still in development.

Chapter 4

Develop and propose alternative model

4.1 Background and objectives

To cope with counterfeit and diverted drugs, there is no different opinion that ePedigree with EPCIS networks could be the best solution for now. Based on EPCIS standard, trading partners on EPCIS network basically do not have to share any event data in real time manner. However, whenever the participants in EPCIS networks inquire about data to the certain trading partners, then they could get the information based on standards or agreements between the trading partners. It makes companies overcome previous ePedigree standard PDMS's issues including storage, speed and cost problems. However, it still could be a big burden to small companies. As it was discussed, cloud based ePedigree systems help those companies with much less priced solutions. For better drug authentication and recall process, modified EPCIS networks have been proposed. For instance, centralized network type of ePedigree is that all trading partners can access the centralized database to get e-Pedigree information (K. NamGung et al 2012). NamGung proposed centralized database is located in big manufacturers' systems, because in general the manufacturers can afford to implement and operate the Centralized ePedigree system for their trading partners. Cloud based ePedigree was also proposed (Cherng-Min et al 2011). Service-oriented architecture is one basic concepts of clouding computing. Sharing the same resource with other participants in the systems could make each company pay less than when it implements and operates its own systems (David Miller 2009). EPCIS Network seems to be working well within trading partners. However, alternative standards or architecture needs to be discussed and developed for data exchange between different networks. For efficient and correct drug authentication and recall process, more high level of integration should be designed. It

could be called '***Upper level of integration above EPCIS networks'***. The object of this paper is to develop and propose an alternative model to improve problems with pharmaceutical supply chain in the USA, it needs to return to two other problems, which are drug diversion and shortage problems. Firstly, ePedigree with EPCIS network might be working fine with normal condition for diverted drugs. However, in this partially integrated EPCIS networks, the authentication process for diverted drugs might not be working as well as intended. Any inconsistent master data with other EPCIS Networks could make authentication process for diverted drugs broken. Secondly, EPCIS network helps the trading partners' inventory control because EPCIS network supplies visibility by EPCIS event repository and related queries. However, since the visibility of the products was implemented and managed within the certain EPCIS networks, the certain products' visibility between trading partners out of the EPCIS network would not be established. Having considered that inventory or production data system could be key factors to improve drug shortage problems, more trading partners or EPCIS networks are needed to join the 'Upper level of integration above EPCIS networks'. Even though EPCIS networks could provide better product visibility or traceability information to the FDA or government agencies coping with counterfeit activities or recall processes, the FDA needs to design, propose, and implement more integrated networks and to have authorities to access and control information in that network. Furthermore, the cost to join the network should be affordable for even small companies including wholesalers or pharmacies. However, no matter how perfect the information and operation system is, the system could be not perfect for securing the pharmaceutical supply chain unless all participants would follow the regulations and standards. The Verified-Accredited Wholesale Distributors (VAWD) and the Verified Internet Pharmacy Practice Sites VIPPS (VIPPS) could be good complimentary measures. The wholesalers need to show that

they are complying with states, federal laws and requirements from National Association of Boards of Pharmacy (NABP) to get accreditation and display VAWD or VIPPS seals (NABP 2013). Based on the all discussions to secure pharmaceutical supply chain, which improve counterfeit, diverted drug, and drug shortages, one conceptual ideal design could be reached. Within that system, all participants follow the requirements from federal or state governments. The integrated and centralized database system supports ePedigree system, data sharing system between not only trading partners but also other companies out the networks, and the products traceability and visibility for better counterfeit drugs and drug shortage control nationwide.

4.2 Literature reviews

For fast and efficient handling drug shortage, diverted and counterfeit drugs, a large number of researchers suggest centralized database concepts. Witworth discussed in his article that a single reliable source of information is very important because this can answer quickly and accurately all questions about the products. He also urged that the participants need to be able to request and share information concerning any phase of processes. The article mentioned again centralized database can supply the information at the right time with right formations to the different customers (Michael Witworth 2012). Chilcutt discussed creating secured and centralized database, which allows authorized parties to access and verify origin of products as one of the solutions for securing the pharmaceutical supply chain (Paul Chilcutt et al 2004). Van Arnum also emphasized the importance of centralized database by saying that the solution to ensuring the safety supply chain should be a portal or fully integrated services having centralized database to supply products' custody information to the trading partners (Patricia Van Arnum 2008). To improve generic injectable medication shortage problems, Accelerated Recovery

Initiative (ARI) was proposed by Generic Pharmaceutical Association (GPA) in 2012. Companies related to the generic drugs including manufacturers and wholesalers join the community voluntarily, and the independent third party manage the systems and supply real-time distribution information of the products to the participants (Bethesda 2013). Real time inventory information sharing system helps manufacturers for better production plan and wholesalers for improved inventory management. FDA can access the transaction data in real time for better drug shortage plan, and the independent corporation as an operator of the system will be able to supply not only real time production or inventory information but also additional valuable services to the participants. One big concern was that the competitors share their data, which could be a key issue again specially involving antitrust law because this kind of data sharing could facilitate collusion among competitors. However, Federal Trade Commission (FTC) approved ARI in 2012 because it judged that the program had safeguards that only the third party, IMS Health Incorporated, collect data from manufacturers, analyze and supply to FDA, and it does not share the data with any other party (Thomas Sullivan 2012). It is very interesting to think whether or not this community could be expanded. Bigger community including more participants and drug types can achieve more common objectives including reducing counterfeit and diverted drugs. Ontario Canada's government and agriculture industry work together to build 'OnTrace Agri-Food Traceability', which was non-profit corporation and to implement agriculture products' traceability and visibility in the case of a recall or withdrawal. Its solution, 'OnTrace Verified Network, uses a unique premises identification (PID) for traceability and visibility processes. Even though this case is about food supply chain, it still has points, which are very necessary ingredients to develop alternative model. Just like ARI, trading partners join this community voluntarily, and the third independent corporation operates the systems and supply visibility and

traceability solutions to the trading partners in the network, which name is 'Ontrace Verified Network' (Neil H.Mermelstein 2011).

4.3 Concepts and features

Is it possible to design one integrated system for handling three big issues with a pharmaceutical supply chain in the USA? EPCIS network would be able to cope with counterfeit and diverted drug issues.

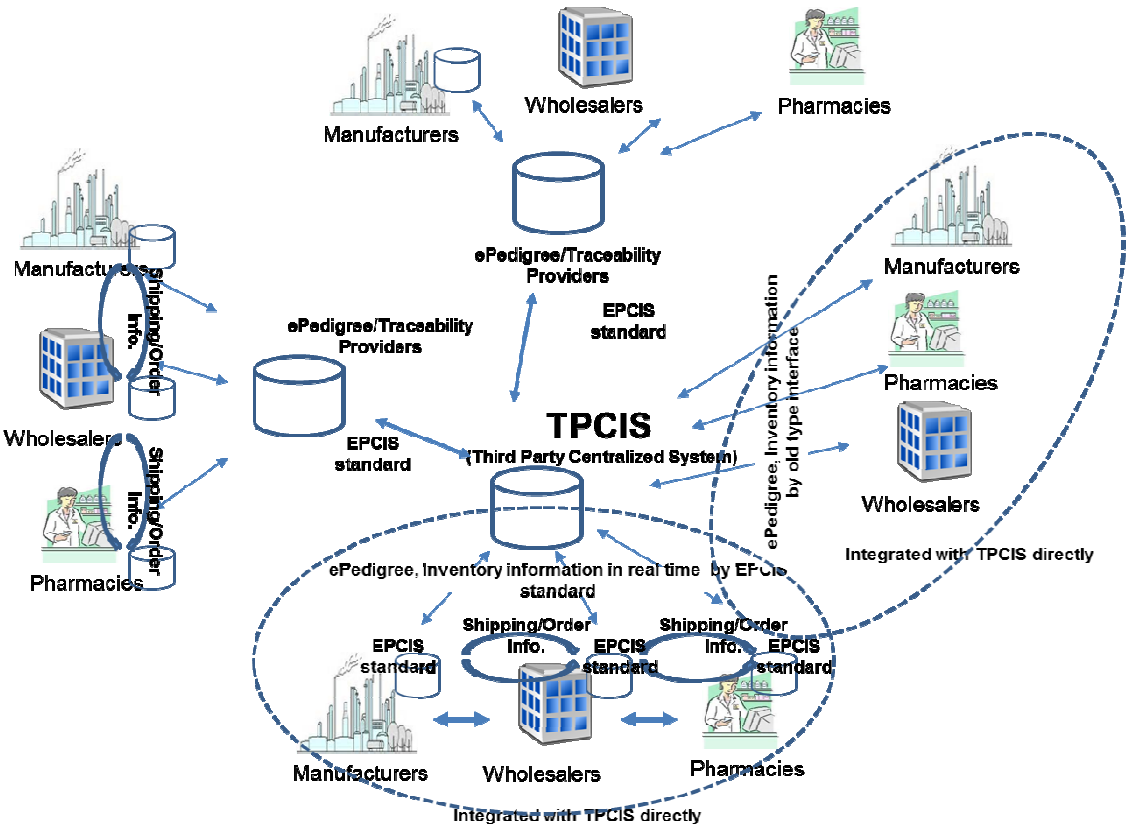


Figure 4-1 Concept of third party centralized integrated system

Centralized database also could supplement EPCIS network's shortcomings for fast and efficient drug authentication and recall process. As previously discussed, participants in the supply chain could join a community to achieve common objectives and share their

information related traceability and visibility with other trading partners. The 'Third Party Centralized Integrated System' was designed and proposed by taking ingredients that are necessary for improving three big problems, blending and mixing them. Figure 4-1 describes the concept of the proposed system. Third Party Centralized Integrated System (TPCIS) integrates participants directly with EPCIS standard or old type ways and integrates other ePedigree and traceability or visibility providers' systems. Unlike that TPCIS can supply real time inventory or traceability to participants within the TPCIS network, there could be limitations of information sharing between TPCIS and other networks. However, the position of TPCIS is in expanding its network continuously to maximize the effectiveness of data sharing. The trading partners which joined TPCIS have to comply with the requirements from TPCIS. By doing this all participants in TPCIS could be verified by TPCIS or FDA because FDA has authority on the TPCIS. One main feature of TPCIS is that FDA can access and manage the data for better drug shortages operation plan, thus coping with counterfeit and diverted drug and recall process. Table 4-1 shows all characteristics of the proposed model, TPCIS.

Table 4-1 Concepts of Third Party Centralized Integrated System

Features	- Track and tracing for unit level Items for counterfeit and diverted drugs - Supply ePedigree information to the participants companies. - Centralized, real time inventory control reduce drug shortages - Fast and efficient recall process - Independent third party manage confidential information and supply them to FDA - Interface with other EPCIS network with EPCIS standards ==> Upper level of integration above EPCIS networks -low cost for small companies with easy data interface solutions
Standard	- EPCIS, old style interface tools (Excel, email and EDI)
Database	- Centralized database has minimum data - Local or Saas (Soft as a Service)
Administration	- Independent third party corporation - Its jobs have to be focused and limited to the certain works - Data has to be carefully handled based on the agreements - FDA has a authority for administration - Requirements for companies, for instance VAWD (Verified-Accredited Wholesale Distributors) and VIPPS (Verified Internet Pharmacy Practice Sites)

Chapter 5

Simulation TPCIS (Third Party Centralized Integrated System)

5.1 Background and objectives

5.1.1 Background

TPCIS was designed and proposed based on several key concepts from literatures and case studies from the industry. Objectives of TPCIS are preventing counterfeit and diverted drug from occurring in a secure pharmaceutical supply chain. A key point of TPCIS is data sharing between trading partners. It should be obvious that unit items having serialized global item number (SGTIN) increase better traceability and visibility system against counterfeit and diverted drugs. However, it is not obvious how much improvement could be expected, what sorts of factors is interacting and what algorithms could be applied. Likewise, there could be motivation to know how well the supply chain handles drug shortages with sharing traceability data through TPCIS, and what other factors including inventory policies, production or delivery lead time are related each other with TPCIS. Simulation models could answer questions with minimized time and resources.

5.1.2 Objectives

The main objective of simulation is to prove the proposed model, i.e., TPCIS could be a good solution to improve the three drug related problems in the USA. Three simulation models have been developed. The first model is ePedigree simulation model, which has its own basic and key features including ePedigree itself and unit level serialized traceability and visibility. This model has to show how the trading partners get pedigree information, how drug authentication for counterfeit and diverted drugs works for the participants, and what algorithm could be applied to that process. The second model

is a drug shortage simulation model, which proves that drug shortage could be reduced by data sharing and how the early drug shortage alert system works. The third one is a recall process model, which can verify that TPCIS helps the recall process become faster and more efficient with low cost and less resources.

5.2 Literature review

Like in nature, there are numerous uncertainties and variables unexpected in business environments. The possibilities of successful business mainly depends on how well the uncertainties and unexpected variables are to be anticipated and controlled. To reach the optimized systems or models, a trial and error way could be used. However, due to costs and limited resources issues, simulation might be a good way to develop the best models with minimized resources. There might still be constraints with developing even simulation models. The deeper into the details, it might need more resources and time, which means that the abstraction of simulation is quite important. Having the clear objective of using simulation model is very important to developing the models with no extras resources. For making right abstraction of simulations, there are several factors to be considered. Those include data availability, expertise of the modelers, simulation software capabilities and time (Sanjay Jain et al 2001). A research paper discussed whole simulation developing processes including modeling of current process, how to include activities or variables into the model, and how to use historic data to simulate 'to-be' models. Sanjay also discussed how to use simulation software ARENA to build models and analyze the results from those models. One of the interesting finds were employed from the paper was that the text or Excel files used for data for the simulation model. By using text or Excel files, simulation code modifications could be minimized for many different scenarios (Sanjay Jain et al 2001). One simulation model with ARENA

was used to generate realistic test data of the pharmaceutical supply chain to be used purposely for testing of software developing. In that paper, the authors used EPCIC network as the system standard, followed process based on that standard and generated related data into two txt type of files. There were two interesting points in the paper. One was that the authors used ARENA's Assign process to assign sgtin, e.g., urn:epc:id:sgtin: MAN_ID:TYPE_ID:PROD_ID. The other was that the authors developed a scenario generator with Visual Basic to generate different scenarios automatically (Jurgen Muller at el 2009).

5.3 Common concepts and conditions or assumptions

In this research, three simulation models have been developed. Although several different simulation conditions could be applied for each simulation model due to the simulation time and its complexity issues, still basically the same common conditions or software architectures would to be applied to all three models.

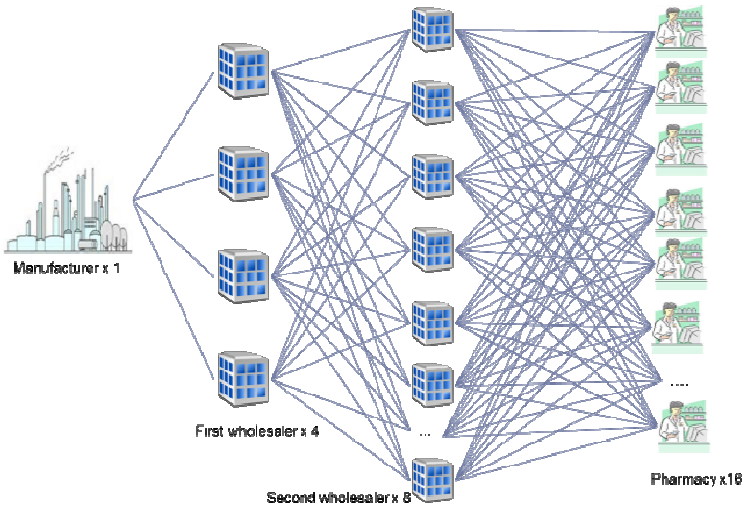


Figure 5-1 Supply chain in simulation models

5.3.1 Conditions

- Pull system, customers initiate orders to pharmacies through wholesalers and manufacturers.
- Includes only finished good and no raw material or work in process
- Handle Unit level Item (serialized global trade item number), i.e., no box or pallet
- Simulation software ARENA generates simulation data, i.e., no real data used.

5.3.2 Software interface architecture

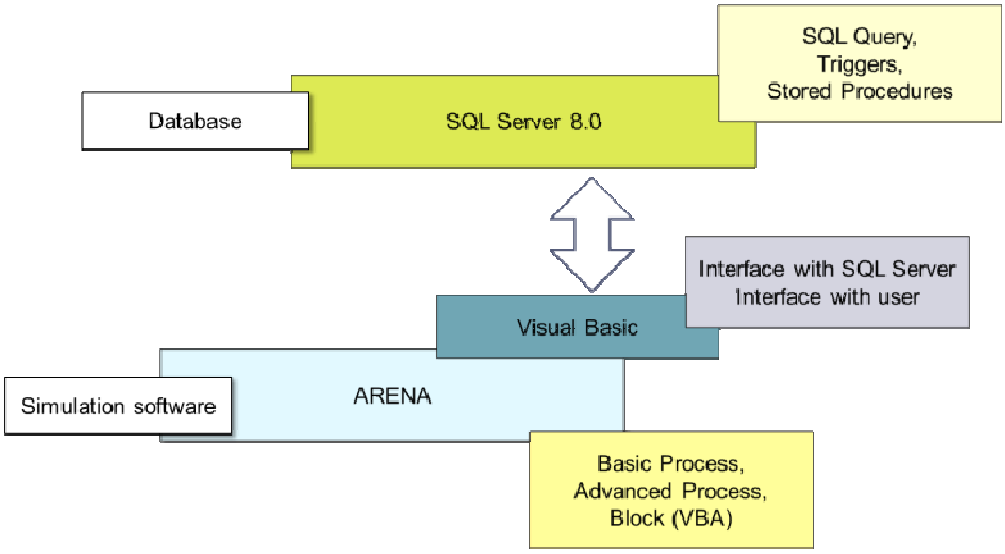


Figure 5-2 Simulation software architecture

Two different individual software tools were basically used for developing simulation models. As a simulation software tool, ARENA was be used. ARENA also supports Visual Basic that allows the models to access separated database software including Excel, Oracle and SQL Server (W. David Kelton et al 2004). SQL Server 8.0 was selected as database software.

5.3.3 ARENA module

Several modules including create, dispose and assign from basic process panel were used. For simulation time was assigned with assign module. Read/Write module from advanced process panel was used for reading data from an external txt file type of data or data from database. VBA module from block panel was used for interface with database, SQL Server 8.0. ARENA supports ADO (Microsoft Active Data Objects) which allows AREAN to connect to SQL Server 8.0. ARENA supports the Visual basic software language, which was used for the user interface and data interface with the database.

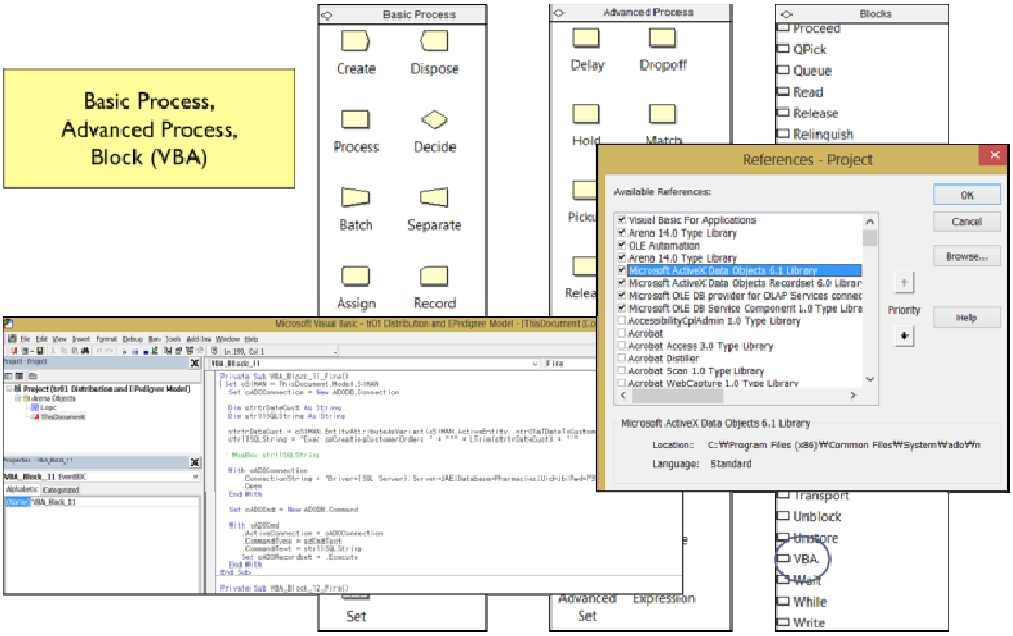


Figure 5-3 Arena components used for models

Figure 5-3 shows how ADO was used to connect to the MS SQL Server 8.0 database. Visual basic integrated with ARENA calls stored procedure in SQL Server 8.0 with ADO.

5.3.4 Database, SQL Server 8.0

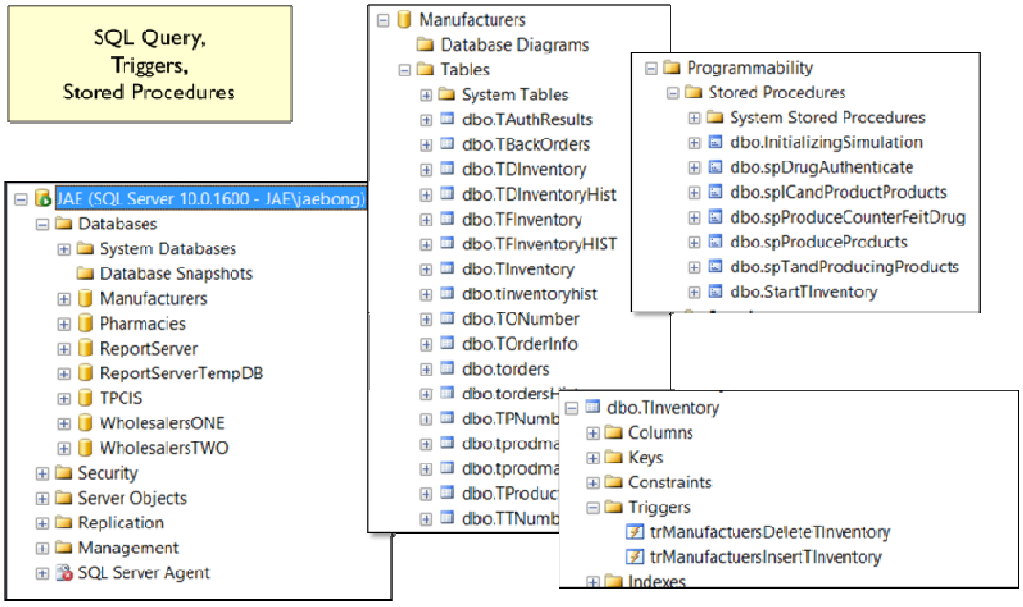


Figure 5-4 SQL server architecture for simulation model

In simulation models, each supply channel type has its own database name, e.g., database name ‘Manufacturers’ is for manufacturers and likewise ‘WholesalersOne’ is for first wholesalers. So there are five database names including TPCIS, which is for centralized database. Two basic components were used to develop simulation model with SQL Server 8.0. One of them is triggers, which did simple jobs e.g., update, insert or delete from tables. The other one, which is stored procedures did complicated jobs, e.g., handling orders, shipping products, assigning SGTIN to each product and more.

5.3.5 Data Interfaces

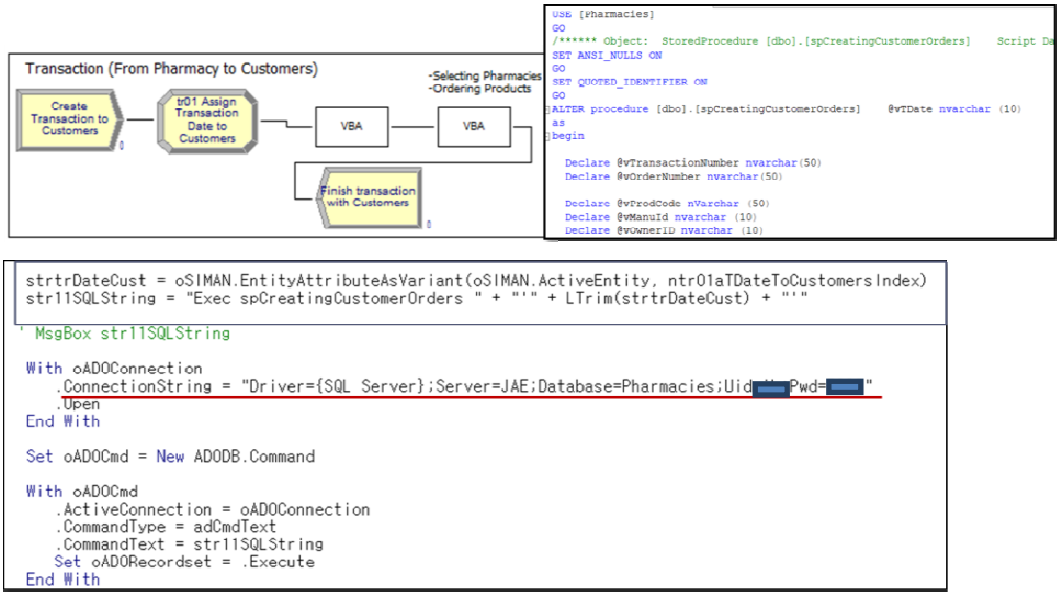


Figure 5-5 Data interface between ARENA and database

Variables assigned in AREAN could be sent to SQL Server as parameters by ADO connection. With ADO component, AREAN could send parameters and get results parameters from database by calling Stored Procedures in SQL Server 8.0.

5.3.6 Basic Modules

The simulation model of Third Party Centralized Integrated System (TPCIS), presented here, has basically four types of supply channels for the pharmaceutical supply chain. In a real pharmaceutical supply chain, there would be much more complicated supply networks. However, it was simplified due to limitation of resources and time while still achieving the objectives of models. Each supply channel has two basic modules.

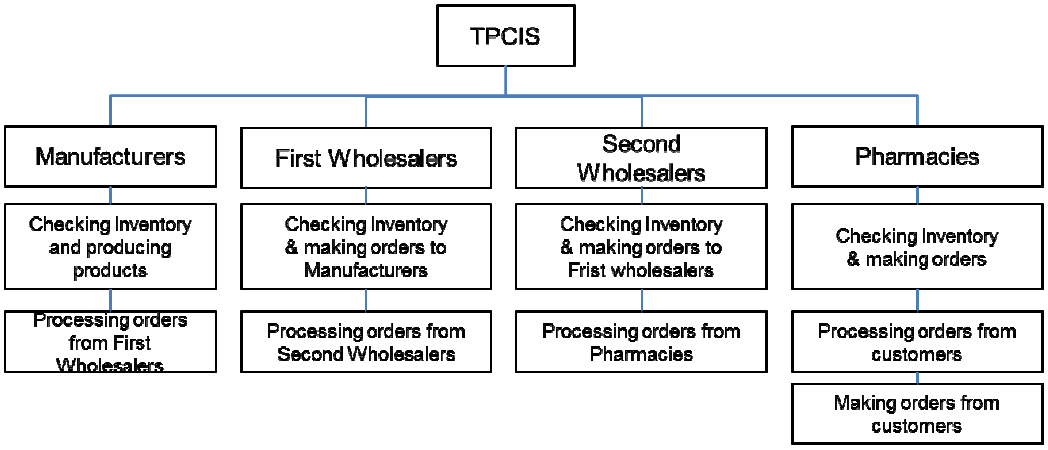


Figure 5-6 Basic modules

Firstly, checking inventory and making orders module makes orders to upper stream supply chain, e.g., for pharmacies, bases on the inventory policy, it generates orders to second wholesalers when it is supposed to do, and likewise the modules in second wholesalers and first wholesalers do the same things. However, the module in manufacturers is somewhat different. Since the module is in manufacturers not in wholesalers, it produces products instead of making orders to suppliers. Secondly, processing orders from downstream supply chain makes transactions, e.g., for pharmacies, they sell the products to the customers who made the orders, and likewise second wholesalers do the same thing to the first wholesalers. The big merit of this proposed TPCIS model is the information integration between supply channels. The centralized database could be located in the third party corporate's local system or a clouding solution provider and this location issue does not make change of the integrated and centralized database concept. Based on this core concept, whenever the trading partners' critical logistical events occur, information related to the events goes to the centralized database in real time manner, e.g., when a pharmacy sells a product to the customer, not only the inventory information in pharmacy local database should be

modified, but also the inventory information in the centralized database should be modified. Likewise, when the manufacturers produce the products and assign SGTIN or other information to the product, the information goes to the centralized database that would be used for drug authentication process later.

5.4 ePedigree model

5.4.1 Background and objectives

The core point of ePedigree system is unit load level of traceability, i.e., the system should be able to manage Serialized Global Trade Item Number (SGTIN) through whole supply chain and whole products' life. By doing this, ePedigree system prevents counterfeit and diverted drugs from occurring by drug authentication with drug pedigrees or transaction information. Different algorithms could be developed for the authentication process and that would be based on standards of ePedigree systems that trading partners applied into their systems. For instance, with Drug Pedigree Messaging Standard (DPMS), digital signature could be used, and destination or transaction information could be used with EPCIS. In this simulation model for ePedigree, the goal is to implement ePedigree system through simplified supply chain, develop drug authentication algorithms and show how the system does work.

5.4.2 Details in model

5.4.2.1 Initial Inventory

Since this model was focused on the unit level of traceability, drug authentication process and its algorithms, initial inventory was not supposed be sensitive to achievement of this model's objectives.

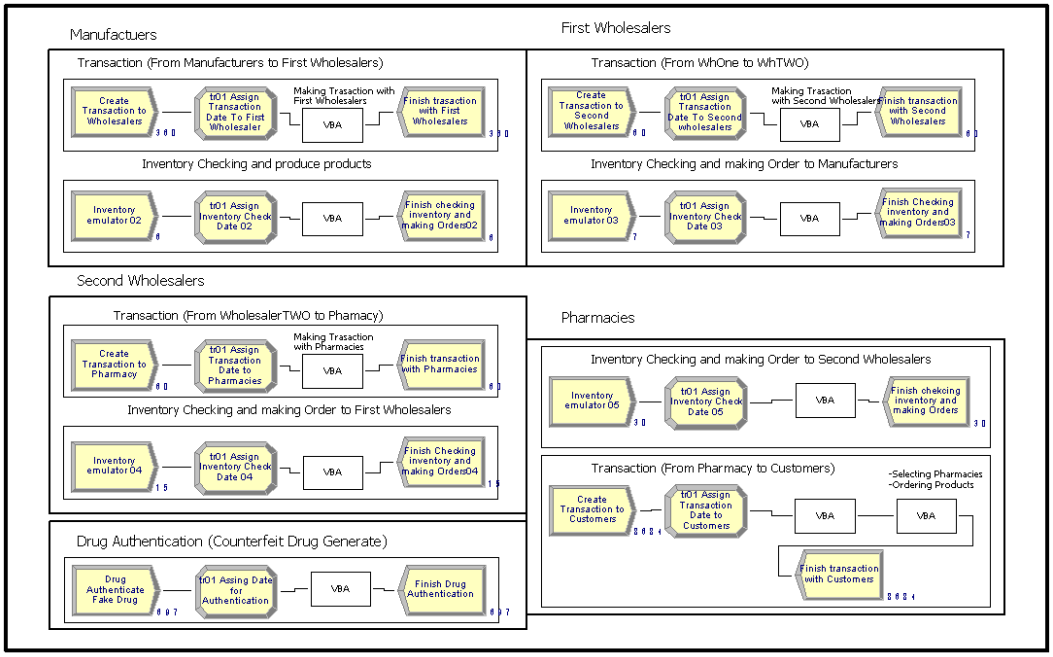


Figure 5-7 Screen capture of ePedigree simulation model

For the same reason initial inventory could be applied to the model before the simulation run. In ARENA, among many events 'RunBeginSimulation' event does something before starting simulation. The stored procedure named 'InitfEPedigree' is called when the 'RunBeginSimulation' event runs, which creates the initial inventory for pharmacies, first and second wholesalers and manufacturers in the database. This stored procedure also creates products and assigns SGTIN, lot number, batch number and expiration date to the product based on each channels' predefined setting.

5.4.2.2 Pharmacies

Table 5-1 shows that the participants in ePedigree simulation model. There are a total of 16 pharmacies. Figure 5-7 shows the main screen with ARENA simulation for the ePedigree model, and each individual sub model has two processes. One is the

inventory checking process and the other is the customer transaction process. Firstly let's start discussing inventory checking process.

Table 5-1 Participants in ePedigree simulation model

Manufacturers	First Wholesalers	Second Wholesalers	Pharmacies
MA01	WHONE01	WHTWO01	PH01
	WHONE02	WHTWO02	PH02
	WHONE03	WHTWO03	PH03
	WHONE04	WHTWO04	PH04
		WHTWO05	PH05
		WHTWO06	PH06
		WHTWO07	PH07
		WHTWO08	PH07
			PH08
			PH09
			PH10
			PH11
			PH12
			PH13
			PH14
			PH15
			PH16

When ARENA creates an entity named "Inventory emulator", it calls the stored procedure names "spICaMOsPHEPedigree". This stored procedure checks inventory every certain period, which could be varied depending on each time setting and it creates replenishment orders to suppliers. However, default setting for ePedigree simulation model has same cycle of that process, which is 2 days. While this inventory checking process is working, each pharmacy checks its inventory level of the products and makes orders to the suppliers when the inventory level reaches a certain low level. The other entity named "Create transaction to customers" calls also stored procedure named "spCCOsEPedigree" and "spTfPHEPedigree". First stored procedure, "spCCOsEPedigree" creates order information for customers. When this stored

procedure is called, it creates order information by selecting customers and products from customers, and also creates product master tables in database respectively in random manner. The second stored procedure, named “spTfPHEPedigree”, makes transaction to customers, i.e., selling the products to customers. In detail, when the pharmacies sell the products to the customers, their inventory information would be changed, e.g., the inventory information of the products sold would be moved from inventory table named “Pharmacies.dbo.TInventory” to inventory history table named “Pharmacies.dbo.TInventoryhist” by a delete trigger named “trPharmacyDeleteTInventory” on inventory table automatically. Order information from customers is to be moved from “Phamrcies.dob.Torders” to “Pharmcies.dbo.TordersHist”.

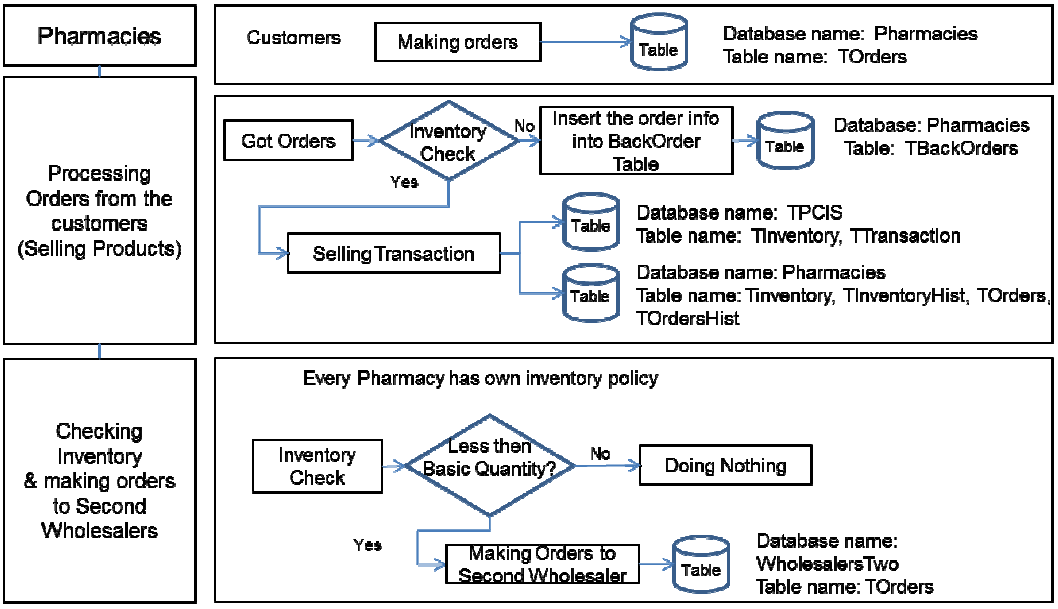


Figure 5-8 Data flows in pharmacies

Basically all permanent information is supposed to be moved from the current tables to history tables. Figure 5-8 describes activities in pharmacies and how data flows based on each activity between databases and tables in the databases.

5.4.2.3 Second Wholesalers

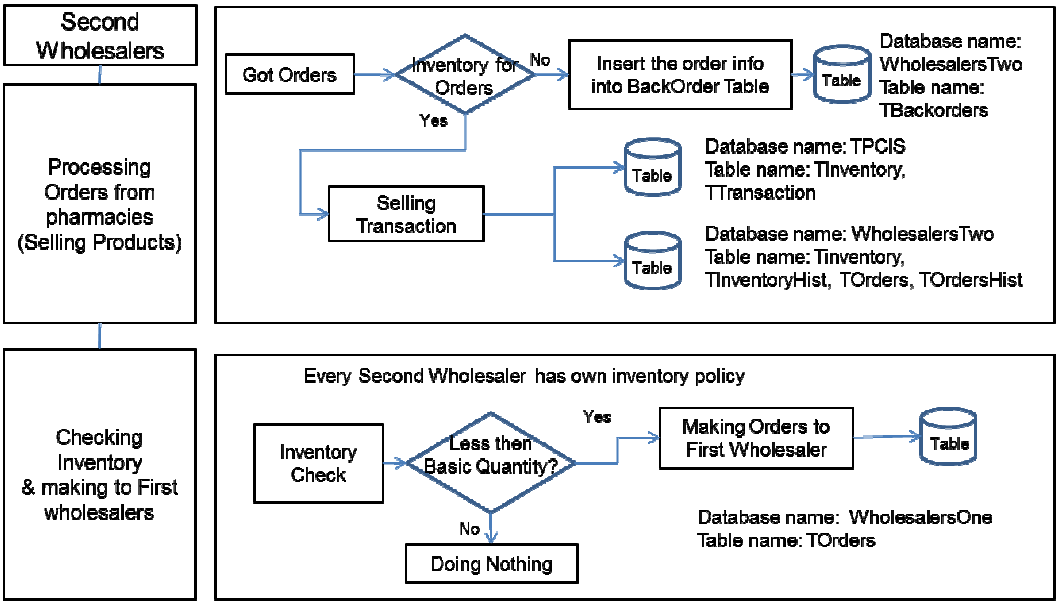


Figure 5-9 Data flow for second wholesalers

Again, two different entities call two different stored procedures in second wholesalers' module. Those two stored procedure do basically the same things for second wholesalers as two stored procedures do for the pharmacies. The entity named "inventory emulator" calls the store procedure named "spICaMOsSWHEPedigree", which checks inventory and creates order information to the suppliers, which are first wholesalers. The other entity named "create transaction to pharmacies" calls the stored procedure named "spTfSWhEPedigree", which make the selling transaction for orders from pharmacies. When the selling transaction occurs, the inventory information is changed. The inventory information of the product sold is to be deleted from the table named "WholesalersTwo.dbo.TInventory" and inserted into the table named "WholesalersTwo.dbo TInvnetoryHist", and this event also makes the inventory information in centralized database. Transaction information is to be recorded in TPCIS

database so that the system supports all trace and tracking information service to the trading partners.

5.4.2.4 First Wholesalers

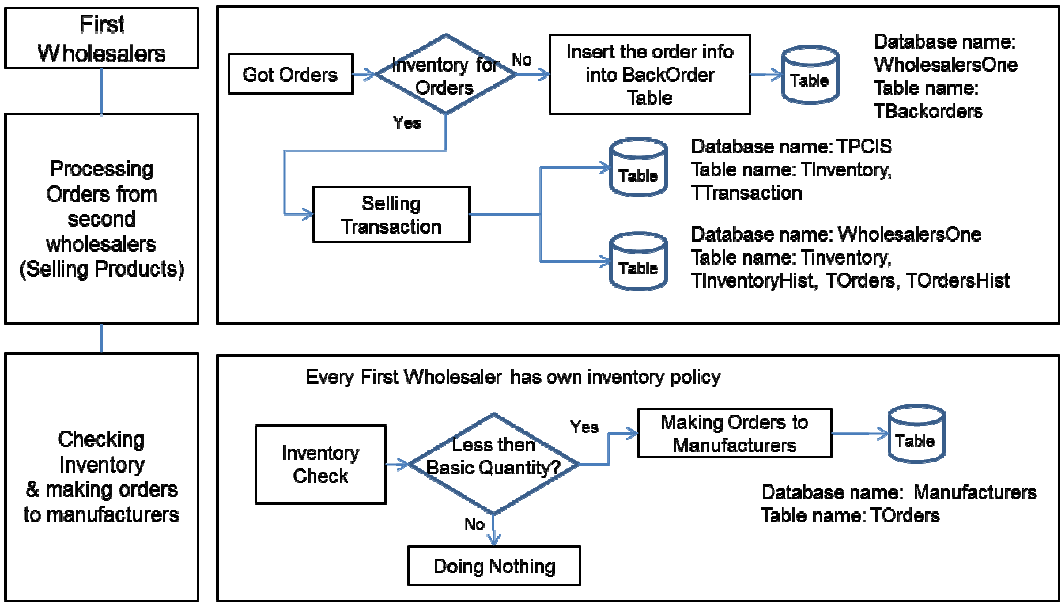


Figure 5-10 Data flow for first wholesalers

The order information from second wholesalers to first wholesalers is to be inserted into table named “WholesalersOne.dbo.TOrders”. When stored procedure named “spTfFWEPedigree” called by an entity named “create transaction to second wholesalers” make a selling transaction, the order information in table “WholesalersOne.dbo.TOrders” is to be deleted and inserted into “WholesalersOne.dbo.TOrdersHist”. The other entity named “inventory emulator” calls the stored procedure named “spICaMOsSWHEPedigree”. This called stored procedure checks each wholesaler’s inventory and creates order information into “Manufacturers.dbo.torders” for manufacturers when it is necessary.

5.4.2.5 Manufacturers

The entity named “create transaction to wholesalers” calls stored procedure named “spTfMaEPedigree”, which makes transaction for orders from first wholesalers. The other entity named “Inventory emulator” calls stored procedure “spICfMaEPedigree”, which checks inventory for each manufacturer and produces the products if it is necessary. When it comes to producing products, the most important and unique job is to assign key information including SGTIN, lot number and expiration date to each product. Especially assigning SGTIN is basic, important and complicated because that number is supposed to be unique through its whole supply chain, which means that the unit product having SGTIN could be traceable through its whole global supply chain, too. The assign SGTIN rule is a little bit different from the standard for simulation convenience. EPC pure Universal Resource Identifier (URI) is urn:epc:id:sgtin: StoredProcedureCode:-CompanyCode:productCode:SeiralNumber(ManufactureDate+Serial), e.g., ‘MAS:MA0131117:2014071120007’ in this model. Setting the SGTIN as a unique key in the database is the way that guarantees the SGTIN is unique throughout the supply chain. When the stored procedure produces products and assigns product-related information to it, the information also goes to the centralized database to update or insert into the transaction and inventory tables in TPCIS.

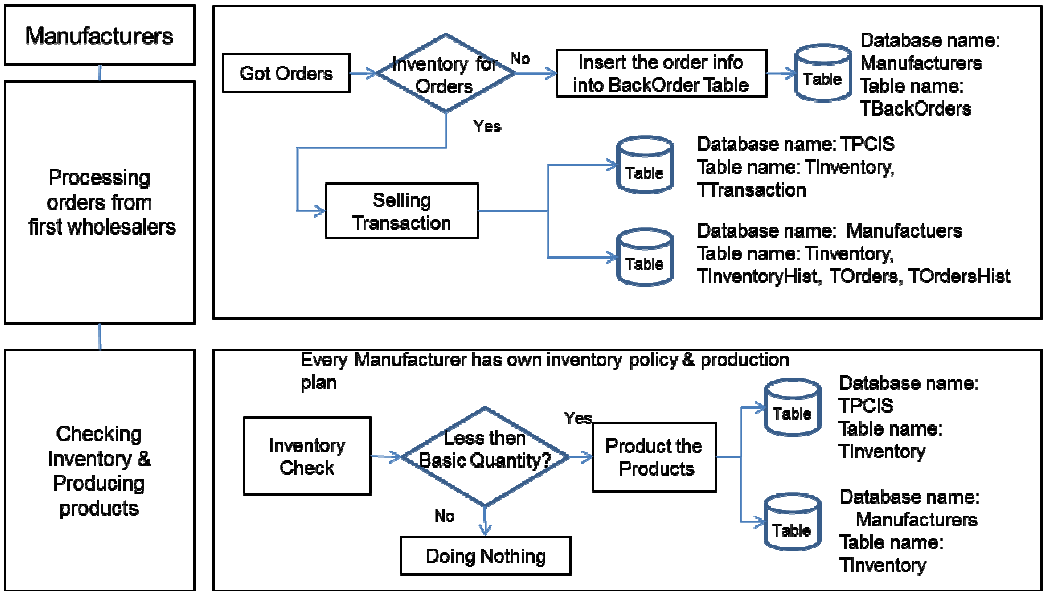


Figure 5-11 Data flow for manufacturers

Figure 5-11 describe this process. Each product has its own production lead time or plan, and the manufacturers produce products based on the setting in this simulation model. The trigger named “trManufactuersInsertTInventory” on ‘Manufacturers.-dbo.TInventory” inserts production information into a table named “TPCIS.dbo.TInventory” in TPCIS when new inventory information enters into “Manufactur-ers.dbo.TInventory”

5.4.2.6 Authentication algorithm

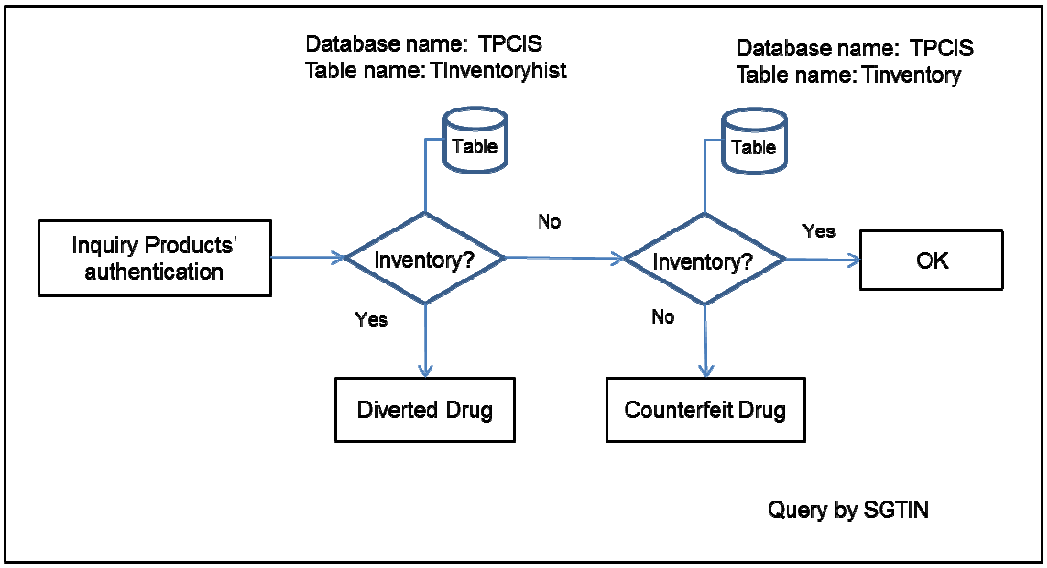


Figure 5-12 Authentication algorithm

The proposed TPCIS integrates other EPCIS networks to manage total integrated traceable item information to cope with counterfeit, diverted drugs and drug shortage issues. However, in this simulation model, the drug authentication algorithm might be applied for only TPCIS, i.e., between trading partners within TPCIS. Since the centralized database has all unit products' transaction and inventory information in real time based on SGTIN, the drug authentication algorithm might be quite simple as in the Figure 5-12. Basically and originally the drug authentication process is supposed to be done when or before the companies receive the products in real situation. However, due the simulation time issues, one stored procedure named "spProduceCounterFeitDrug" in the manufacturers' database creates counterfeit and diverted drugs and inserts that information into "manufacturers.dbo.TFInventory" when it is called by the entity named "Drug Authenticate Fake Drug". When stored procedure for making transaction in each supply channel is called, another stored procedure named "spDrugAuthenticate" is called

for counterfeit and diverted drug authentication. For drug authentication, SGTIN basically is used because it is unique. When the simulation model checks whether or not the drug is counterfeit or diverted, it firstly checks the inventory history data named "TPCIS.dbo.TInventoryHist" in centralized database. If the product information or SGTIN was found in the inventory history table, then the drug might be diverted because the drug information would be stored into the inventory history table when pharmacies sold the drug to end consumers, i.e., the drug's life in its supply chain was complete. Those drugs that are already sold to the customers are not supposed to move around supply chain again. If SGTIN was not found either in inventory history table or inventory table named "TPCIS.dbo.TInventory", then the drug might be counterfeited because the centralized database does not have that product's SGTIN.

5.4.3 Run model

Before running the ePedigree simulation model, several conditions are supposed to be set. The main object of this model is to develop the ePedigree system.

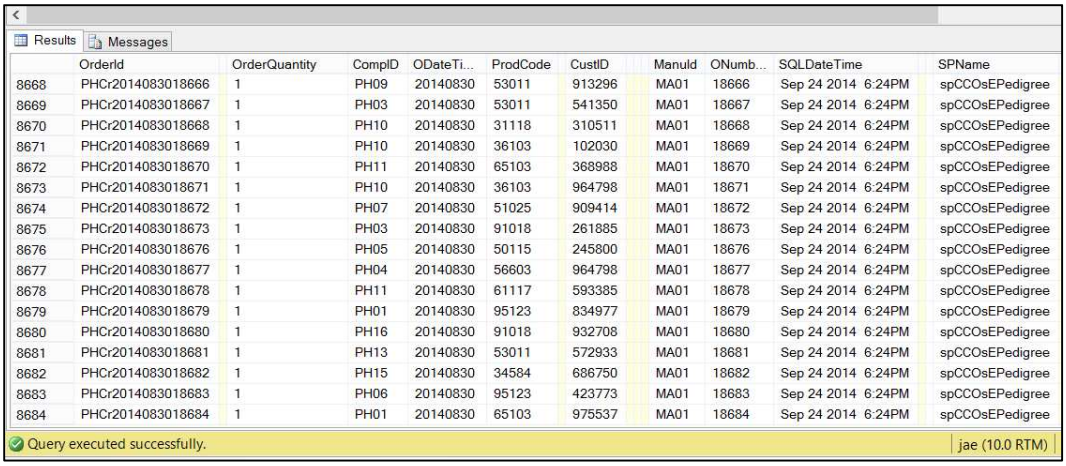
Table 5-2 Run conditions for ePedigree model

Replication Length	**60 days (12 hr/day)**
Inventory Policy	(Q, r) & Q and r fixed
Customers' Demand distribution	Expo(5) min
Lead time (From Order to Receiving)	Pharmacies (2), Second wholesalers(4), First Wholesalers (8day)

The Table 5-2 shows some basic conditions for running of the model. Simulation length is 60 days, which is quite enough to check the model does work as it was intended. The run conditions in the Table 5-2 are not sensitive factors to get to the results of this ePedigree model. However, those conditions should be different for the drug shortage simulation model.

5.4.4. Model Verification

From creating customers' orders for pharmacies to production of manufacturer, there are so many data transactions between trading partners and even process events within one company. Checking that the data flow is correct as it was designed is very important to have trustable results of the simulation models. This process is a quite tedious job because there are many data inquiries within database, between database and with ARENA simulation models. However, very detailed model verification, which is basically data transaction checking, has been done to make sure that all the data transactions are correct.



Results | Messages

	OrderId	OrderQuantity	CompID	ODateTi...	ProdCode	CustID	ManuId	ONumb...	SQLDateTime	SPName
8668	PHCr2014083018666	1	PH09	20140830	53011	913296	MA01	18666	Sep 24 2014 6:24PM	spCCOsEPedigree
8669	PHCr2014083018667	1	PH03	20140830	53011	541350	MA01	18667	Sep 24 2014 6:24PM	spCCOsEPedigree
8670	PHCr2014083018668	1	PH10	20140830	31118	310511	MA01	18668	Sep 24 2014 6:24PM	spCCOsEPedigree
8671	PHCr2014083018669	1	PH10	20140830	36103	102030	MA01	18669	Sep 24 2014 6:24PM	spCCOsEPedigree
8672	PHCr2014083018670	1	PH11	20140830	65103	368988	MA01	18670	Sep 24 2014 6:24PM	spCCOsEPedigree
8673	PHCr2014083018671	1	PH10	20140830	36103	964798	MA01	18671	Sep 24 2014 6:24PM	spCCOsEPedigree
8674	PHCr2014083018672	1	PH07	20140830	51025	909414	MA01	18672	Sep 24 2014 6:24PM	spCCOsEPedigree
8675	PHCr2014083018673	1	PH03	20140830	91018	261885	MA01	18673	Sep 24 2014 6:24PM	spCCOsEPedigree
8676	PHCr2014083018676	1	PH05	20140830	50115	245800	MA01	18676	Sep 24 2014 6:24PM	spCCOsEPedigree
8677	PHCr2014083018677	1	PH04	20140830	56603	964798	MA01	18677	Sep 24 2014 6:24PM	spCCOsEPedigree
8678	PHCr2014083018678	1	PH11	20140830	61117	593385	MA01	18678	Sep 24 2014 6:24PM	spCCOsEPedigree
8679	PHCr2014083018679	1	PH01	20140830	95123	834977	MA01	18679	Sep 24 2014 6:24PM	spCCOsEPedigree
8680	PHCr2014083018680	1	PH16	20140830	91018	932708	MA01	18680	Sep 24 2014 6:24PM	spCCOsEPedigree
8681	PHCr2014083018681	1	PH13	20140830	53011	572933	MA01	18681	Sep 24 2014 6:24PM	spCCOsEPedigree
8682	PHCr2014083018682	1	PH15	20140830	34584	686750	MA01	18682	Sep 24 2014 6:24PM	spCCOsEPedigree
8683	PHCr2014083018683	1	PH06	20140830	95123	423773	MA01	18683	Sep 24 2014 6:24PM	spCCOsEPedigree
8684	PHCr2014083018684	1	PH01	20140830	65103	975537	MA01	18684	Sep 24 2014 6:24PM	spCCOsEPedigree

Query executed successfully. jae (10.0 RTM)

Figure 5-13 Order information from customers to pharmacies

5.4.4.1 Order transactions

Figure 5-13 shows total order information from customers to each pharmacy. Each order has basically 1 order quantity. The total order quantity from customers, which is 8,684, in Figure 5-13 is the same as the numbers in Table 5-3. This means order transactions with the simulation model have been done correctly because the orders and the shipments information for each pharmacy is exactly the same.

Table 5-3 Order and shipment information for pharmacies

Company Id	Sum of Order Quantity	Owner Id	Sum of Shipped Quantity
PH01	518	PH01	518
PH02	518	PH02	518
PH03	533	PH03	533
PH04	524	PH04	524
PH05	513	PH05	513
PH06	543	PH06	543
PH07	580	PH07	580
PH08	541	PH08	541
PH09	546	PH09	546
PH10	559	PH10	559
PH11	600	PH11	600
PH12	550	PH12	550
PH13	562	PH13	562
PH14	495	PH14	495
PH15	564	PH15	564
PH16	538	PH16	538
Total	8,684	Total	8,684

After checking orders and shipping information for each supply tier and trading partner, it has been verified that transactions between trading partners have been done correctly.

Table 5-4 Order and shipment information for second wholesalers

Company Id	Sum of Order Quantity	Owner Id	Sum of Shipped Quantity
WHTWO01	830	WHTWO01	830
WHTWO02	685	WHTWO02	685
WHTWO03	600	WHTWO03	600
WHTWO04	755	WHTWO04	755
WHTWO05	645	WHTWO05	645
WHTWO06	930	WHTWO06	930
WHTWO07	730	WHTWO07	730
WHTWO08	695	WHTWO08	695
Total	5,870	Total	5,870

Table 5-5 Order and shipment information for first wholesalers

Company Id	Sum of Order Quantity	Owner Id	Sum of Shipped Quantity
WHONE01	970	WHONE01	970
WHONE02	1,150	WHONE02	1,150
WHONE03	1,010	WHONE03	1,010
WHONE04	980	WHONE04	980
	4,110		4,110

Table 5-6 Order and shipment information for manufacturer

Company ID	Sum of Order Quantity	Owner Id	Sum of Shipped Quantity
MA01	2,060	MA01	2,060

5.4.4.2 Data integration between participants and TPCIS

One of feature of Epedigree simulation model is centralized database. TPCIS has basically the same inventory information for each trading partners' product code and SGTIN (Serialized Global Trade Item Number). Inventory quantities of each participant's database and TPCIS' database are supposed to be the same. Table 5-7 shows one of the inventory information for pharmacies and TPCIS. This shows that every single trading partner in the pharmacy supply tier has the same inventory quantities as the number in TPCIS, which means that every single transaction between trading partners is correctly updating the data in TPCIS.

5.4.4.3 SGTIN

The most important feature of this ePedigree simulation model is SGTIN, which is the unique number and every single transaction including verification process for counterfeit or diverted drugs is based on the number. Firstly it should be shown that SGTIN is very unique through its entirety and secondly trace and tracking information should be inquiry based on the SGTIN.

Table 5-7 Inventory quantity in each pharmacy and TPCIS

Individual Pharmacy		TPCIS	
Owner ID	Inventory Quantity	Owner ID	Inventory Quantity
PH01	417	PH01	417
PH02	430	PH02	430
PH03	422	PH03	422
PH04	420	PH04	420
PH05	417	PH05	417
PH06	432	PH06	432
PH07	419	PH07	419
PH08	427	PH08	427
PH09	425	PH09	425
PH10	424	PH10	424
PH11	417	PH11	417
PH12	422	PH12	422
PH13	427	PH13	427
PH14	417	PH14	417
PH15	424	PH15	424
PH16	426	PH16	426
Total	6,766	Total	6,766

First, uniqueness of SGTIN is proved in a very simple way. If the column of the SGTIN in database is set as unique key, then no duplicated data is allowed in a table. All the columns for SGTIN in all tables are set as unique key, so that SGTINs are unique numbers is obvious. Figure 5-17 shows that setting screen for unique key in a database.

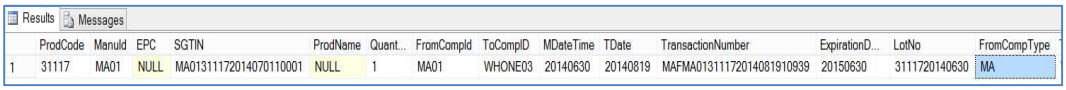


Figure 5-14 Transaction information for a SGTIN

Figure 5-14 shows that the transaction information for the SGTIN, ‘MA01311172014070110001’. It shows that the product was shipped from manufacturer, ‘MA01’ to ‘WHONE03’ , the transcation date is ‘20140819’ and more information about

the transaction. Figure 5-15 shows that shipping information about the SGTIN, which includes shipping date, order date from first wholesaler and more.

Results | Messages

	ProdCode	ManuId	SGTIN	MDateTime	LotNo	ExpirationDate	ShippingDateTime	Quant...	SPName	ODateTime
1	31117	MA01	MA01311172014070110001	20140630	3111720140630	20150630	20140819	1	spTfMaEPedigree	20140818

Figure 5-15 Shipping information of manufacturer of a SGTIN

Figure 5-16 shows that inventory information of same SGTIN in first wholesaler, which bought that product from the manufacturer, ‘MA01’. It shows that received date and more.

Results | Messages

	ProdCode	OwnerID	ManuId	SGTIN	Quant...	MDateTime	ExpirationDate	LotNo	OwnerName	RDateTime
1	31117	WHONE03	MA01	MA01311172014070110001	1	20140630	20150630	3111720140630	NULL	20140825

Figure 5-16 Inventory information for a SGTIN in first wholesaler

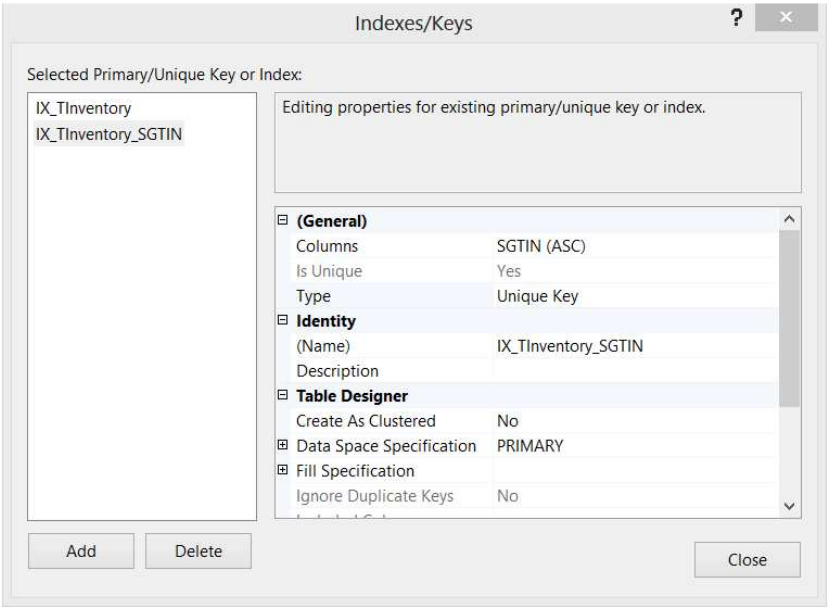


Figure 5-17 Setting for unique key with SQL Server 8.0

There are much more data transactions and communication points including data flow from the ARENA simulation module to the SQL database through the VBA (Visual Basic Application) module. Simulation date, one the most important data, should be integrated

through all three main different modules. All those data flow has been checked and proved during developing simulation models.

5.4.5 Results of the model

The results might be quite straightforward. Figure 5-18 shows that total 8,684 customers' orders were created for the pharmacies. Since the distribution used in this model for creating customers' orders was exponential distribution, average 2 minute, there was not big fluctuation.

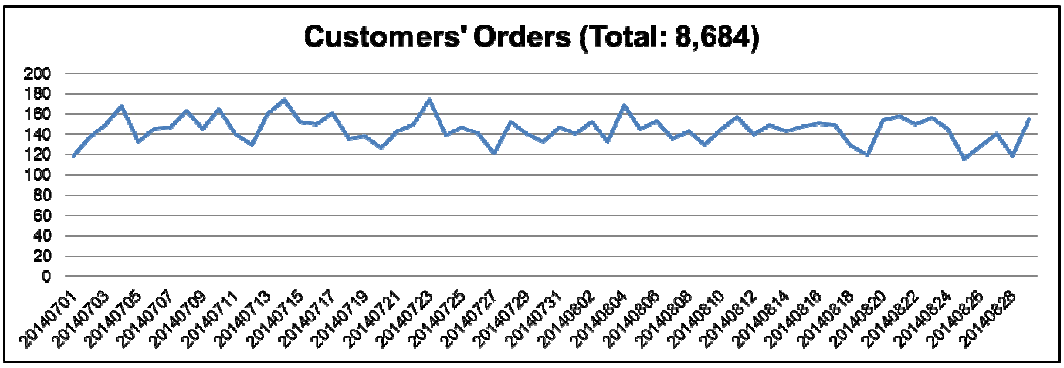


Figure 5-18 Number of customers' orders

Figure 5-19 shows partial of inventory information in manufacturers. It shows SGTIN, product code, manufactured date, lot number and expiration date.

Results | Messages

	manufactu...	ProdCode	sgtin	ownerId	manufactured date	lotno	ExpirationDate date
1	MA01	31117	MA01311172014082812529	MA01	20140827	3111720140827	20150827
2	MA01	31117	MA01311172014082812607	MA01	20140827	3111720140827	20150827
3	MA01	69355	MA01693552014082812672	MA01	20140827	6935520140827	20150827
4	MA01	69355	MA01693552014082812737	MA01	20140827	6935520140827	20150827
5	MA01	69355	MA01693552014082812802	MA01	20140827	6935520140827	20150827
6	MA01	50115	MA01501152014082812867	MA01	20140827	5011520140827	20150827
7	MA01	50115	MA01501152014082812932	MA01	20140827	5011520140827	20150827
8	MA01	60015	MA01600152014082812997	MA01	20140827	6001520140827	20150827
9	MA01	60015	MA01600152014082813062	MA01	20140827	6001520140827	20150827
10	MA01	60015	MA01600152014082813127	MA01	20140827	6001520140827	20150827
11	MA01	51025	MA01510252014082813192	MA01	20140827	5102520140827	20150827
12	MA01	51025	MA01510252014082813257	MA01	20140827	5102520140827	20150827
13	MA01	61117	MA01611172014082813309	MA01	20140827	6111720140827	20150827

Figure 5-19 Inventory information in manufacturers

As was mentioned, the objective of this ePedigree simulation model is about traceability and visibility with SGTIN. All transaction information of the product is supposed to be searched and displayed based on basically SGTIN. Figure 5-20 shows some of the basic information of the transaction of one product. It shows that the transaction number, product code, lot number, expiration date, selling company code, buying company code and most importantly SGTIN. As it was designed, all transaction information was stored and modified in the centralized database in TPCIS. Based on the Figure 5-20, the product having product code as '51015' was manufactured July 1st , 2014, by manufacturer code 'MA01' and sold from a second wholesaler coded 'WHTWO04' to a pharmacy coded 'PH02' on Aug 1st ,2014. Its SGTIN, lot number and expiration date are 'MASMA0-15101520140711120538', 'MASMA015101520140711' and '20150711' respectively.

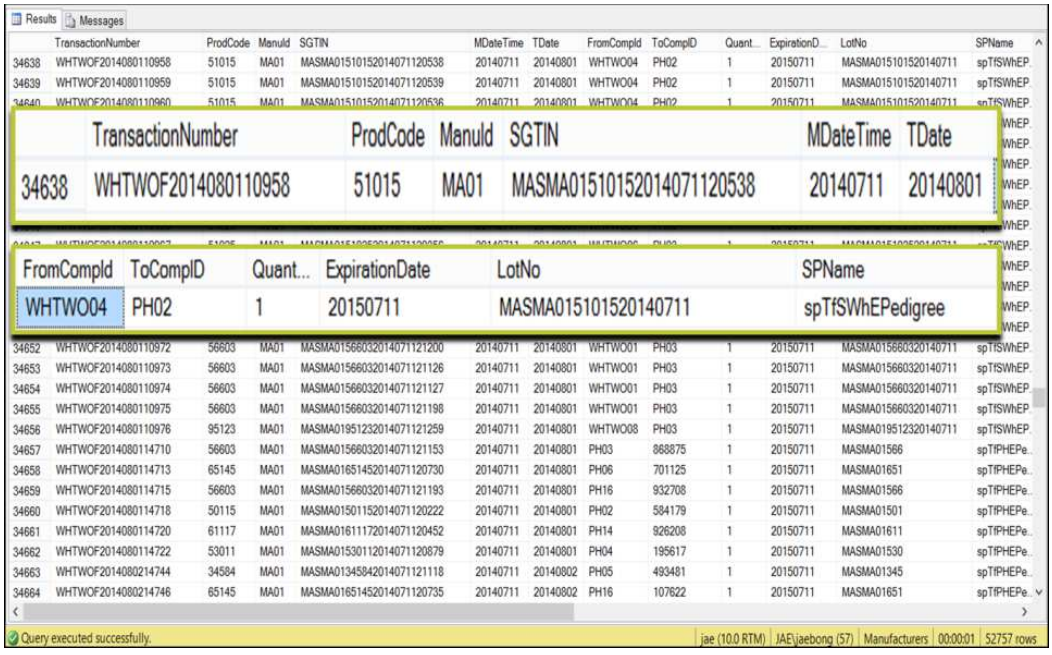


Figure 5-20 Transaction information on TPCIS

Figure 5-21 shows that all trading partners are in the transaction table for the product by inquiry based on the SGTIN. This system was designed to support a traceability and visibility based on the SGTIN. It shows that first trading was July 29th , 2014, and the product was sold from a manufacturer coded 'MA01' to a first wholesaler coded 'WHONE02'. It also shows that final trading was September 26th , 2014, from a second wholesaler coded 'WHTWO01' to a pharmacy coded 'PH14', which means that the pharmacy PH14 still is an owner of the products whose SGTIN is 'MA01951232014063027065'.

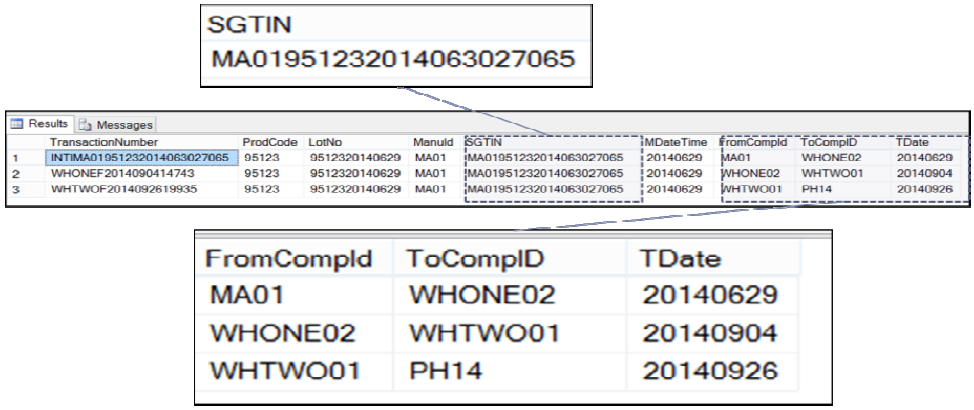


Figure 5-21 SGTIN and transaction information

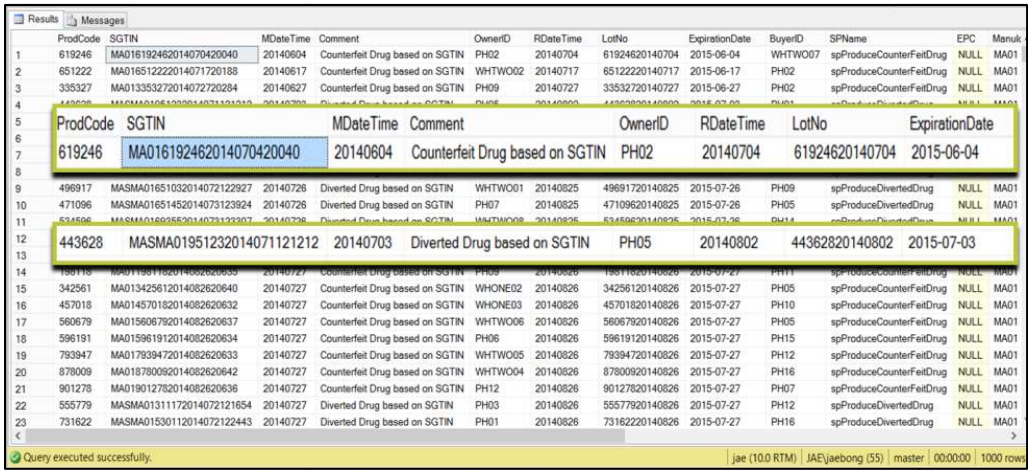


Figure 5-22 Results of drug authentication

Figure 5-22 shows that the most important figure of ePedigree simulation model, which is drug authentication for counterfeit and diverted drugs. The algorithms were explained in an earlier chapter. This simulation model checks the SGTIN at centralized database, which has all transaction and inventory information. By the drug authentication algorithms, the counterfeit and diverted drugs were filtered. Based on the Figure 5-22, the product coded '619246' having SGTIN as 'MA016192462014070420040' was counterfeited because the TPCIS does not find that SGTIN in the centralized database systems. The product coded '443628' having SGTIN as 'MASMA01951232014071121212' was diverted because the TPCIS found that SGTIN in the table named 'TPCIS.dbo.TInventoryHist' in the centralized database systems.

5.5 Drug shortage model

5.5.1 Background and objectives

One of the most important features of TPCIS is the data sharing, and specially inventory information sharing is supposed be very critical for prevention of drug shortage from occurring or mitigate the impact on patients. In the simulation model for drug shortage, the objectives are to figure out how much difference between the current system and TPCIS occur by simulation model, and sensitivity of some factors for results of this model. Before discussing the simulation model in detail, one concept, 'Drug shortage early alert system' should be introduced. This is not like FDA's early notification program, on which the manufacturers have to notify their expected manufacturing issues before stopping producing their products. Since the TPCIS knows each trading partner's current products' inventory information, it could sense that drug shortage before its occurrence. Figure 5-21 describes the concept of Drug shortage Early Alert System (DSEAS). Second wholesalers basically send drug shortage alerts to TPCIS when they

do not have certain product inventory in hand and no more delivery from suppliers. Several reasons that make drug shortage happen were mentioned in an earlier chapter. This drug shortage simulation model only includes drug shortage situations that are caused from temporary production, which could be long or short, e.g., when certain products' production lead times lengthened due to production planning or other issues. The algorithm of the drug shortage early alert system in this drug shortage simulation model for this situation is described in Figure 5-23.

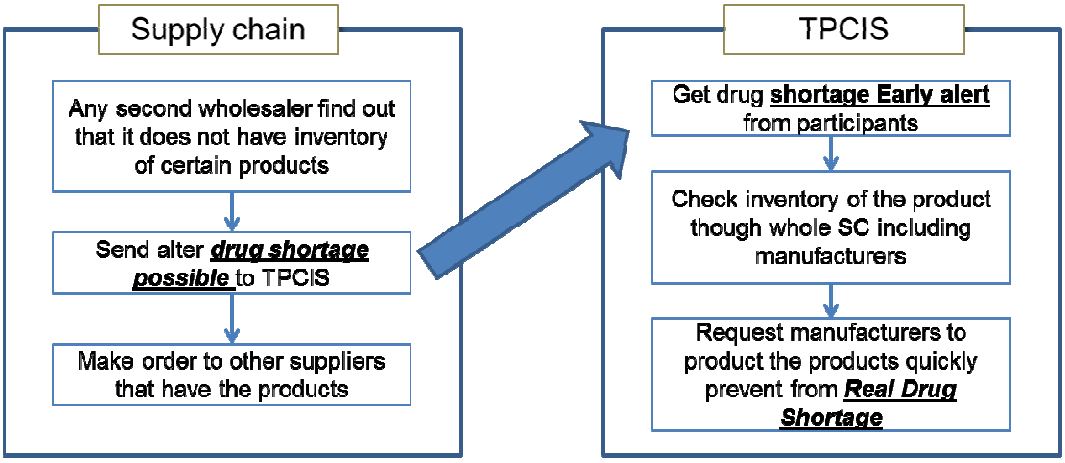


Figure 5-23 Concept of drug shortage early alert system

The Figure 5-24 also describes that when and how the system senses the drug shortage and sends that signal to TPCIS and also to the manufacturer of the products. Pharmacies make purchase orders to second wholesalers. Second wholesalers do that same process to the first wholesalers. However, when none of second wholesalers have certain product inventory so that no pharmacies could buy the product from second wholesalers, TPCSI could send that drug shortage early alert to the manufacturer of that product. It is possible because all trading partners share inventory information so that the TPCIS could sense

certain events that might be the beginning of the drug shortage. When the manufacturer receives the drug supply issues, then the manufacturer needs to produce that product right away, which means that it makes the production lead time short in this simulation model.

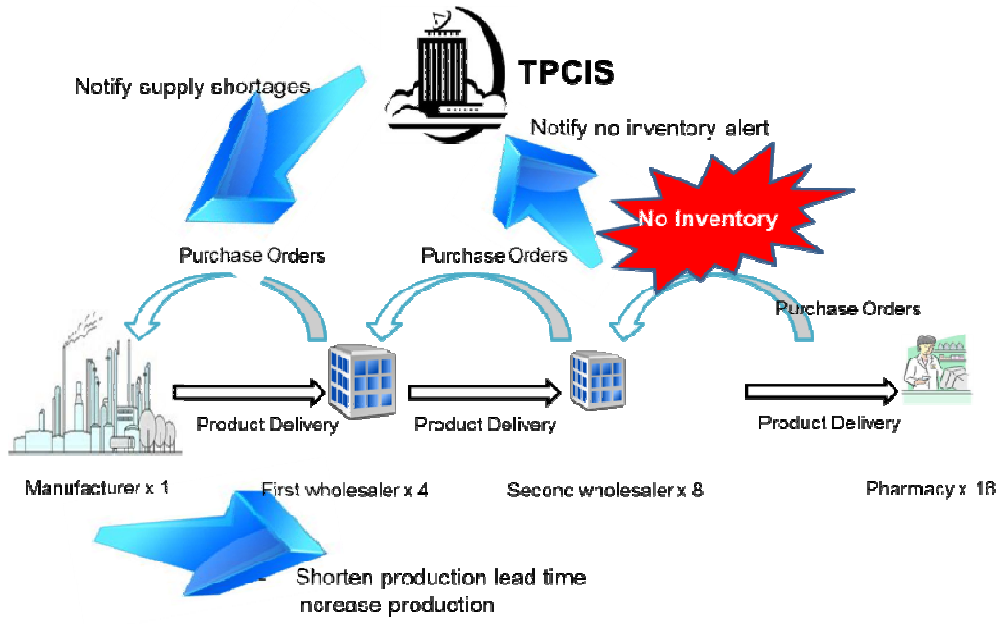


Figure 5-24 Drug shortage early alert system process

5.5.2 Details in model

Since the objectives of the drug shortage model is to figure out how TPCIS could work for drug shortage issues. Several scenarios could be developed for a comparison between them to prove that TPCIS works better for improving drug shortage problems. 'AS-IS' and 'TO-BE' models, two different models need to be developed for each scenario. Main difference assumption between the two models is that the trading partners through the supply chain in 'AS-IS' model do not share inventory information with each

other so that the total inventory quantities of certain products are unknown, and pharmacies or wholesalers do not know which suppliers have inventory for that needed product. However, the participants in the supply chain with 'TO-BE' model share inventory information so that pharmacies know which second wholesalers have inventory of the product in hand, likewise second wholesalers know which first wholesalers have the product in hand. The best feature of 'TO-BE' model is that it applies drug shortage early alert system, which makes the manufacturers handle drug shortage cases more efficiently and faster. This drug shortage simulation model needs to show that TPCIS is working on two different models with different scenarios. Table 5-8 describes these two different models and scenarios. The number of drug shortages in pharmacies would be counted and compared between two models and scenarios. In this drug shortage simulation model, what the drug shortage means is the situation of the trading partners, particularly pharmacies, do not have inventory of certain products for their customers. This drug shortage simulation model counts the number of the cases for comparison between models.

Table 5-8 Simulation design conditions

Simulation design conditions (assumptions)	
AS-IS	-Pharmacies or wholesalers are making orders to upstream suppliers only one time in random manner without knowing whether or not the suppliers have products in hands.
TO-BE (TPCIS)	- Unlike ordering in AS-IS, pharmacies or wholesalers are making orders to the suppliers that have the products in hands. Inventory sharing system makes it possible and it reduces time or resources for order process. - Drug shortage early alert system requests manufacturers to make production as soon as possible.
Common	Assigns different production lead times from originals that do not generate drug shortages to simulate drug shortage during the simulation running

Before applying the scenarios, default models need to be developed, and this model does not generate drug shortages at pharmacies for customers, nor any other

supply tier levels for their trading partners. Modified basic stock model was used for inventory policy for all trading partners and Q, r was determined by certain calculation method, which minimized Q, r and generated no drug shortages for any trading partners. It is quite obvious that r is not supposed to be big, in which case the possibility of drug shortage might be almost zero. The basic condition of determining the value of Q, r for default simulation model is stable inventory level enough prevent drug shortage but not too much for drug shortage case when the different simulation scenario applied.

5.5.2.1 Default simulation model development

As it was mentioned, the default model is the basic model on which 'AS-IS' and 'TO-BE' models are developed for different scenarios. The default model does not generate drug shortage. It is quite important to determine Q, r values, with which no drug shortages happen. All partners make purchase orders to the suppliers every two days and the values of Q are the summation of shipping quantity since the last order, i.e., accumulated shipping quantity during order interval. However, the orders are to be made when the inventory quantity go below reorder points of quantity, which is r values (Wallace J. Hopp, et al 2008).

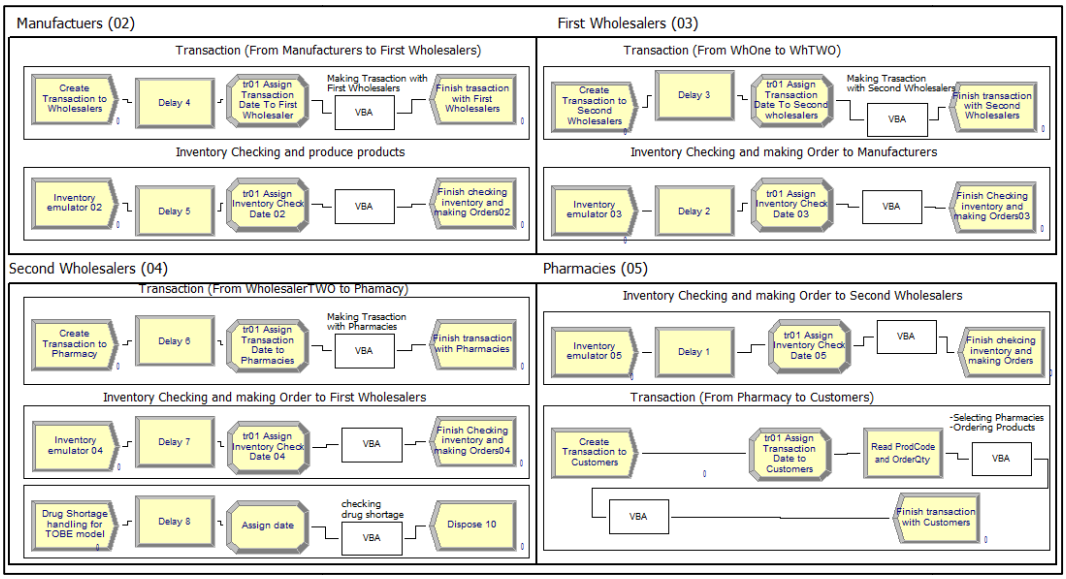


Figure 5-25 Screen captured for drug shortage simulation model

For determining r value of pharmacies, customers demand data should be analyzed. Figure 5-26 shows that there is not much variation from the customers' demand for pharmacies. This figure includes the demand data for a total of 10 products and 16 pharmacies, and this data was generated by the order creating simulation model.

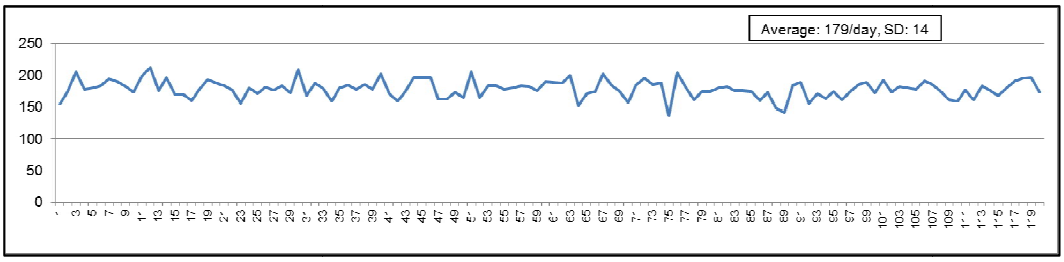


Figure 5-26 Customers' demand for pharmacies for 120days

Based on the Table 5-9, average demands per day for each pharmacy are 1.1. So value 2 is to be used as for the demand data to minimize back orders. r values could be calculated by the formula, = ((Wallace J. HOPP et

al 2008). = 2 x 4 (maximum lead time) = 8, so = 3.49 for 100 % fill rate level. = 8 + 3.49 x = 17.87. So 20 is to be used for r to minimized back orders.

Table 5-9 Average demand for supply tiers per day & product code

Product Code	Average demand/day			
	Pharmacy	Second Wholesaler	First Wholesaler	Manufacturer
31117	1.1	2.1	4.5	17.9
50115	1.1	2.2	4.6	18.6
51015	1.1	2.0	4.2	16.9
51025	1.1	2.2	4.4	17.7
60015	1.1	2.1	4.4	17.5
61117	1.2	2.3	4.4	17.6
65145	1.1	2.2	4.3	17.4
69355	1.1	2.2	4.4	17.4
91017	1.1	2.2	4.3	17.2
91018	1.1	2.2	4.5	17.8

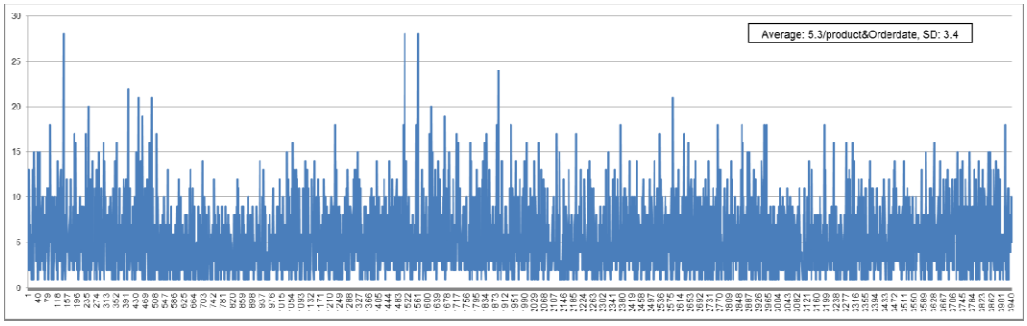


Figure 5-27 Demand from pharmacies to second wholesalers

Again demand data from pharmacies to second wholesalers should be analyzed for r value of second wholesalers. Based on the Table 5-10, the average demands per day for each second wholesaler are 2.2. So value 3 is to be used as for the demand data to minimize back orders. r values could be calculated by the same formulas that were used for pharmacies. Figure 5-27 shows the average order quantity per order and standard deviation. The ratio of average demand is 0.65 so value of the average demand per

day could be calculated as 18 x 0.65 = 11.7 since is 18, = 3 x 6 (maximum lead time) = 18, so = 3.49 for 100 % fill rate. = 18 + 3.49 x 11.7 = 58.8. So 60 is to be used for r to minimize back orders. Based on the demand data from second wholesalers to first wholesalers, the r values could be calculated. = 5 x 10 (maximum lead time) = 50, so =50 x 0.77 = 38.5, the value 0.77 is the ratio of to the average demand per product and order date. = 3.49 for 100 % service level. = 50 + 3.49 x 38.5 = 184. So 190 is to be used for r to minimize back orders.

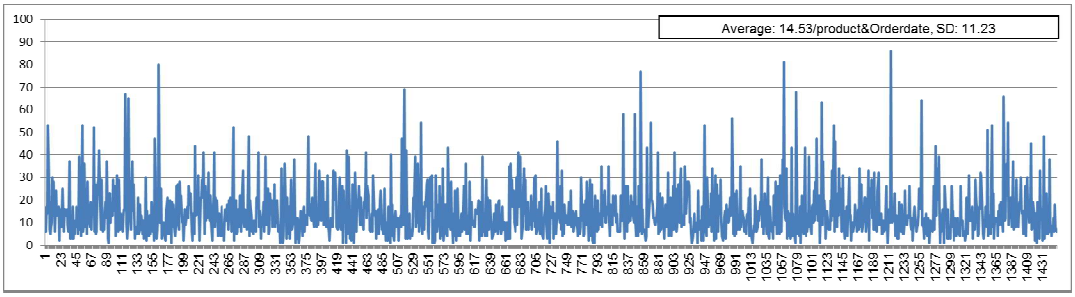


Figure 5-28 Demand from second wholesalers to first wholesalers

Again the r value for manufacturer could be calculated based on the demand information from first wholesaler to manufacturer. Average demand per day is 18 based on the Table 5-9. = 18 x 10 (maximum lead time) = 180, so =180 x 0.56 = 100.8, the value 0.56 is the ratio of to the average demand a product and order date. = 3.49 for 100 % service level. = 180 + 3.49 x 100 = 529. So 530 is to be used for r to minimize back orders.

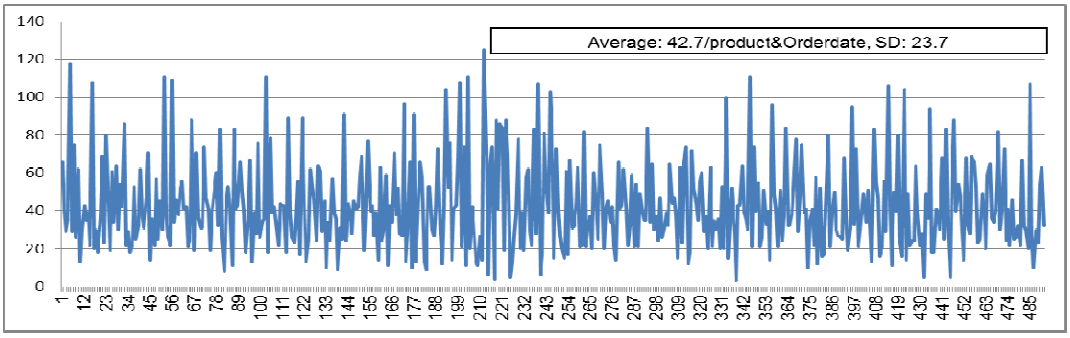


Figure 5-29 Demand from first wholesalers to a manufacturer

Basic processes for drug shortage simulation default model are basically the same as the ones for ePedigree model. However, there are several processes and conditions that differ from the original model to generate drug shortages and compare the number of drug shortages between models. One of them is production lead time. Even though the manufacturer could produce certain products within one day, unless it produces that product every day, it needs more than one day. It might be dependent on product production plan or schedule. So the production lead times for products were set 10 days in default model, which means that the total time for production of products is basically 10 days for all products, which is also different from the delivery lead time from manufacturers to first wholesalers.

5.5.2.2 'AS-IS' simulation model development

The main different condition between default model and 'AS-IS' model is the product production lead time change. After certain days, the product production lead times are to be changed. Table 5-11 shows that each product has its own product lead times to be changed. From the 'AS-IS' model it should be figured out how production lead time might be interacting with the drug shortages. More drug shortages could be expected with longer production lead times. Some very long production lead time means that production might be stopped for quite a long time for any reason in this drug shortage simulation model. After certain products' production problems, there could be drug shortages because no more production along with continued demand from customers. No action from trading partners for drugs shortages for 'AS-IS' simulation model makes the problems worse.

5.2.2.3 ‘TO-BE’ simulation model

Unlike ‘AS-IS’ simulation model, there is the system for handling drug shortages with ‘TO-BE’ simulation model. One of them is the drug shortages early alert system that was explained in an earlier chapter. The other is how to select suppliers when it makes orders. With ‘AS-IS’ model, the participants do not know which suppliers have the inventory for the product that they order so that only one chance of making an order might make back orders to the suppliers. However, with ‘TO-BE’ simulation model the trading partners know which suppliers do have inventory so that they could make orders to the suppliers that have the inventory for the only one opportunity to order, which definitely makes drug shortages reduced.

5.5.3 Run model

5.5.3.1 Default simulation model

Table 5-10 shows the basic simulation running conditions for default simulation model, and there is no drug shortage expected as it was designed and developed originally. Modified basic stock inventory policy model is to be used for drug shortage simulation model and the way to determine each supply tier and product was explained in a previous chapter. Unlike the simulation model for ePedigree, this drug shortage model needs enough simulation length to observe drug shortages. It was quite obvious that the longer the simulation length, the bigger number of drug shortages could be observed. However, 365 days was set for the simulation model due to the simulation running time.

Table 5-10 Simulation run condition for default model

Replication Length		**365 days (12 hr/day)**
Inventory Policy		Modified basic Stock model (Q, r) r is fixed
Customers' Demand distribution		Expo(4) min
Lead time (day)	Delivery	Pharmacies (2), Second wholesalers(4), First Wholesalers(8)
	Production	10 (all products)
Number of Products		10

5.5.3.2 ‘AS-IS’ and ‘TO-BE’ simulation model

‘AS-IS’ and ‘TO-BE’ simulation models are developed from the default drug shortage simulation model. All run conditions are the same as the ones for default simulation model. Table 5-11 shows that basic different run conditions from default simulation model, which is lead time changing during the simulation running and drug shortage early alert system between ‘AS-IS’ and ‘TO-BE’ simulation model. There are supposed to be drug shortage cases with two models for scenario one but the number of drug shortages could be different. That is the main purpose of running two simulation models. The number of drug shortages which could be expected depends on the product production lead times, e.g., the longer production lead time could generate a greater number of drug shortages. The number of drugs shortage with ‘TO-BE’ model is supposed to be smaller than the one with ‘AS-IS’ model. Drug shortage early alert and inventory information sharing system between suppliers might be able to help reduce drug shortages.

Table 5-11 Simulation run condition for ASIS and TOBE models for scenario one

<table>
<tr><th colspan="2"></th><th>AS-IS</th><th>TO-BE</th></tr>
<tr><td colspan="2">Replication Length</td><td colspan="2">Default</td></tr>
<tr><td colspan="2">Inventory Policy</td><td colspan="2">Default</td></tr>
<tr><td colspan="2">Customers' Demand distribution</td><td colspan="2">Default</td></tr>
<tr><td rowspan="2">Lead time (day)</td><td>Delivery</td><td colspan="2">Delivery lead times are default</td></tr>
<tr><td>Production</td><td colspan="2">To be changed after 20 days
<table>
<tr><th>Product Code</th><th>Lead Time</th><th>Product Code</th><th>Lead Time</th></tr>
<tr><td>31117</td><td>10</td><td>61117</td><td>40</td></tr>
<tr><td>69355</td><td>10</td><td>51015</td><td>50</td></tr>
<tr><td>50115</td><td>10</td><td>91018</td><td>60</td></tr>
<tr><td>60015</td><td>20</td><td>91017</td><td>70</td></tr>
<tr><td>51025</td><td>30</td><td>65145</td><td>80</td></tr>
</table></td></tr>
<tr><td colspan="2">Drug Shortage early alert system</td><td>None</td><td>Applied</td></tr>
</table>

5.5.4 Model verification

There are several points that should be verified even though drug shortage simulation model has been developed based on the ePedigree simulation model, which was verified. Firstly, it should be shown that the default model, in which the production lead times are not to be changed, does not have drug shortage cases at all. Two different models, which are ‘AS-IS’ and ‘TO-BE’ model were developed based on the default model. So it is very important that drug shortage default model does not have drug shortage cases because the comparing point between next two simulation models is the number of drug shortage cases during simulation run. The different process between default simulation model and two developed models is the product production lead time changes. Secondly, the production lead time change process needs to be checked. The production lead times of certain products are to be changed to longer days during simulation run, which are different for each product, at certain times. This process generates drug shortages for ‘AS-IS’ and ‘TO-BE’ simulation models.

5.5.4.1 Default simulation model

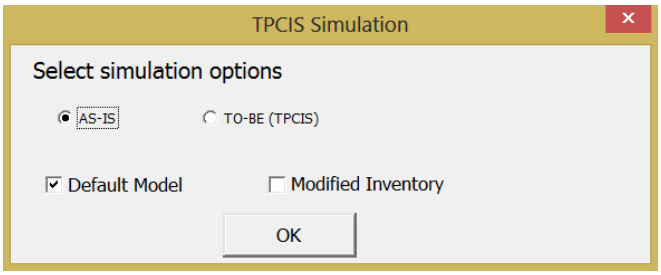


Figure 5-30 User interface for choosing option for simulation run

First of all, the product production lead times need be checked. For the default model, all production lead times are 10 days for all products. Manufactured date in Table 5-12 shows that there is a 10 day interval time between productions for the same product, which is the minimum time for production. Secondly data transactions need to be checked as they are for ePedigree simulation model.

Table 5-12 Inventory sample data in manufacturer

Product_ Code	manufactured_Date	Inventory_Quantity	Product_ Code	manufactured_Date	Inventory_Quantity
31117	20150615	67	61117	20150615	119
31117	20150625	167	61117	20150625	154
31117	20150705	235	61117	20150705	203
50115	20150615	145	65145	20150615	92
50115	20150625	139	65145	20150625	140
50115	20150705	188	65145	20150705	225
51015	20150615	118	69355	20150615	86
51015	20150625	140	69355	20150625	164
51015	20150705	213	69355	20150705	209
51025	20150615	61	91017	20150615	107
51025	20150625	134	91017	20150625	151
51025	20150705	245	91017	20150705	206
60015	20150615	87	91018	20150615	54
60015	20150625	157	91018	20150625	179
60015	20150705	217	91018	20150705	233

Table 5-13 Order quantity and shipped quantity for pharmacies

Company ID	Order quantity	Owner ID	Shipped quantity
PH01	4,148	PH01	4,148
PH02	4,160	PH02	4,160
PH03	3,919	PH03	3,919
PH04	3,969	PH04	3,969
PH05	4,105	PH05	4,105
PH06	4,144	PH06	4,144
PH07	4,133	PH07	4,133
PH08	4,211	PH08	4,211
PH09	3,982	PH09	3,982
PH10	4,032	PH10	4,032
PH11	4,066	PH11	4,066
PH12	4,085	PH12	4,085
PH13	4,066	PH13	4,066
PH14	4,128	PH14	4,128
PH15	4,160	PH15	4,160
PH16	4,103	PH16	4,103
Total	65,411	Total	65,411

Table 5-14 Order quantity and shipped quantity for second wholesalers

Company ID	Order quantity	Owner ID	Shipped quantity
WHTWO01	8,129	WHTWO01	8,129
WHTWO02	8,039	WHTWO02	8,039
WHTWO03	7,876	WHTWO03	7,876
WHTWO04	8,340	WHTWO04	8,340
WHTWO05	7,771	WHTWO05	7,771
WHTWO06	7,884	WHTWO06	7,884
WHTWO07	8,276	WHTWO07	8,276
WHTWO08	8,611	WHTWO08	8,611
Total	64,926	Total	64,926

Table 5-15 Order quantity and shipped quantity for first wholesalers

Company ID	Order quantity	Owner ID	Shipped quantity
WHONE01	15,961	WHONE01	15,961
WHONE02	16,276	WHONE02	16,276
WHONE03	16,566	WHONE03	16,566
WHONE04	16,123	WHONE04	16,123
Total	64,926	Total	64,926

Table 5-16 Order quantity and Shipped quantity for Manufacturer

Company ID	Order quantity	Owner Id	Shipped quantity
MA01	64,600	MA01	64,600

Table 5-13, Table 5-14, Table 5-15, and Table 5-16 all prove that all transactions between participants in the supply chain have been done without any error. Those tables also prove that there are no drug shortage cases in drug shortage simulation default model. It is quite obvious that if there is a drug shortage case, then the order quantity and shipped quantity could not be the same. During the simulation run the drug shortage information is to be inserted into TBackOrders table for each database for each supply tier.

5.5.4.2 Production lead time changes for ‘AS-IS’ and ‘TO-BE’ models

When the simulation day is 20 after the simulation starts, some production lead times are to be changed to make conditions for generating drug shortage cases for ‘AS-IS’ and ‘TO-BE’ model.

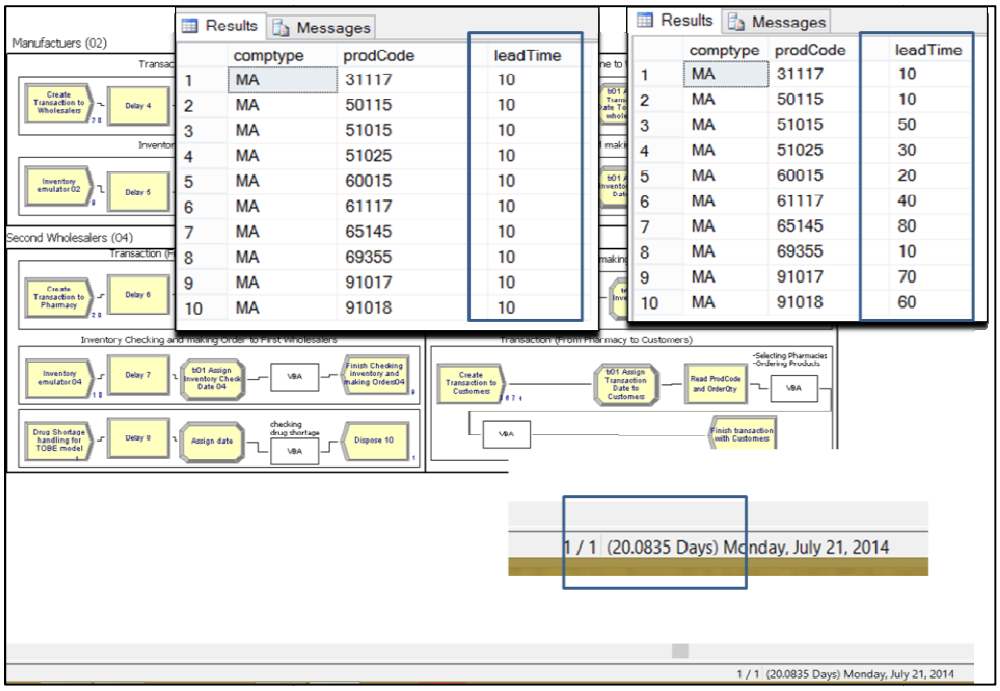


Figure 5-31 Screen captured for production lead time change

Figure 5-31 shows that the production lead times were changed to the longer lead times, which were set originally when the simulation days were 20. These production lead times are not to be changed until the end of simulation run for 'AS-IS', but they are to be changed at a certain time for 'TO-BE' model when drug shortage early alert system senses that drug shortage is a possibility.

5.5.4 Results of the model

As it was expected, the products that have longer production lead times had drug shortage cases in pharmacies at earlier simulation times and more numbers than those of the other products that have shorter production lead times.

Table 5-17 Total numbers of drug shortages

	Default	AS-IS	TO-BE (TPCIS)
Total numbers of Drug shortage at Pharmacies	None	25,511 (Average from 3 replication)	3,786 (85% reduced) (Average from 3 replication)

Table 5-17 shows that the number of drug shortages from 'TOBE' simulation model was significantly reduced, which was 85% from 25,511 to 3,786. This means that the features with Third Party Centralized Integrated System (TPCIS), which has drug shortage early alert system and inventory sharing system, really helps reduce drug shortage cases in the supply chain.

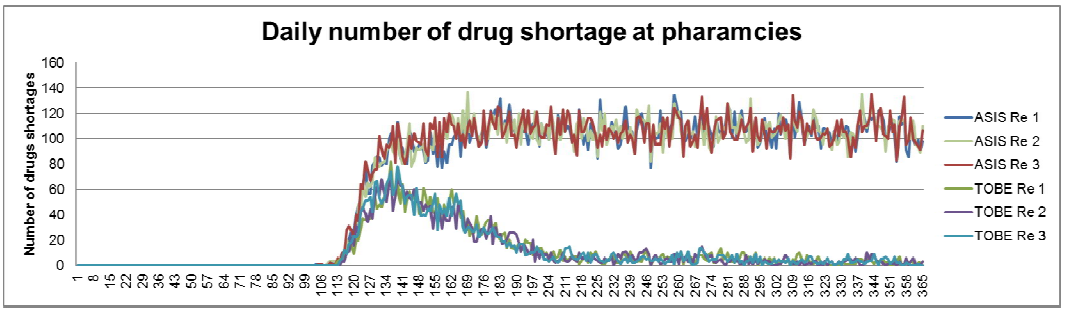


Figure 5-32 Daily number of drug shortage at pharmacies

Figure 5-32 describe the pattern of drug shortage for each different model and each simulation replication. After 111 days drug shortage started and increased drastically until the numbers of drug shortages reached the demand from customers to the pharmacies, which meant the there was no more inventory so that all the demand went to the drug shortages. Figure 5-33 shows the average number of daily drug shortages from the simulation.

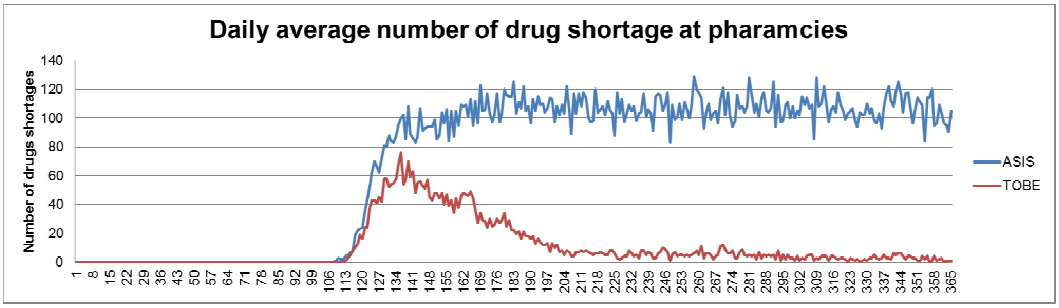


Figure 5-33 Daily number of drug shortages at pharmacies

However, the pattern of drug shortages was different with the 'TOBE' simulation model. It started at a similar time, but after the number reached a certain level, it went down again. The drug early shortage alert system sensed and notified the expected drug shortage and caused the manufacturer to produce again. The interesting thing was that there were still drug shortage cases. The reason for this was because of the inventory policy the simulation models used, which was modified basic stock inventory policy. Even though the manufacturer produced again the product having drug shortages, inventory quantity in the participants in the supply chain did not reach the basic inventory quantity level. That was because the trading partners could only make orders based on the order from their customers. Based on the inventory policy in these simulation models, the pharmacies could not order more than the orders from customers. This situation could be modified and run gain for different results later in this chapter. The Figure 5-34 shows that the pattern of drug shortage with AS-IS simulation model. It describes that the productions have longer lead times and have relatively early drug shortage cases during the simulation running as the result expected in an earlier chapter. It shows the main difference between two groups, which are the group that have production lead time 30 days and the rest of them. However, there is not much difference within the second group. Before completing this chapter, one more modified simulation model could be developed and run.

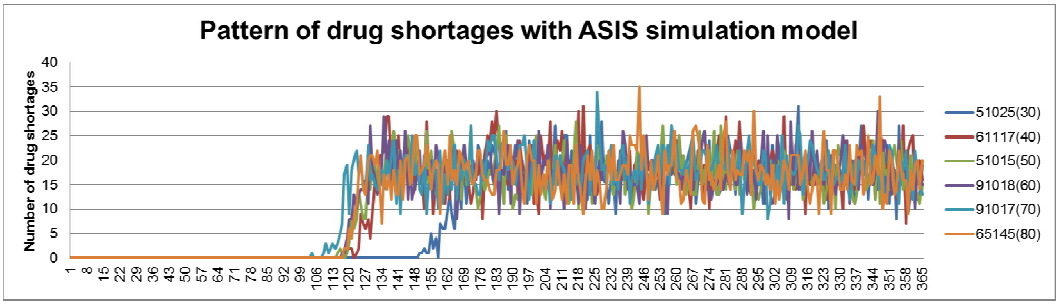


Figure 5-34 Pattern of drug shortages with AS-IS simulation model

As it was mentioned, even 'TO-BE' simulation model had drug shortages after the production went back to the normal status due to the inventory policy the models used. So one model that applied somewhat different inventory policy from that applied for the 'AS-IS' or 'TO-BE' models was developed. Suppose half of the basic stock is defined for safety stock. And if the inventory level of certain products goes down below the safety stock level, then increase the purchase order to half of the basic inventory quantity instead of the demand from customers. In this model condition, the number of drug shortage cases with 'TO-BE' model would be decreased and even after a certain time that number would be zero. By changing the inventory policy, the pharmacies could have order-ready quantity more than the orders from their customers, which makes them have safety stock inventory quantity sooner.

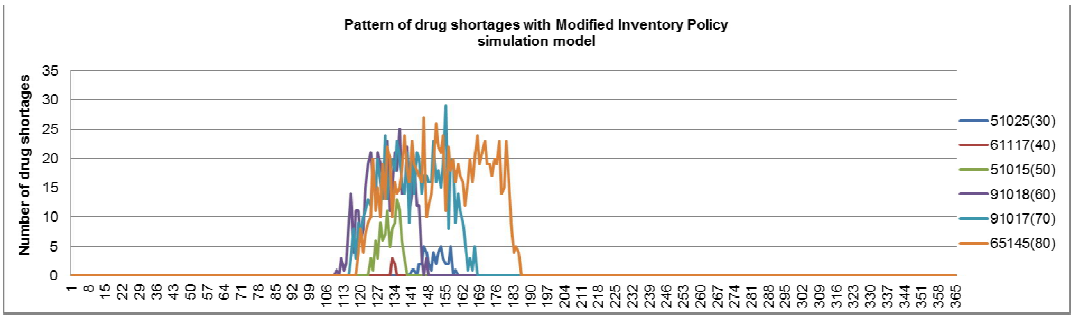


Figure 5-35 TO-BE model with modified inventory policy

Figure 5-35 shows that products that have long production lead time have drug shortages for quite a short time and that drug shortage disappeared. With the modified inventory policy, the pharmacies could have larger inventory quantity so that they could not only delay the drug shortages but also get back to normal condition quite quickly by ordering more quantity. This implies that the TPCIS model might be basically working to improve drug shortage issues and there could be various options that can be applied for better results.

5.6 Recall process model

5.6.1 Background and objectives

Previously, two simulations models including ePedigree and drug shortage models were developed and discussed. Finally, this research will discuss one last model, which is recall process simulation model. With TPCIS, the two simulation models showed or proved how ePedigree and inventory information sharing could be critical factors for Drug authentication and drug shortage reductions respectively. The object of the recall process simulation model is to show that recall process would be much faster and more efficient with TPCIS by simulation. Before taking recall process simulation model, brief explanation of drug recall including definition and case study should be discussed. FDA defines recall as “Recalls are an appropriate alternative method for removing or correcting marketed consumer products, their labeling, and/or promotional literature that violate the laws administered by the Food and Drug Administration” (FDA 2013). Baxter International in USA started serial recall of its heparin products because the raw heparin from China was contaminated and the heparin products were associated with serious injuries and even death (NYTimes 2008). Based on the report from New

York Times, at least 81 deaths, 785 serious injuries in 11 countries were linked to heparin production problems (NYTimes 2008 April). This case implied not only how the pharmaceutical supply chain was not secure and were flawed, but also the recall process was not very efficient and was slow enough to have more victims. The California State Board of Pharmacy (CSBP) inspected all 533 hospitals in California and found recall heparin products in 94 facilities and 7,000 patients were possibly contaminated. There was a also very interesting point that the heparin product had been returned by one hospital to a wholesaler and was sold to another hospital (Kate Traynor 2011). The problems and causes of this event have to be discussed for developing solutions for better recall process. If the recall process was quite slow, then farther sales or resale of the product recalled was not possibly prevented, e.g., the wholesaler did not get notification of recall for that heparin product so that there was nothing that could stop the wholesaler from resale. This implies that the recall process should be fast in ultimately real time. If the recall process could not stop flow of the product in supply, then more casualties would be unavoidable. As it was discussed in the heparin cases, currently recall process or method the FDA and companies are using is very inefficient and a time consuming process. Figure 5-36 describes that how FDA and companies gather related information for recall process. Inspecting 533 hospitals by email, fax and telephone might take a great deal of time, and that may make recall notification late for hospitals and patients. The recall process has to be not only very fast, but also efficient. For developing simulation model for recall process, firstly recall the process that is currently used needs to be studied and discussed.

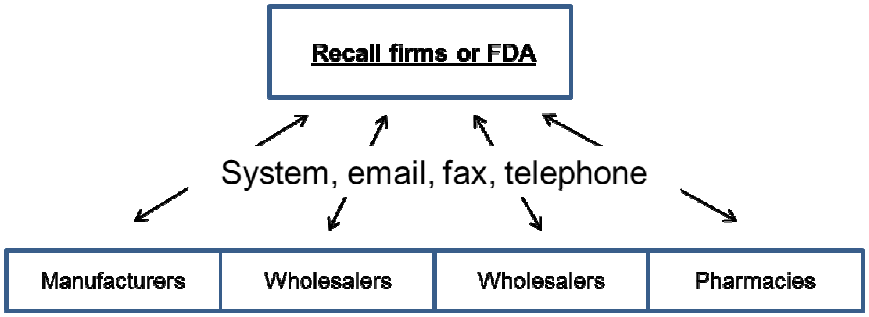


Figure 5-36 Methods for recall process

Before a recall initiation, recalling firms including manufacturers or wholesalers send recall early notification to FDA with related information to the possible recall product. That information is basically everything about the drugs themselves and manufacturing information. It includes that product name, description, product code, lot/unit number, serial number and many more items about the products, and manufacturer name, address and more information about the recalling firms. The information that should be notified to FDA also includes quantity on hold by recall firm, its distribution centers, estimated amount remaining in marketplace and more about the volume of the recalled product. The main issue discussed above is how to collect on that large and wide distributed data, not to mention credibility of the data. With TPCIS, which has centralized integrated data information system, this collection of information could be very fast and effective. Figure 5-37 shows how the recalling firms, TPCIS and participants on TPCIS could exchange recall information. By benefit of the TPCIS' centralized real time production master information sharing system, collecting recall information could not only be fast, but also be correct so that recall process could be done very efficiently with minimized additional casualties.

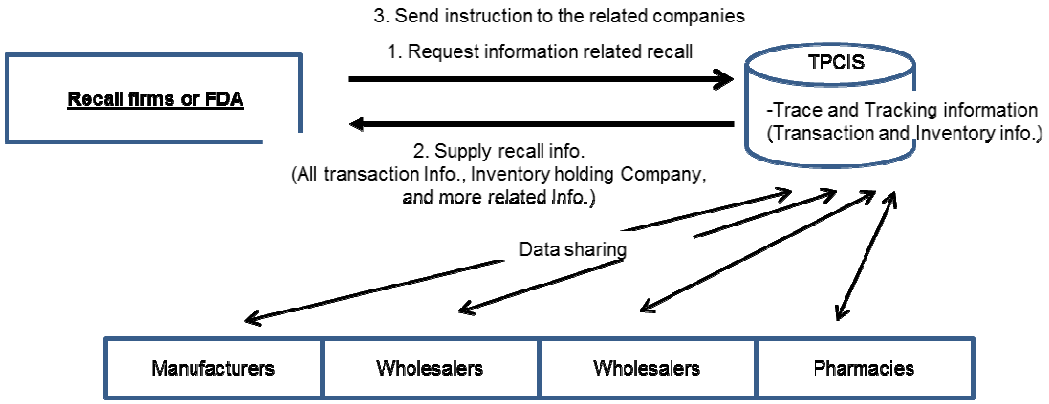


Figure 5-37 Recall related data sharing with TPCIS

5.6.2 Details in model

The basic processes and components of the recall simulation models are the same as the ones for ePedigree or drug shortage simulation models. However, as some of those were changed with the drug shortage simulation model to generate drug shortage cases, some of algorithms or processes were changed to achieve the objectives of recall process simulation model again. One of the key points of this simulation model is how to differentiate the recall processes, how comparison between the model with TPCIS and the model without the TPCIS and finally what point could be compared between simulation models. In this paper, the number of orders shipped to the customers from all trading partners after recall initiation would be counted. By comparing the numbers, two different simulation models could be compared and then determine which one is better for drug recall process. The model which fewer shipped orders would be better than the model which has more shipped orders to the customers. So for the recall process simulation model, more complicated models having more participants in the model need to be developed. Comparing the participants in previous models, the participants in recall

process simulation models were increased to 5 times more. Table 5-18 describes the details of them.

Table 5-18 Participants in the supply chain with recall process simulation model

Manufacturer	First Wholesalers	Second wholesalers	Pharmacies
1	20	40	80

The main difference of two models including 'AS-IS' and 'TO-BE' models is the time for recall process after initiation of recall process. Every participant in the supply chain might not have similar recall processes which make different recall process time for them. All trading partners would be assigned recall process time which is supposed to be different for each simulation run. In this recall simulation model, the recall process for the participant in the supply chain is to basically get recall notification and send that to their customers. In a real market, the supply chain participants could take recall information from FDA website (http://www.fda.gov/Drugs/drugsafety/DrugRecalls/default.htm) or other related web sites including Drug Watch (http://www.drugwatch.com/recalls/), http://www.recalls.gov/medicine.html, however, there is a significant assumption in this simulation model, which is the trading partners get recall information from their suppliers. Figure 5-38 shows some of the sequential process for recall in the simulation model. During the simulation run, the recall process would initiate at a certain time, which is 20 days after simulation run. One entity created by one of the modules from ARENA simulation model calls the one stored procedure that determines which product and lot number would be recalled by selecting that one from inventory information in pharmacies. The stored procedure selects the product code and lot number from the table, Pharmaci-es.dbo.Tinventory and inserts them into the table, Manufactuers.dbo.TrecallInfo. At the same time the stored procedure, Manufactuers.dbo.spRecallHoldMF, updates the

inventory data in the manufacturer to hold the recalled product and not ship it to its customers.

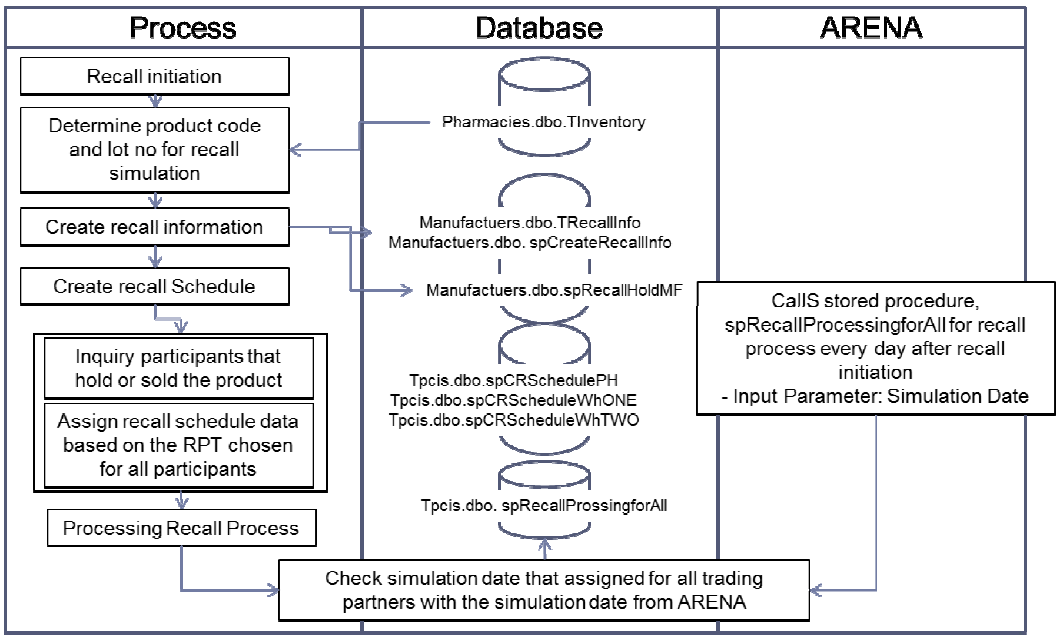


Figure 5-38 Recall process in the simulation model

In this process, all inventory information in all trading partners needs to be updated for checking whether the products are shipped or not after recall process. After the product is selected for recall process, then the recall schedules are to be created. There are 3 different selections for recall process time, which is described in Table 5-21. Three different recall process time (RPT) types could be selected and this selection might make different results with different simulation models. The stored procedure, Tpcis.dbo.spCRSchedule for each supply tier, selects the recall process day in a random manner dependent upon the RPT types, e.g., RPT type ONE, which has 1, 2 and 3 days and its selective percentage is 70%, 20% and 10 % respectively. The stored procedure in database, spCRScheduleWHONE creates the recall schedule, recall date assigned for

each first wholesaler and stores procedures, spCRScheduleWHTWO, spCRSchedulePH create the recall schedule for second wholesalers and pharmacies respectively.

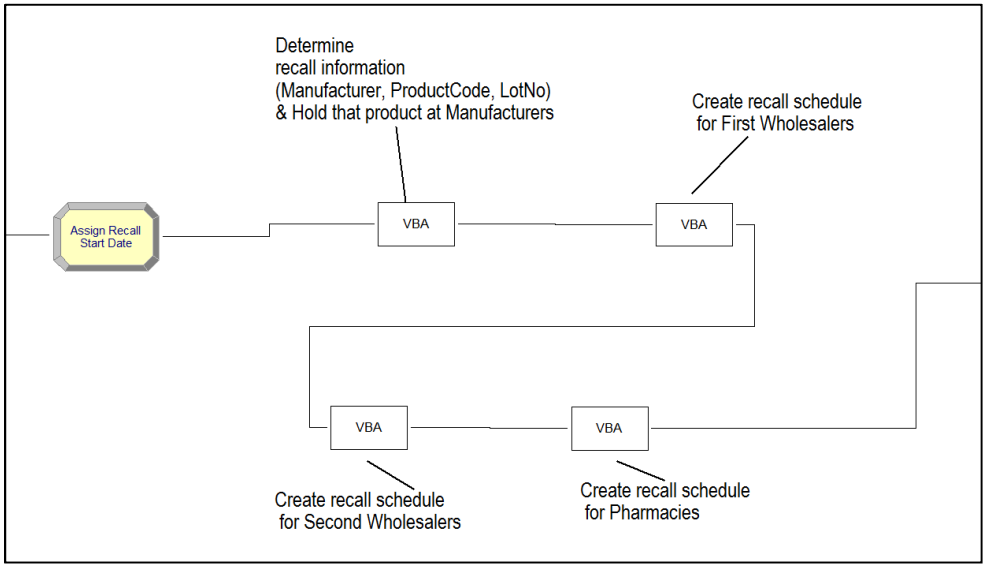


Figure 5-39 Sub model for recall process simulation

After the model finishes creating the recall schedule, it does recall processing by calling stored procedure, spRecallProssingforAll. Figure 5-40 shows that the screen captured for the recall process simulation model, which is almost the same as the two previous models but adds recall processing module. After recall initiation and creating schedule date for each individual first wholesaler, second wholesaler and pharmacy, as the simulation is running, the recall processes would be done by the stored procedure, spRecallProssingforAll when the simulation date that is being sent from ARENA module into the database is the same data assigned for recall process. When this recall process is done, all inventory of the recalled product would be on hold, not to be shipped. With this process, the information of the products shipped after recall initiation could be collected and by this information the recall simulation models could be evaluated. This

stored procedure does the recall process for only the trading partners that traded the recalled product.

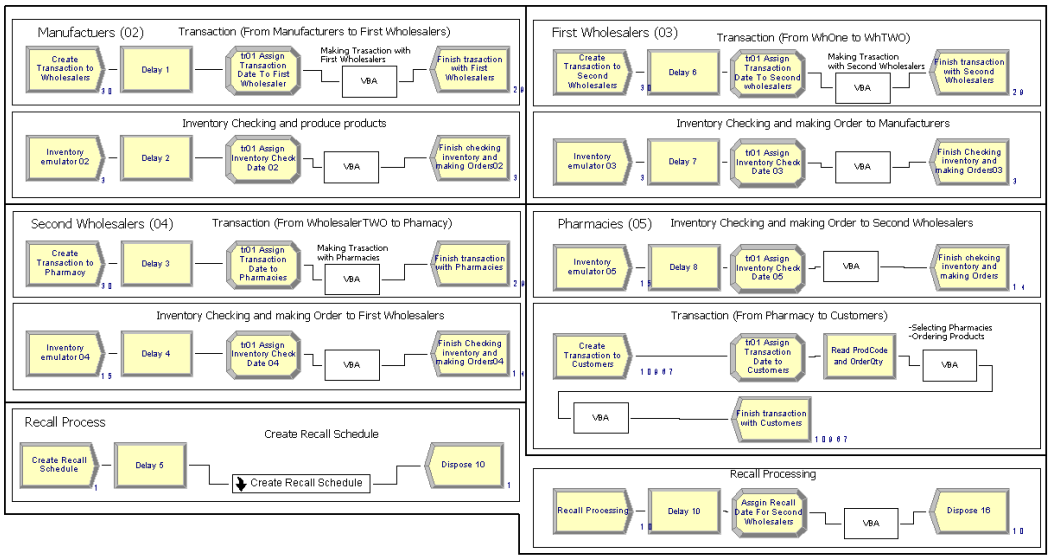


Figure 5-40 Screen captured for recall process simulation model

If one company bought the product from more than two different suppliers, then the recall process should be done based on the earliest date for only one time. In terms of this matter, suppose that one second wholesaler could buy one product from all first wholesalers in this simulation model, then the recall process time the second wholesaler need for recall processing in this simulation might not be different between the suppliers because the earliest recall date should be selected, which makes the recall simulation model useless. That is why the trading partners need to have their own suppliers in this simulation. Each pharmacy has 10 suppliers and each second wholesaler has 5 suppliers.

5.6.2.1 ‘AS-IS’ simulation model

‘AS-IS’ simulation model is the model without TPCIS, which means that no inventory information system integrated, so that it might delay recall process. The number of the products shipped at pharmacies to the customer after recall initiation might be expected to be more than the number from the ‘TO-BE’ simulation model.

5.6.2.2 ‘TO-BE’ simulation model

This simulation model is with the TPCIS, which means that inventory data sharing system help speed recall process. One time notification from the TPCIS to the all trading partners is supposed to be able to prevent the product from shipping to the customers. So the number of the products shipped at pharmacies to the customers after recall initiation might be expected less than the number from the ‘AS-IS’ simulation model.

5.6.3 Run model

Table 5-19 Simulation run condition for recall process model

Replication		**3**
Replication Length		40 days (12 hr/day)
Inventory Policy		Modified Basic Stock Model (Q, r): r values fixed
Customers' Demand distribution		Expo(2) min
Lead time (day)	Delivery	Pharmacies (80), Second wholesalers(40), First Wholesalers(20)
	Production	10 (all products)
Number of Products		5

Table 5-19 shows the run conditions for recall process simulation model. One of the big conditions is the increased number of trading partners and demands from the customers. For better comparison results of different simulation models, same order data

from customers to pharmacies is to be used, which is different from previous ePedigree or drug shortage simulation model. Data text file is generated from separated AREN simulation model, which developed only for generating order data based on different formation or needs. Figure 5-41 shows basic processes for creating order data from customers. After a customer entity is created, the simulation date and order quantity are assigned to that customer's entity. When the entity passes the VBA module, stored procedure, named 'spCCOsfRecall' is called, which obtains order quantity and simulation date from ARENA simulation module and create order data for pharmacies in table 'Pharmaceis.dbo.TTORDERS' in database. Figure 5-42 shows the sample of order data from customers, which is generated by order creating simulation module, Figure 5-41.

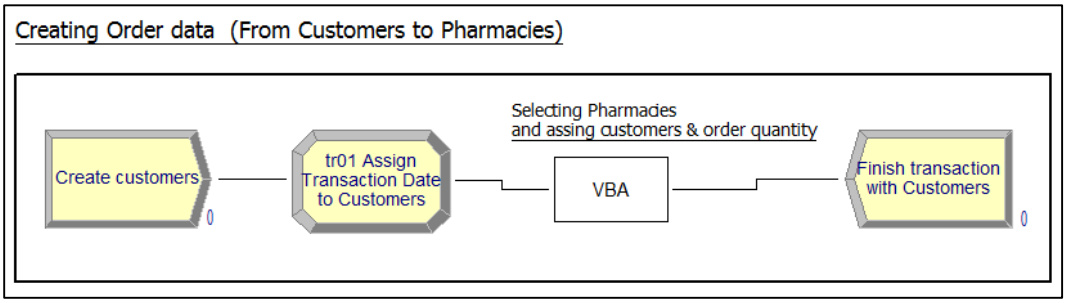


Figure 5-41 Creating customers order data for pharmacies

Results Messages

	OrderId	OrderQuan...	ProdCode	CustID	ODateTime	ManuId	ComplD	ONumber	SPName	SQLDateTime
1	PHCr2014092110049	1	69355	183537	20140921	MA01	PH41	10049	spCCOsfRecall	Sep 20 2014 10:12PM
2	PHCr2014092110098	2	51025	179591	20140921	MA01	PH51	10098	spCCOsfRecall	Sep 20 2014 10:12PM
3	PHCr2014092110147	2	69355	927967	20140921	MA01	PH52	10147	spCCOsfRecall	Sep 20 2014 10:12PM
4	PHCr2014092110196	3	91017	195617	20140921	MA01	PH51	10196	spCCOsfRecall	Sep 20 2014 10:12PM
5	PHCr2014092110245	1	51025	581216	20140921	MA01	PH08	10245	spCCOsfRecall	Sep 20 2014 10:12PM
6	PHCr2014092110294	1	69355	892628	20140921	MA01	PH47	10294	spCCOsfRecall	Sep 20 2014 10:12PM
7	PHCr2014092210343	1	51025	281455	20140922	MA01	PH45	10343	spCCOsfRecall	Sep 20 2014 10:12PM
8	PHCr2014092210392	2	69355	281455	20140922	MA01	PH66	10392	spCCOsfRecall	Sep 20 2014 10:12PM
9	PHCr2014092210441	3	51025	218045	20140922	MA01	PH26	10441	spCCOsfRecall	Sep 20 2014 10:12PM
10	PHCr2014092210490	2	91017	165264	20140922	MA01	PH21	10490	spCCOsfRecall	Sep 20 2014 10:12PM
11	PHCr2014092210539	1	51025	572933	20140922	MA01	PH42	10539	spCCOsfRecall	Sep 20 2014 10:12PM
12	PHCr2014092210588	2	91017	388539	20140922	MA01	PH05	10588	spCCOsfRecall	Sep 20 2014 10:12PM

Figure 5-42 Screen captured for customers' order data for pharmacies

From those data, Figure 5-42 only columns ‘Prodcode’, ‘CompId’, ‘OrderQuantity’ are selected for one large order data, which is text file type, for recall process simulation model.

5.6.4 Model Verification

As it was mentioned, drug shortage simulation was designed and developed based on the ePedigree simulation model, and recall process also was designed and developed based on the drug shortage simulation models. So, basically new processes or algorithms of recall process simulation model need to be verified. One of them is how or when it selects the product for recall and the other one is the assigning of recall process time for each trading partner. The other one is assigning recall process time and it needs to be checked. The recall process times are to be selected for each trading partner during simulation run, which is the very core process of this recall process simulation model.

5.6.4.1 Recall product information

The product for recall has been selected from inventory information in pharmacies database 20 days after the simulation was started, and all afterward procedures processed based on the information. When the product and lot number are selected, all inventory data through all participants in the supply chain is updated, Figure 5-44 shows that column name ‘recallcheck’ is update as ‘RS’ for the product having prodcode, ‘91017’ and lot number, ‘MSAMA9101720140915’ in recall information data in Figure 5-43, which means that one product for recall process was selected correctly and afterword processes have been done correctly.

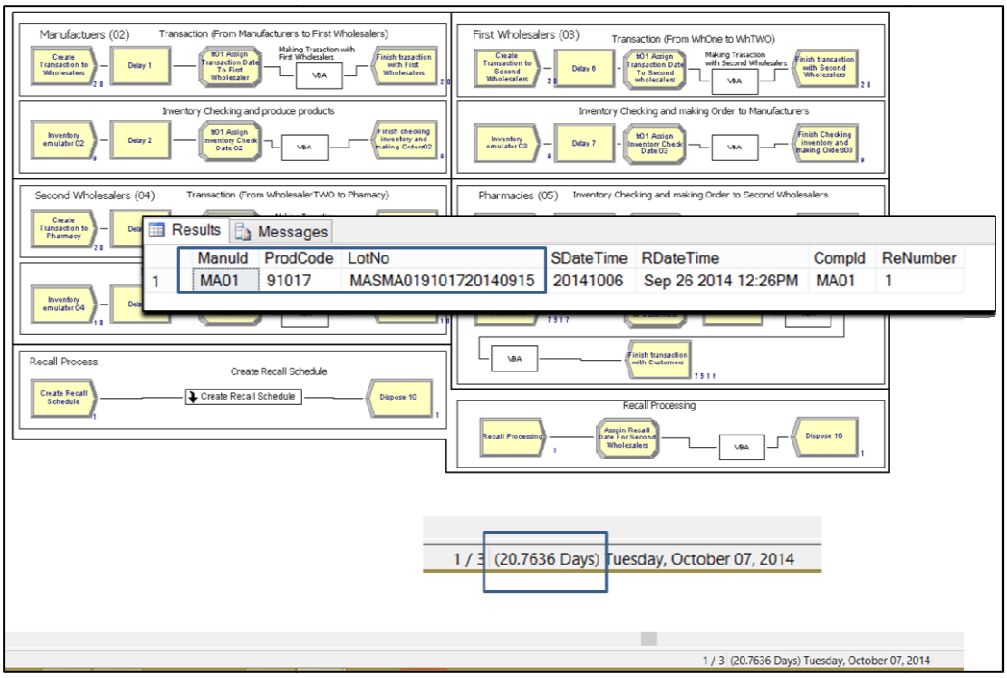
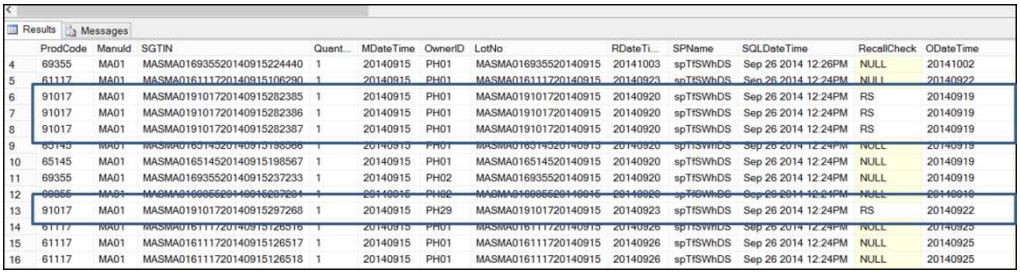


Figure 5-43 Screen captured for recall product information



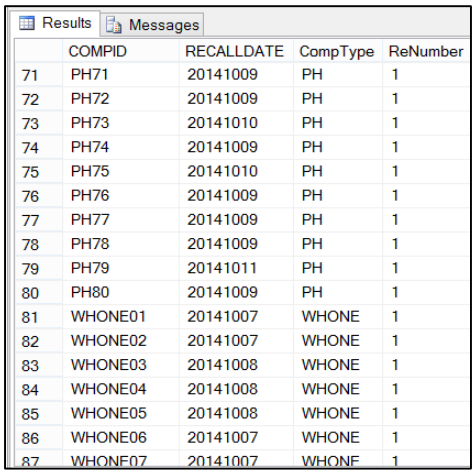
Results Messages

	ProdCode	ManuId	SGTIN	Quant...	MDateTime	OwnerID	LotNo	RDateTi...	SPName	SQLDateTime	RecallCheck	ODateTime
4	69355	MA01	MASMA016935520140915224440	1	20140915	PH01	MASMA01693552014091	20141003	spTfSWhDS	Sep 26 2014 12:26PM	NULL	20141002
5	61117	MA01	MASMA016111720140915106290	1	20140915	PH01	MASMA01611172014091	20140923	spTfSWhDS	Sep 26 2014 12:24PM	NULL	20140922
6	91017	MA01	MASMA019101720140915282385	1	20140915	PH01	MASMA01910172014091	20140920	spTfSWhDS	Sep 26 2014 12:24PM	RS	20140919
7	91017	MA01	MASMA019101720140915282386	1	20140915	PH01	MASMA01910172014091	20140920	spTfSWhDS	Sep 26 2014 12:24PM	RS	20140919
8	91017	MA01	MASMA019101720140915282387	1	20140915	PH01	MASMA01910172014091	20140920	spTfSWhDS	Sep 26 2014 12:24PM	RS	20140919
9	65145	MA01	MASMA016514520140915198566	1	20140915	PH01	MASMA01651452014091	20140920	spTfSWhDS	Sep 26 2014 12:24PM	NULL	20140919
10	65145	MA01	MASMA016514520140915198567	1	20140915	PH01	MASMA01651452014091	20140920	spTfSWhDS	Sep 26 2014 12:24PM	NULL	20140919
11	69355	MA01	MASMA016935520140915237233	1	20140915	PH02	MASMA01693552014091	20140920	spTfSWhDS	Sep 26 2014 12:24PM	NULL	20140919
12	69355	MA01	MASMA016935520140915237234	1	20140915	PH02	MASMA01693552014091	20140920	spTfSWhDS	Sep 26 2014 12:24PM	NULL	20140919
13	91017	MA01	MASMA019101720140915297268	1	20140915	PH29	MASMA01910172014091	20140923	spTfSWhDS	Sep 26 2014 12:24PM	RS	20140922
14	61117	MA01	MASMA016111720140915126516	1	20140915	PH01	MASMA01611172014091	20140926	spTfSWhDS	Sep 26 2014 12:24PM	NULL	20140925
15	61117	MA01	MASMA016111720140915126517	1	20140915	PH01	MASMA01611172014091	20140926	spTfSWhDS	Sep 26 2014 12:24PM	NULL	20140925
16	61117	MA01	MASMA016111720140915126518	1	20140915	PH01	MASMA01611172014091	20140926	spTfSWhDS	Sep 26 2014 12:24PM	NULL	20140925

Figure 5-44 Sample of inventory data for pharmacies

5.6.4.2 Recall process time assigning process

Figure 5-45 shows the different recall schedule dates based on the replication of simulation. Since the replication is 1, the recall process time is supposed to be selected based on the table that has 1, 2, and 3 days in 70, 20, 10 % respectively.



Results | Messages

	COMPID	RECALLDATE	CompType	ReNumber
71	PH71	20141009	PH	1
72	PH72	20141009	PH	1
73	PH73	20141010	PH	1
74	PH74	20141009	PH	1
75	PH75	20141010	PH	1
76	PH76	20141009	PH	1
77	PH77	20141009	PH	1
78	PH78	20141009	PH	1
79	PH79	20141011	PH	1
80	PH80	20141009	PH	1
81	WHONE01	20141007	WHONE	1
82	WHONE02	20141007	WHONE	1
83	WHONE03	20141008	WHONE	1
84	WHONE04	20141008	WHONE	1
85	WHONE05	20141008	WHONE	1
86	WHONE06	20141007	WHONE	1
87	WHONE07	20141007	WHONE	1

Figure 5-45 Recall date assigned for each trading partner

Table 5-20 shows that recall process time assigned for first wholesalers during simulation run for replication 1. The percentage of RPT is not exactly 7:2:1 for 1:2:3 days respectively, however it shows that the RPT was selected from the correct table.

Table 5-20 Recall process time in simulation run

Recall Process Type	Company Type	Replication Number	Count	Percentage (%)
1	WHONE	1	24	60.000
2	WHONE	1	12	30.000
3	WHONE	1	4	10.000
	Total		40	100.000

5.6.5 Results of the model

One of the big factors that might be affecting the result of the recall process simulation model is recall process time. The recall process time for each company in the supply chain is to be selected from the table containing time data, which includes 1, 2 and 3 days in 70%, 20 % and 10% respectively. If the data is changed to longer recall

process time such as 3, 4, and 7 days in at the same rate, then the result might be changed. So different scenarios may need to be designed and run to figure out how the recall process time affects the result of the models.

Table 5-21 Recall process time (days)

RPT Type	RPT (Recall Process Time, day)	Percentage (%)
ONE	1	70
	2	20
	3	10
TWO	3	70
	4	20
	5	10
THREE	5	70
	6	20
	7	10

Table 5-21 shows different recall process time (day) that might be selected during the simulation run. RPT Type TWO has longer recall process time than the one for Type ONE and RPT Type THREE has the longest recall process times. Figure 5-46 shows that the recall schedule dates that are assigned for each participant in the supply chain based on the recall date assign algorithm with recall process type, e.g., one first wholesaler was assigned 1 day, one second wholesaler was assigned 2 days, and finally one pharmacy was assigned 2 days for recall process, then total 5 days was needed to process for the pharmacy. In this simulation model, the recall process time for each trading partner is to be selected in a random manner as it was mentioned. Again based on the Figure 5-46, the first wholesaler, WHONE01's recall schedule is '20140921' and

WHONE02's recall schedule is '20140923', so there is a 2 day difference between two first wholesalers.

	COMPID	RECALLDATE	TOCOMPID	CompType	ReNumber	SDateTime
80	WHTWO36	20140922	PH12	WHTWO	2	Sep 18 2014 12:15PM
81	WHTWO36	20140922	PH27	WHTWO	2	Sep 18 2014 12:15PM
82	WHTWO36	20140922	PH75	WHTWO	2	Sep 18 2014 12:15PM
83	WHTWO38	20140922	PH02	WHTWO	2	Sep 18 2014 12:15PM
84	WHTWO38	20140922	PH46	WHTWO	2	Sep 18 2014 12:15PM
85	WHTWO38	20140922	PH69	WHTWO	2	Sep 18 2014 12:15PM
86	WHTWO39	20140922	PH09	WHTWO	2	Sep 18 2014 12:15PM
87	WHTWO39	20140922	PH73	WHTWO	2	Sep 18 2014 12:15PM
88	WHTWO40	20140922	PH28	WHTWO	2	Sep 18 2014 12:15PM
89	WHONE01	20140921	WHTWO34	WHONE	3	Sep 18 2014 12:28PM
90	WHONE01	20140921	WHTWO39	WHONE	3	Sep 18 2014 12:28PM
91	WHONE02	20140923	WHTWO35	WHONE	3	Sep 18 2014 12:28PM
92	WHONE03	20140921	WHTWO16	WHONE	3	Sep 18 2014 12:28PM
93	WHONE04	20140923	WHTWO06	WHONE	3	Sep 18 2014 12:28PM
94	WHONE04	20140923	WHTWO07	WHONE	3	Sep 18 2014 12:28PM
95	WHONE04	20140923	WHTWO14	WHONE	3	Sep 18 2014 12:28PM
96	WHONE04	20140923	WHTWO21	WHONE	3	Sep 18 2014 12:28PM
97	WHONE05	20140921	WHTWO17	WHONE	3	Sep 18 2014 12:28PM
98	WHONE05	20140921	WHTWO30	WHONE	3	Sep 18 2014 12:28PM
99	WHONE05	20140921	WHTWO37	WHONE	3	Sep 18 2014 12:28PM

Figure 5-46 Recall schedule for each replication and participants

5.6.5.1 'AS-IS' model

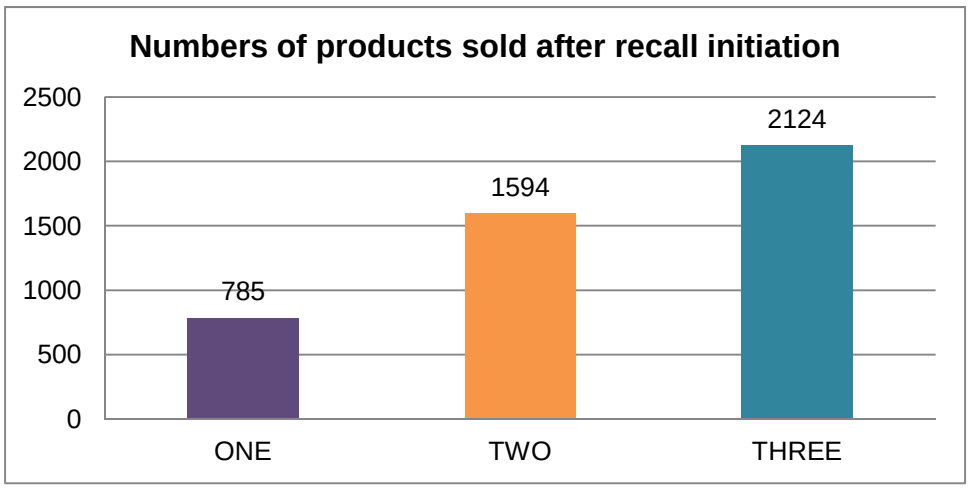


Figure 5-47 Numbers of products sold after recall initiation

Figure 5-47 shows that the total numbers of the products that sold after recall initiation for each replication, also for RPT (recall process time) types. Those products were not

supposed to be sold, however it happened because the participants in the supply chain did not get the recall information before they sold the products. The unit of that number is unit product having Serialized global trade Item Number (SGTIN). The number is getting increasing when the RPT (Recall Process Time) is longer. In the Figure 5-47, ONE is the resulting with RPT type ONE, which has mostly recall process type 1 day and 3, 5 day with RPT TWO and THREE respectively. This graph implies that the participants have longer RPT, the greater numbers of the products shipped out after recall initiation for their customers. Table 5-22 shows the product and lot number selected for recall process simulation. First replication is for RPT type ONE, second and third replication of simulation is for RPT type TWO and THREE respectively. Since the recall initiation date was set at the same time in the simulation model, the same date was selected for recall process.

Table 5-22 Product code and lot number selected for simulation

Product code	Lot Number	Recall Start date	Replication
91017	MASMA019101720140915	20141006	1
91017	MASMA019101720140915	20141006	2
61117	MASMA016111720140915	20141006	3

Figure 5-48 shows the number of products that shipped after recall initiation for each supply chain tier for a replication. Pharmacies have the largest number because order delivery lead time is short, which is a just minutes of time to the customers. First wholesalers have a time between ship which is quite long, and surely makes smaller numbers. More numbers could be expected if the order interval time is reduced in the models. One of the reasons that the first wholesaler has almost zero shipment of recall products after recall initiation is the big current inventory second wholesalers have.

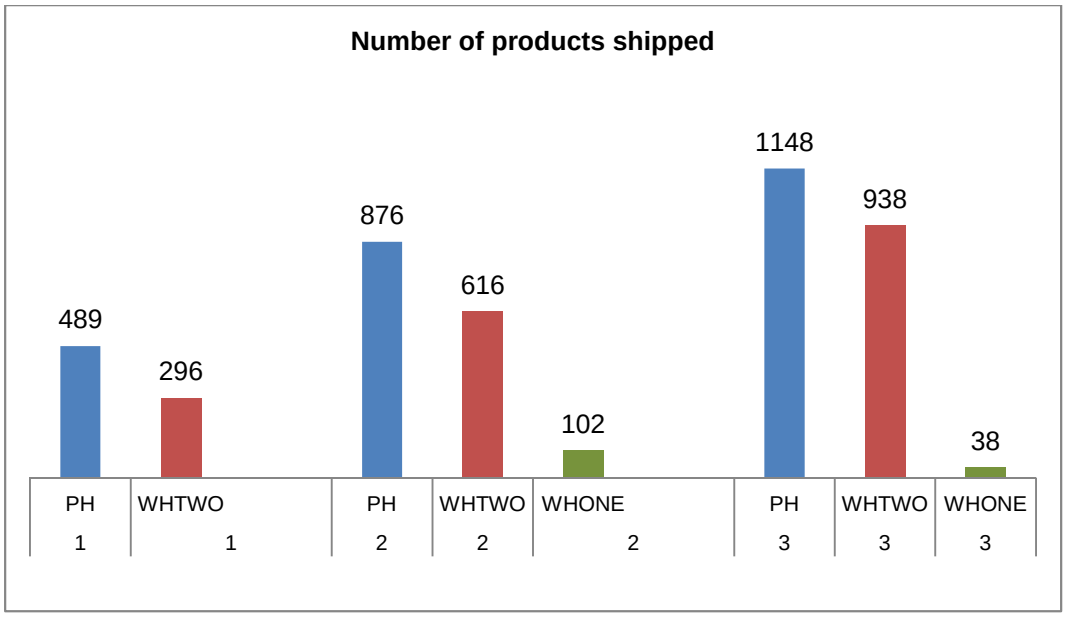


Figure 5-48 Number of products shipped for the supply chain tiers

This made less number of orders to first wholesalers. Unfortunately, these whole inventories of recall products they should have been returned. Figure 5-49 shows inventory information of the recalled product.

Results Messages

	ProdCode	ManuId	EPC	SGTIN	MDateTime	Comment	OwnerID	RDateTi...	LotNo	ODateTi...	RecallHold	RecallD...	RecallCheck
15787	61117	MA01	NULL	MASMA016111720140915134513	20140915	NULL	WHONE06	20140915	MASMA01611172014091	20140915	RHOLD	20141011	RS
15788	61117	MA01	NULL	MASMA016111720140915133502	20140915	NULL	WHONE06	20140915	MASMA01611172014091	20140915	RHOLD	20141011	RS
15789	61117	MA01	NULL	MASMA016111720140915133503	20140915	NULL	WHONE06	20140915	MASMA01611172014091	20140915	RHOLD	20141011	RS
15790	61117	MA01	NULL	MASMA016111720140915133504	20140915	NULL	WHONE06	20140915	MASMA01611172014091	20140915	RHOLD	20141011	RS
15791	61117	MA01	NULL	MASMA016111720140915133505	20140915	NULL	WHONE06	20140915	MASMA01611172014091	20140915	RHOLD	20141011	RS
15792	61117	MA01	NULL	MASMA016111720140915133506	20140915	NULL	WHONE06	20140915	MASMA01611172014091	20140915	RHOLD	20141011	RS
15793	61117	MA01	NULL	MASMA016111720140915133507	20140915	NULL	WHONE06	20140915	MASMA01611172014091	20140915	RHOLD	20141011	RS
15794	61117	MA01	NULL	MASMA016111720140915133508	20140915	NULL	WHONE06	20140915	MASMA01611172014091	20140915	RHOLD	20141011	RS
15795	61117	MA01	NULL	MASMA016111720140915133600	20140915	NULL	WHONE06	20140915	MASMA01611172014091	20140915	RHOLD	20141011	RS
15796	61117	MA01	NULL	MASMA016111720140915133724	20140915	NULL	WHONE06	20140915	MASMA01611172014091	20140915	RHOLD	20141011	RS
15797	61117	MA01	NULL	MASMA016111720140915133835	20140915	NULL	WHONE06	20140915	MASMA01611172014091	20140915	RHOLD	20141011	RS
15798	61117	MA01	NULL	MASMA016111720140915133946	20140915	NULL	WHONE06	20140915	MASMA01611172014091	20140915	RHOLD	20141011	RS
15799	61117	MA01	NULL	MASMA016111720140915134057	20140915	NULL	WHONE06	20140915	MASMA01611172014091	20140915	RHOLD	20141011	RS
15800	61117	MA01	NULL	MASMA016111720140915132601	20140915	NULL	WHONE06	20140915	MASMA01611172014091	20140915	RHOLD	20141011	RS

Figure 5-49 Inventory of the recalled product

5.6.5.2 ‘TO-BE’ model

Unlike the ‘AS-IS’ model, ‘TO-BE’ model is the model with Third Party Centralized Integrated System (TPCIS), which means that the supply chain participants

get recall notification instantly with the systems. So in this recall process simulation model, it does not use recall process time that the 'AS-IS' model used for differentiation of recall process time for each trading partner. When the product and lot number is determined for recall, this information should be sent to all the supply chain participants systematically and the system that the participants are using holds the product so that those products could not be shipped to their customers. Therefore it should be expected that a very small or no number of product shipped after recall initiation. However, the communication time between the participants could be different based on the type of system integrations they implemented into their own information systems. If some of the participants use batch type of system integration, they might not be able to get the recall notification in real time. So for the simulation technical issues, two scenarios could be applied. First scenario is real time, which holds every product in all trading partners in TPCIS at the same time when the product and lot number is determined for recall process, and second scenario is 1 day, which might be much longer than the recall process time with TPCIS. The number of shipped product after recall initiation of the first scenario was 0, which was not different from the expectation. This is quite obvious because all inventory information in all trading partners is updated so that the recalled product cannot be shipped to the customers. The result of the second scenario was not much different from the expectation too. Figure 5-50 shows that the number of products that shipped after the product's recall initiation with second scenario. There were 3 replications and the results of the three replications were almost the same. The recall process time with TPCIS might be real time, which means the recall process could be done when the recall information was created.

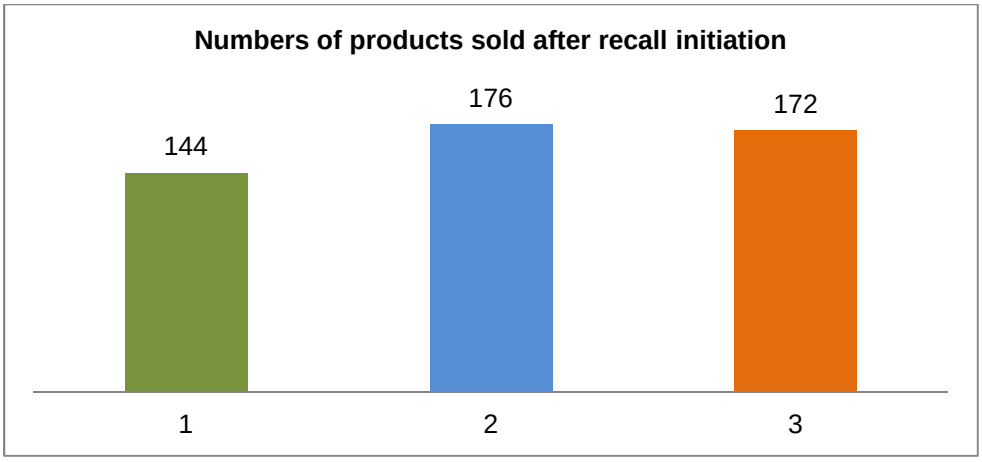


Figure 5-50 Numbers of product sold after recall initiation with TOBE model

If the time might be less than 1 day for all trading partners together in TPCIS, the number in Figure 5-50 surely reduced to almost nothing. From the result of 'TO-BE' simulation models, that recall process with TPCIS certainly will be much better than 'AS-IS' simulation model which has been proved.

Results | Messages

	OwnerId	CompType	ProdCode	LotNo	Quantity
393	PH78	PH	61117	MASMA016111720140915	40
394	PH78	PH	61117	MASMA016111720140915	40
395	PH78	PH	61117	MASMA016111720140915	40
396	PH79	PH	61117	MASMA016111720140915	39
397	PH79	PH	61117	MASMA016111720140915	39
398	PH79	PH	61117	MASMA016111720140915	39
399	PH79	PH	61117	MASMA016111720140915	39
400	PH79	PH	61117	MASMA016111720140915	39
401	PH80	PH	61117	MASMA016111720140915	30
402	PH80	PH	61117	MASMA016111720140915	30
403	PH80	PH	61117	MASMA016111720140915	30
404	PH80	PH	61117	MASMA016111720140915	30
405	PH80	PH	61117	MASMA016111720140915	30
406	WHONE01	WHONE	61117	MASMA016111720140915	800
407	WHONE01	WHONE	61117	MASMA016111720140915	800
408	WHONE01	WHONE	61117	MASMA016111720140915	800
409	WHONE01	WHONE	61117	MASMA016111720140915	800
410	WHONE01	WHONE	61117	MASMA016111720140915	800
411	WHONE02	WHONE	61117	MASMA016111720140915	800
412	WHONE02	WHONE	61117	MASMA016111720140915	800
413	WHONE02	WHONE	61117	MASMA016111720140915	800
414	WHONE02	WHONE	61117	MASMA016111720140915	800
415	WHONE02	WHONE	61117	MASMA016111720140915	800
416	WHONE03	WHONE	61117	MASMA016111720140915	800
417	WHONE03	WHONE	61117	MASMA016111720140915	800
418	WHONE03	WHONE	61117	MASMA016111720140915	800
419	WHONE03	WHONE	61117	MASMA016111720140915	800
420	WHONE03	WHONE	61117	MASMA016111720140915	800

Figure 5-51 Sample of screen capture for inventory information with TPCIS

One of the good features of the TPCIS is visibility of the products, not only recalled products, but also all products throughout the supply chain. Figure 5-51 shows which companies have how many products that were recalled in one screen. This is possible because the trading partners share their inventory information with other supply chain partners. However again, this does not necessarily mean that the companies are able to see other partners' inventory or other type of information. This is totally based on the design or contract condition of joining TPCIS.

Chapter 6

Conclusions

The Third Party Centralized Integrated System (TPCIS) was designed and proposed to improve the main issues including counterfeit and diverted drugs and drug shortages in the pharmaceutical supply chain in the USA. With the system all participants in TPCIS are willing to share not only their inventory data but also tracking information with other trading partners, which might be suppliers and some wholesalers or pharmacies. However, with information sharing systems, the company has limitation of the access to the database. Most of management should be done by the third party independent company. To prove that the TPCIS is really improving the main three issues, three simulation models for each issue were developed and run, which are ePedigree, drug shortages and recall process models. With the ePedigree simulation model, the counterfeit and diverted drug issues are handled appropriately, and the simulation model proved that counterfeit and diverted drugs are easily filtered with TPCIS. The drug shortage simulation model showed that TPCIS might be working for reducing drug shortage cases by sharing inventory information and integrated systems that make the trading partners communicate easily and fast. Finally, the recall process simulation model proved that the integrated system contains really efficient and fast recall process for the participants in the supply chain.

- Contribution of this research

1. **Developing and proposed unique model, TPCIS (Third Party Centralized Information System).**
2. **Developing specialized simulation models for ePedigree, Drug shortages and recall process.**
3. **Showing that how the parameters including inventory policy, lead time for production interact each other for drug shortage, recall process in the supply chain by simulation models.**

1. Uniqueness of TPCIS

It applied some valuable features from different systems

- **Integrated 1) individual participants 2) groups of networks**
- **Integrated with other network with EPCIS (Electronic Product Code Information services)**
- **Participants join the systems and share information with other trading partners voluntarily**
- **The independent company operate the system**
- **Government agency (FDA) can access the data**

2. Simulation models

Simulation models	AS-IS (Simulation Models)	TO-BE (Simulation Models)
ePedigree	Current Pharmaceutical Supply Chain (No Simulation Model)	Filter counterfeit drugs and diverted drugs systematically ← Creating and managing ePedigree information ← Share ePedigree information with trading partners.
	- Counterfeit drugs - Diverted drugs - Drug shortages	
Drug shortages	25,511 (SGTIN) (Average from 3 replication) ← Late response of drug shortage ← No inventory data sharing system	3,786 (85% reduced) (Average from 3 replication) ← Drug shortage early alert system ← Inventory data sharing system
Recall Process	785 (SGTIN,RPT Type ONE) - Take lots of time and resources - Inefficient recall process (Sequential notification of each member of the supply chain.)	164 (SGTIN, RPT is one day) - Fast and less resources - Efficient recall process (All parties in the supply chain are notified immediately)

Chapter 7

Future works

A large framework for the supply chain simulation has been designed and developed. This could be modified or applied to many different simulation models. Since this framework is designed with database, which is SQL Server 8.0, it could be modified a in very low level simulation model, which means that this framework is very flexible and has good scalability. More sophisticated inventory policy and production or delivery type including box or pallet package unit could be applied. Any research about logistics cost, including inventory or transportation costs could use this simulation model after modification.

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