QUANTITATIVE-SCIENTIFIC COMPANY AND PRODUCT SCORECARD CONSIDERATIONS AND MODELING

by

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A Thesis

Submitted to the Faculty of Purdue University

In Partial Fulfillment of the Requirements for the degree of

Master of Science

Department of Technology Leadership & Innovation

West Lafayette, Indiana

August 2019

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GLOSSARY

21st -Century manufacturing- A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high-quality drugs without extensive regulatory oversight (Yu & Woodcock, 2015, p.1)

Counterfeit drugs-defines a counterfeit drug product as a drug sold under a product name, without proper authorization, that is represented, labeled, or packaged in a manner that suggests it is an authentic approved product. Note: Counterfeit products may include products without active ingredient (contain only inactive ingredients), products with incorrect ingredients, improper dosages, sub-potent or super-potent ingredients, insufficient quantity of active ingredient, the wrong active ingredient, or products that are contaminated. (U.S. Food and Drug Administration, 2013, p.2)

Drug quality- The suitability of either a drug substance or drug product for its intended use. This term includes such attributes as the identity, strength, and purity. (ICH, 1999, p.19).

Drug recalls-A drug recall is an action taken by a firm to remove a product from the market that FDA considers to be in violation of the law. Recalls are classified as Class I, Class II, or Class III. Class I recalls are the most serious and involve situations where there is a reasonable probability that the use of or exposure to a volatile product, will cause serious adverse health consequences or death. A drug may be recalled due to factors such as problems with packaging, manufacturing, or contamination (Recalls, n.d., para.6)

Drug shortages- "A period of time when the demand or projected demand for the drug within the United States exceed the supply of the drug. In general, the DSS focuses on shortages of medically necessary product that have a significant effect on public health." (Gottlieb, 2016, p.14)

Education length: refer to years of schooling, average numbers of years of education received by people ages 25 and older, converted from education attainment levels using official durations of each level. (Human Development Reports., n.d.)

Education index: calculated using mean years of schooling and expected years of schooling (Human Development Reports., n.d.)

FDA- The Food and Drug Administration (FDA) is an agency within the U.S. Department of Health and Human Services. It consists of the Office of the Commissioner and four directorates overseeing the core functions of the agency: Medical Products and Tobacco, Foods and Veterinary Medicine, Global Regulatory Operations and Policy, and Operations. (FDA, n.d., para.1)

Inspection-A careful examination by an official to make certain that something is in good condition, or that rules are being obeyed (Inspection, n.d., para.1)

No Action Indicated (NAI): which means no objectionable conditions or practices were found during the inspection (or the objectionable conditions found do not justify further regulatory action). (Office of Regulatory Affairs., n.d.)

Official Action Indicated (OAI) which means regulatory and/or administrative actions will be recommended. (Office of Regulatory Affairs., n.d.)

Quality defects-attributes of a medicinal product or component which may affect the quality, safety and/or efficacy of the product, and/or which are not in line with the approved Product Authorisation (PA) or Veterinary Product Authorisation (VPA) file, or other marketing authorisation (Management & Global, 1993)

Quantitative and expertise-based assessment- FDA OPQ is organized based on discipline and expertise (e.g., drug substance, drug product, microbiology, process, and biopharmaceutics). A structured risk assessment will be utilized to facilitate quantitative regulatory evaluations and will serve as a communication vehicle internally and externally. This will increase the efficiency and effectiveness of quality assessments by focusing on the specific risks to the consumer and individual product failure modes. (Yu & Woodcock, 2015, p.5)

Regulatory oversight- The management or supervision of a group by an outside body in order to control or direct according to rule, principle, or law. (WHO, 2009, p.13)

Stringent regulatory authorities (SRA) nations that are recognized by WHO with stringent regulations.

Voluntary Action Indicated (VAI) which means objectionable conditions or practices were found but the agency is not prepared to take or recommend any administrative or regulatory action. (Office of Regulatory Affairs., n.d.)

Warning letter- A Warning Letter is the Agency's principal means of achieving prompt voluntary compliance with the FD&C Act. The use of Warning Letters is based on the expectation that most individuals and firms will voluntarily comply with the law. Warning letters are considered advisory actions, and the FDA’s position is that these letters are issued only for violations of regulatory significance. (Glossary, n.d., para. 4)

LIST OF ABBREVIATIONS

EMA-European Medicines Agency

FDA- U.S. Food and Drug Administration

NAI- No action indicated

NCR-Noncompliance report

OAI-Official Action indicated

SRA-Stringent Regulatory Authority

VAI-Voluntary Action Indicated

WHO-World Health Organization

ABSTRACT

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Institution: Purdue University
Degree Received: August 2019
Title: Quantitative-Scientific Company and Product Scorecard Considerations and Modeling
Committee Chair: Kari Clase

FDA has long served as the front safeguard to the U.S. citizen public health, is also perceived as one of the world-leading drug regulators. Despite the tremendous efforts and progress have been made to promote the public health, FDA was criticized for putting the agency's trust icon at stake and was questioned of its ability to serve the agency's ultimate mission to protect the public. In the wake of the arousing concerns, FDA sought the transformation the oversight model of the medicinal products. One of the actions is to launch quality metrics program. However, this program has been unanimously opposed by the industry. Instead of the current conventional approach, which is constrained by the high dependence on industry cooperation, we try to explore the measurement of company and product quality risk with public domain data, try to help in visualizing quality and risk. To that end, we develop conceptual frameworks for both company and product quality, examine some of the factors (education, local authority intensity, historical inspection results, physiochemical, physiological, formulation factors, etc.), further developed a warning letter and product recall prediction model with machine learning method referenced to the data analysis outcome.

CHAPTER 1. INTRODUCTION

1.1 Background

The U.S. The Food and Drug Administration (FDA) acts as the upfront safeguard to promote public health and assure highly-regulated, good quality drugs are available to the patients. The agency was established in 1906 in the form of federal consumer protection agency, while, the root could be traced back to early colonial times for food regulation, and 1848 for the beginning of drug supply control (Commissioner, n.d.). "The agency regulates approximately 25 percent of the Gross National Product in the U.S. , and roughly one-third of all commercial lines of entry declared at U.S. ports of entry fall under FDA's regulatory oversight" (Inspections et al., n.d, p 9-2). When looking back to the history of the food and drug laws, it's not difficult to find out that the drug laws and regulation journey advanced in the wake of a series of tragic accidents, Elixir sulfanilamide disaster, 1937; sulfathiazole tragedy, 1941; chloramphenicol incident, 1952; Thalidomide tragedy, 1962 (Commissioner, n.d.); They are all hard lessons to learn and come at the price of numerous life deprivations or severe health damages, these tragedies help to shape today's regulatory oversight framework: rigor premarket approval and focus on both safety and efficacy aspects (Charatan, 2004).

FDA is missioned to protect and promote public health with safety and efficacious medication timely. This task is enabled by rigorous premarket approval, high regulation standards for drug lifecycle management. With the significant and successful efforts, FDA has made, the public has gradually to accept "FDA approval" as a trust icon (Charatan, 2004). FDA also conveyed a brighter vision for 21st-century drug manufacturing, which is characterized with the key attributes as highly efficient, flexible, agile manufacturing, but of a high-quality medicinal product, and minimized regulatory oversight effort (U.S. Food and Drug Administration, 2004).

1.2 Research Problem

Nevertheless, despite all the diligent works and tremendous progress FDA has made in the past decades, evidence still suggests that there are still intolerable high drug safety concerns and shortages crisis existed; The pursuit of a high-quality life and progressive lowering of risk-tolerance of the patient also put drug safety concerns and quality issues under the microscope, amplify the risk to the society, and consequently jeopardizes the trust icon FDA has built (Bush & Services, 2005). Meanwhile, the FDA was challenged by its chronic understaffed and under founded (Swider, 2011), not to mention the constant challenges from the rapidly emerging technology (United States Government Accountability Office, 2009). Nevertheless, according to FDA's white paper (2015), FDA tends to treat the product and company equally, which aggravated the situation. However, a significant number of foreign establishments, who are playing an increasingly significant role in the U.S. medication landscape, are somehow escaping from the rigorous regulation examination (United States Government Accountability Office, 2013). The FDA has been questioned by the U.S. Government Accountability Office (GAO) of ongoing inability to serve its mission to protect public health because of the identification of weaknesses in multiple areas of regulatory oversight, these weakness been put into the high-risk list since 2009 (United States Government Accountability Office, 2013), and still remain on the list (United States Government Accountability Office, 2019).

There is an imperative need for the FDA to frame the oversight with risk and knowledge-base. In the FDA's white paper (2015), the FDA announces its intention to transform the current qualitative to a "quantitative and expertise-based" oversight model (p.4). Till this paper, the quantitative and expertise-based assessment program is still ongoing, the quality metrics program which tries to gather vital performance metrics for the live monitoring of a company, however, has

raised a broad opposition from the industry. Meanwhile, the majority of the metrics study all target on the company metrics, and not much has been done from product aspects.

1.3 Research Question

In view of the unanimous opposition of the industry for the quality metrics program, is it possible to build the quantitative and scientific scorecard with available public data? This study tries to address the following questions:

- Company metrics
    1. For the pharmaceutical companies that have business with the U.S. and EU, is there relationship between the compliance status with education level?
    2. For the pharmaceutical companies that have business with the U.S. and EU, is there relationship between the local authority regulation intensity with the companies' compliance behavior?
    3. Do the historical inspection results indicate the company future compliance state?
- Product metrics
    1. What are the variable factors that may contribute to considerable efficacy variations?
    2. Are there relationships between the manufacturing variables with the product recalls that associated with the processing variables?

1.4 Scope

This study would primarily scope to drug sector, use observatory data from the public domain, explore the relationships of the variable factors with the companies' compliance state and drug quality, ultimately inspire or feed to the built of a quantitative and scientific evaluation framework for company and product.

1.5 Significance

Yu and Kopcha (2017) stated that the present drug manufacturing possesses two to three sigma of quality defects, roughly 30% defective rate (2 sigma), astoundingly larger than other delicate industries, i.e., electronic, automobile industries, etc. for which industries the number is about 0.0003% (p. 354). High-quality defect rate not only burdens the industries with a number of deviations or nonconformance investigation, high possibly to waste in product reprocess or rework, even product recalls, also the built-in risk from the process endanger the patients with the defective drug without being effectively detected. Drug and biologics product recalls figures (figure 1.1) retrieved from FDA data dashboard are still unbearable high, which may arise in part because of the above-mentioned defective product without being detected or severe laws or regulations violations (figure 1.2) as presented by FDA (2017) published data on enforcement actions. Behind this formidable numbers, vulnerable patients are paying health prices for the defective drug delivered to their hands.

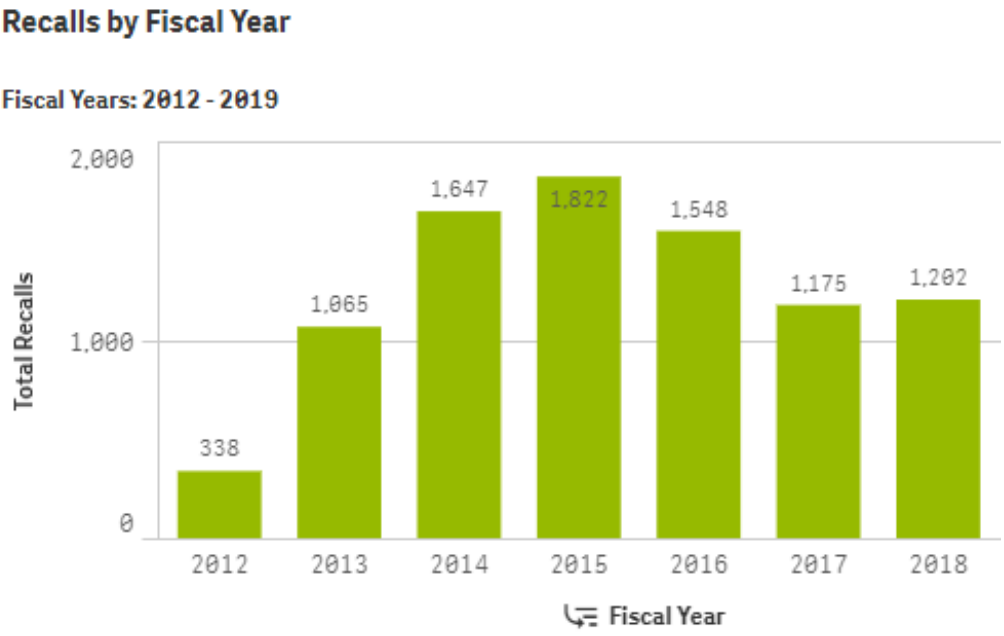


Figure 1.1 Biologics & Drug Recall Event 2012-2018 (FDA data dashboard, accessed on 11/12/2018)

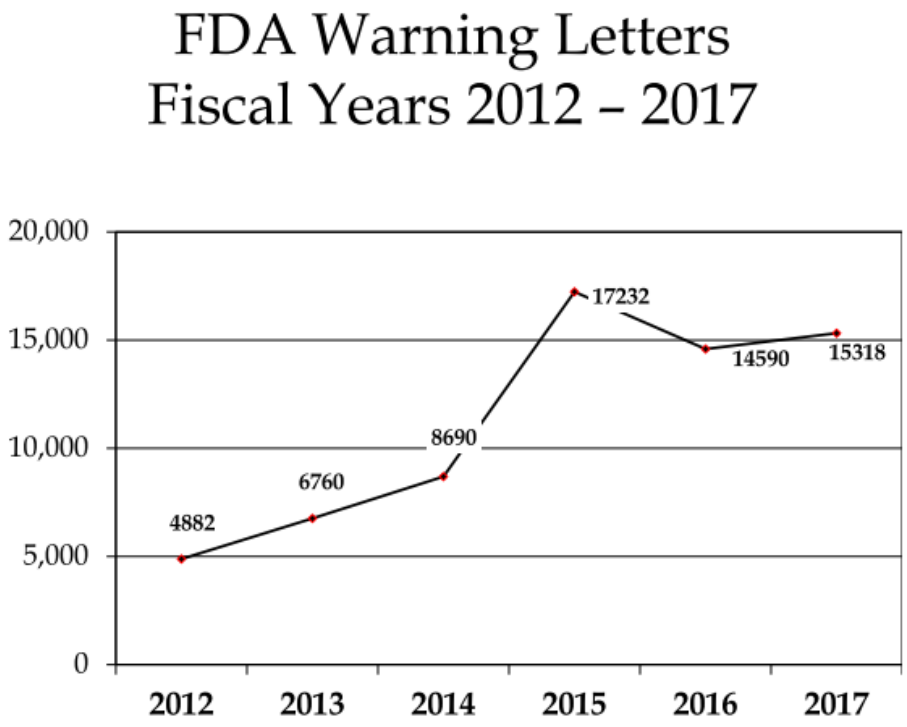


Figure 1.2 *FDA Warning Letter Issuance 2012-2017 (FDA,2017)*

Although with the prompt joint efforts of the agency and the industry, the shortages number have been greatly cut down, the severity of the consequences (medication errors, collapse of the health care system, burden on the physician or doctors, patients unmet treatment need, or increased risk of safety or comprised efficacy, etc.) make the shortages still a concern to be reckoned with. Kweder and Dill (2013) found that 46% of the drug shortages for all dosage forms are contributed to quality issues, and this number increases to 56% for injectable drug product (p. 247).

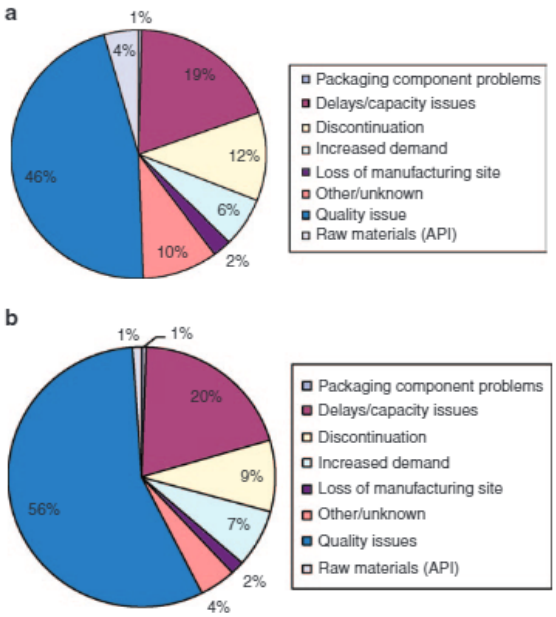


Figure 3 Reasons for drug shortages in 2011. (**a**) All dosage forms. (**b**) Sterile injectables. Data from the US Food and Drug Administration Drug Shortage Program.

Figure 1.3 *Reasons for Drug Shortages in 2011 (Kweder and Dill (2013), p.247)*

1.6 Assumptions

The inherent assumptions of this study include:

- Education length and education index data from United Nations report are accurate.
- The inspections data obtained from the FDA data dashboard and Euradex GMP public layout are accurate and complete.
- Companies that have inspection data in the FDA data dashboard and Euradex GMP public layout represent the companies that have business with the US and EU.
- The business type of a company got from the FDA drug establishment and registering list website is accurate.
- The stringent regulatory authority list per WHO is assumed to be well received by the pharmaceutical field.
- Companies historical inspection list from FDAZilla database are complete.

- The searching of product recalls with parts of the core product name in FDA enforcement reports are accurate and replicable.
- Drug information from drugs @ FDA is accurate and complete.
- Product commercial status got from drugs @ FDA are assumed to be accurate.

1.7 Limitations

The limitations that are associated with this study include the follows;

- In terms of regulatory compliance, everybody should take responsibility, which may take a very diverse background (in this sense, a company can be viewed as an epitome of a society), it is expected and assumed in the education study, national education data may represent as a rough estimation of the education of the pharmaceutical field. However, it is not deniable that as the core business is pharmaceutical activities, it is anticipated that there might be lean toward the pharmaceutical education, therefore the national education data may still bear some limitations, consequently the correlation results may be compromised.
- Companies that are not actively registered with FDA is not included in the sampling.
- Constrained by the fact that FDA inspection classification are not complete, cross verification of FDAzilla is not feasible at this moment.
- Product recalls associated with the process variables may need judgmental call.

1.8 Delimitations

The delimitations inherent in this study include:

- For the compliance behavior in the relationship with the education study, the compliance ratio data are obtained from both U.S.FDA and EU EMA data. U.S. FDA

and EU EMA are very high recognized regulatory authority in the world, however, due to resources limitations, logistic challenges and language barriers, etc., The foreign inspections are not commensurate as the domestic inspections, therefore, these two authorities' results are collectively used to eliminate some extent of the geographic concerns to have a better understanding of the country's general compliance concept.

- As the companies selected in the education and local authority studies might not be representative of the country's population, therefore the study only scopes to the companies that have business with the U.S. and EU.

1.9 Chapter Summary

FDA is missioned to protect the U.S. public with safety and efficacious drugs, the agency wants to proceed with this task in a highly efficient and quality manner, however, its ability has been questioned, notably the lack of full coverage and efficient oversight for the foreign establishments, concerns of drug shortages, and intolerable high product recall events caused by quality issues. The imperative need to make a difference to the regulatory oversight has been raised. FDA is seeking a transform from a qualitative oversight to a quantitative and expertise-based assessment; to that end, FDA launched several programs in expecting to achieve the 21st manufacturing vision, quality metrics, very controversial trial program, has elicited almost consentaneous objection from the industry may stem from the concerns of increased financial burden, time expense, little value added compared to the benefits, or even trigger more frequent inspections, etc. In view of the difficulty of that route to collect confidential data from companies, this study tends to gather observatory data from public domain to identify factors that may inform the companies' compliance state or product quality risk, ultimately serve as inspiration for future study or feed the built of the quantitative and scientific scorecard for both company and product,

therefore to inform the risk of a drug product and company to the patients, the physicians, provide FDA insights for the resources leverage, and ultimately aid the maximization of the oversight effect with limited efforts.

CHAPTER 2. LITERATURE REVIEW

This literature review will try to identify the significance of the safety concerns, uncover the reasons beneath the iceberg of drug safety and drug quality concerns, summarize the efforts have been done so far to tackle the problems, therefore, to shape the gap for this study.

2.1 The Significance of the Problem

2.1.1 Drug Safety Concerns

Although by all means, the FDA is building its trust icon to the public as a vehicle of safe and efficacious drugs' delivery, however, it should be aware that it does not necessarily mean every drug approved by the FDA is unrealistically risk-free. The FDA developed the benefit-risk balance approach for human drug review since 2009 (Thompson & Graham, 2018), the core concept is the benefits should outweigh the risk at a reasonable level and ensure patients have the timely access to the medication with affordable price. The FDA also implement post-marketing safety monitoring and compliance status confirmatory inspections after bringing the drugs into the market. But it also needs to stress that this risk balance approach does not exempt the FDA's obligation to protect the public from the damage of the problematic drugs.

Despite the bitter, rigorous, high demanding premarket approval process, the FDA still is questioned for releasing unsafe or ineffective drugs to market. The FDA's post-marketing safety systems have been long criticized, more than 30 years (United States Government Accountability Office, 2013). It has been reported that 86% of adverse event reactions are unreported (Levinson, 2012, p.12). Product recalls and drug shortages, often perceived as signals of severe quality defects, are still beyond public and the agency's tolerance. A report released by the FDA (2017), shows in 2017, there is a significant number of defective products have to be recalled from the markets and

also the number of severe violations of laws and regulations has been greatly elevated since the 2012 year (p.7). There is also a phenomenon that “higher post-market safety problems were observed under the pressure to meet “just-before-deadline” approvals”, (Nall, 2012, p.98), Yu and Kopcha (2017) also found that the present drug possesses two to three sigma of quality defects, roughly 30% defective rate (2 sigma), astoundingly greater than other delicate industries, i.e., electronic, automobile industries, etc. for which industries the number is about 0.0003% (p. 354).

2.1.2 Drug Shortage Crisis

As the severe consequences to the health care system, the significant number, and frequency of drug shortages in the past decades, drug shortages have risen to a crisis. Per data released by FDA (2016), “as the height of the drug shortage crisis, the number of new shortages tracked by CDER quadrupled from approximately 61 shortages in 2005 to more 250 in 2011.” The apparent consequence of drug shortages would be the patient’s delayed therapy; however, study surveys reveal much more impacts. Survey on over 1800 healthcare professionals by the Institute for safe medication practices (Kaakeh et al., 2010), observed a very high level of frustration and safety concerns due to the drug shortages, “more than 1000 of near misses, medication errors, and adverse outcomes reported by respondents that occurred during the past year due to drug shortages” (Institute for Safe Medication Practices, 2010, para.6). Drug shortages stem from handful of common issues, wherein quality issues are the major causes, contributes to 46% to all dosage forms of drug shortages. This number of injectable products elevates to 56% (Kweder & Dill, 2013).

To respond with this drug shortage crisis, the FDA has taken promoted actions to address these concerns as a high priority. Earlier notification of drug shortages by the manufacturer is required; Swift collaboration efforts of FDA and manufacturer will be integrated shortly; the FDA is also powered with regulatory flexibility and discretion calling as deemed necessary. All these

together make a powerful instrument to successfully prevent some drug shortages, for example, "FDA helped to prevent 282 drug shortages in 2012, 170 shortages in 2013, 101 shortages in 2014, and 142 shortages in 2012, 170 shortages in 2013, 101 shortages in 2014, and 142 shortages in 2015."(Gottlieb, 2016,p.3). While not all the drug shortages are eliminated, there are still a handful of drug shortages. The residual drug shortages number from 2010 to 2016 Sep. is displayed in figure 2.1.

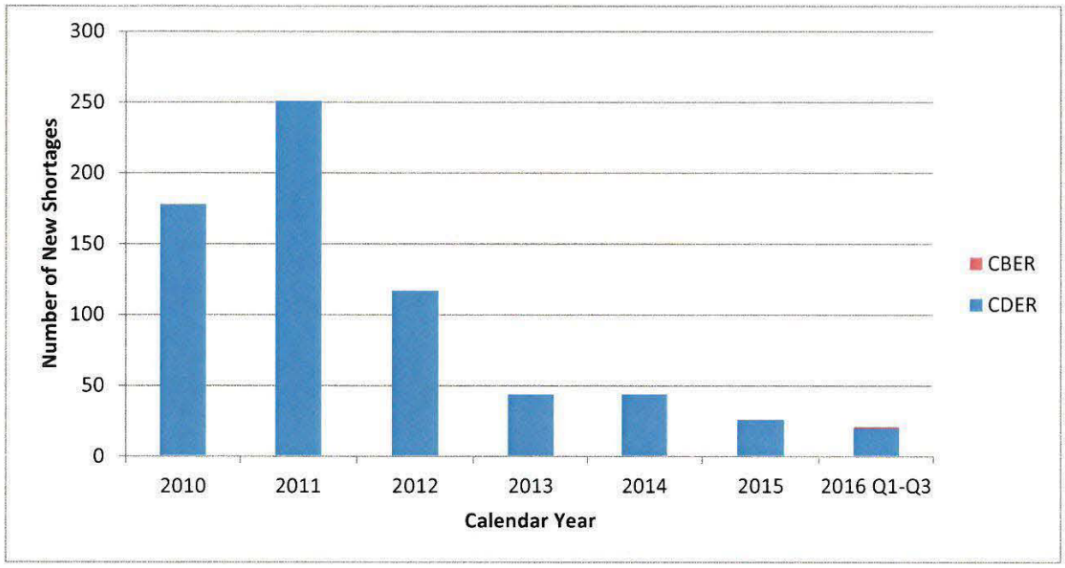


Figure 2.1 *Number of New Drug Shortages 2010 to September 30, 2016 (Gottlieb, 2016)*

Despite there is a remarkable decline of drug shortages since 2011, the drug shortages still are considered to pose a severe and growing challenge to the public health, especially by the critical drugs for cancer treatment, or parenteral nutrition, etc. (Gottlieb, 2016). As discussed above, the drug shortages will not only cause a potential lapse in the medical care system, increase in medication errors, burden the doctors and physicians, but also introduce a high potential of compromised effectiveness and raised safety concerns to patients due to the second-line alternative drugs (Gottlieb, 2016).

2.1.3 Drug Quality Defects

Yu and Kopcha (2017) stated that the present drug possesses two to three sigma of quality defects, roughly 30% defective rate (2 sigma), astoundingly larger than other delicate industries, i.e., electronic, automobile industries, etc. for which industries the number is about 0.0003% (p. 354).

Quality system, although not the direct measurement of the drug quality defects, it's the least instrument to enable the drug quality, after all, only tiny proportions of the drugs delivered to the markets will be actually tested against the proper agreed upon standards. Weakness in the quality system will most likely put the drug quality in questions, it especially so when severe violations of the laws and regulations are observed, wherein appropriate enforcement actions (e.g., warning letters issuing, junctions, seizures, etc.) will be put in place by the FDA or voluntarily corrected by the companies (e.g., product recalls, etc.) As presented in figure 1.2, FDA (2017) published data on enforcement actions reveals that the numbers of warning letter issued for the companies who were observed with severe violations of laws and regulations have greatly elevated since the 2012 year (p.7), the numbers for recalls events and products in figure 1.2 are still unbearable high (p.11). Behind this formidable numbers, vulnerable patients are paying health prices for the defective drug delivered to their hands.

2.2 Underneath Causes

Per the analysis of GAO (2013), the challenges that hinder FDA to fulfill its mission to protect public health effectively include "the complexity of new products submitted to FDA for premarket approval, the emergence of challenging safety problems, the globalization of the industries that FDA regulates, and new statutory responsibilities" (United States Government Accountability Office, 2013, p.16). FDA was also questioned by GAO about "ongoing ability to

fulfill its mission of ensuring the safety and efficacy of drugs, biologics, and medical devices." (United States Government Accountability Office, 2013, p.16). The weaknesses were identified in areas of foreign establishment inspections, post-marketing safety monitoring, promotional materials review, and clinical trials oversight, etc. Further, to streamline and align with the concept of least burdensome approval process, remediation actions which could be posted after approval, are therefore asked to be studied afterwards, however, there is serious disconnection between the the Office of New Drugs (OND), the office of Drug Safety (ODS) and the Office of Compliance (OC), which left the post approval studies are not empowered for its intention or serve the feedback loop. Levinson (2012) found that there is an astounding under-reported of adverse event reactions (86% unreported) (p.12). Systematic management and monitoring of the post-market studies are imperative (Senate, 2009). All these weakness undermined FDA's missions to protect the public health.

2.2.1 Outsourcing and Importation Safety Challenging

Along with the rapid advancement of technologies and extensive competition in the pharmaceutical field, drug manufacturing has become increasingly complex. Efficiency is very valuable to survive in an overly competitive market. Driven by the cost reduction and improvement in manufacturing efficiency, there is an upsurge of outsourcing for over decades. It is estimated that the outsourcing activities grew at a rate of about 30-40% annually between 2003 to 2008, and a survey also suggests this trend is still accelerating (Swider, 2011).

The outsourcing service could take multiple forms, functions for testing, active ingredients and excipient manufacturing, research and clinical trial conducting, etc. The increased complexity in production introduces challenges for both the FDA's resources (Swider, 2011), and patient safety concerns (Liu, 2012). Swider (2011) found that a positive relationship existed between

participants in the manufacturing and the number of the FDA inspections, this increased hype of outsourcing aggravates FDA's chronically understaffed, underfunded situation.

The increased number of the participants in drug manufacturing, especially overseas manufacturers also brings safety concerns, due to the hindering an in-depth rigorous as a result of the language barrier, limitation in resources, or unfeasible unannounced inspection to capture the most real company operations and status (Stuart, 2008). These safety concerns are not just literately hypothetical. According to Levine (2008), "A spate of widely publicized injuries, deaths, product recalls, and the FDA import bans involving adulterated foreign-sourced products have drawn the attention of the press, members of Congress, and U.S. consumers." (para.6).

However, the foreign inspections are no way commensurate with the risk the public are bearing. Kramer and Kesselheim (2012) found that, "80% of all active ingredients and 40% of finished product sold in the United States originate overseas" (p.1279), however, at most, only approximately 7% of foreign establishment was inspected in a given year, the time to inspect all the foreign establishment will cost the agency over 13 years (Stuart, 2008). It has also been noticed by GAO (2009) that the FDA conduct foreign inspections mostly for a new drug application, whereas the already marketed foreign establishments are overly neglected. According to GAO (2016), "FDA has reduced its catalog of drug establishments with no inspection history to 33 percent of foreign establishments, compared to 64 percent in 2010." (p.21), although FDA has significantly increased foreign inspections since 2009, while, the number of foreign establishments not being inspected is still remarkable, about 1000 out of the 3,000-foreign establishment (United States Government Accountability Office, 2016, p.21). Overseas offices are also opened to facilitate foreign inspection efforts, i.e., offices in China, Europe, India, and Latin America, etc.

However, the effectiveness of foreign offices' contributions to drug safety has not been assessed (United States Government Accountability Office, 2016).

Constrained by the limited resource and language barriers, FDA seeks cooperation with the local authority of the exporting countries to share the regulation governance to secure the drug safety and efficacy. However, this does not always yield in favorable result because of these limitations or misconceptions: limited information about how the medical products are produced in a foreign country; limited resources to conduct the commensurate ratio or frequency of overseas inspections as domestically; local authority does not have as many intensive regulations as the U.S. does, or gold standards are not implemented at less developed nations (Levine, Liu, & Lip, 2008, para.4). There is a crying need to have more understanding and control of foreign establishments, to seek for a balanced benefit over the reduced manufacturing cost.

2.2.2 FDA limited and Unleveraged Resources

It was well known that the FDA was chronically understaffed, underfunded. The situation has improved since the enact of PDUFA (Prescription Drug User Fee Act) in 1992; the PDUFA act allows the FDA to collect user fee to support its increase in staffing. Studied showed that "NDA review times shortened by 3.3 months for every 100 additional FDA staff" (Carpenter, Chernew, Smith, & Fendrick, 2003). Although the FDA's effort in staffing is continuously augmenting, the agency's resources are still continually being challenged by the extensive regulatory oversight needs, emerging novel technology, modernization, and global trading. For instance, in 2007, the FDA have only 44 full time staff available to review over 68, 000 promotional materials, only a very small portion of the materials is able to be assessed (United States Government Accountability Office, 2009), 64% of foreign establishment has never been inspected till the 2010 year (United States Government Accountability Office, 2016). The limited resources are

overstretched further by the emerging technologies, not only the financial resources but also the personal competency. It is criticized that "FDA is understaffed, underfunded, and currently ill-equipped to deal with the nanotech revolution" (Traynor, 2006). The emerging techniques of stem-cell development also pose a severe challenge to the FDA; for instance, the non-compliant stem cell clinics and the use of unapproved stem cell related biological products (Knoepfler, 2015). The proactive cost-saving solutions of the pharmaceutical company by contracting out manufacturing, especially to the overseas manufacturer has necessitated the FDA's regulatory oversight expansion abroad. The FDA has opened ten offices abroad and partnered with the local authority to ensure the quality compliance and safety of the products imported to the United States (Torres, 2010). Another notable challenge is the regulating drug promotion, advertising, and sales on the internet, misleading and untruthful advertising may present a public health hazard (Henney, 2000), ill-regulated online drugs sales has incubated the counterfeit drugs' growth and thriving (Mackey & Liang, 2011).

The inefficient of the resources allocation aggravate the issues even further, according to the FDA's white paper (2015), "current regulatory review and inspection practices tend to treat all products equally, in some cases without considering specific risks to the consumer or individual product failure modes. A disproportionate amount of regulatory attention is devoted to low-risk products and issues, diverting resources needed for the assessment of high-risk products." (p.1). It is imperative for the FDA to optimize the utilization of the limited resources with a robust, and scientific oversight model.

2.2.3 Manufacturer Lack of Incentive to Invest in Quality

Apart from the authority FDA's weakness in oversight, as another main stakeholder of medical products, the pharmaceutical company also plays an essential role in the drug sector.

Pharmaceutical company's perception and appreciation of the drug quality is the vital factor, as there is a big gap in drug quality assurance regulatory governance. After all, it is not feasible for FDA to inspect every single batch of the medical products released to the product, and the compliance status of a company is continuously evolving, the periodic inspections by FDA cannot capture all the product deviations or system defects (Yu et al., 2017). Further, FDA current oversight heavily relies on the industry proactively compliant with the laws and regulations, to name some: voluntary drug recalls, drug adverse event reporting at company's discretion with reasonable justification, changes, and deviations evaluated by the companies, etc. It's fair to say medical product quality assurance lean very heavily towards the control at the pharmaceutical manufacturing site.

Pharmaceutical companies are reluctant to embrace investment for improvement or innovative technology. "From a technical standpoint, the capital equipment technologies have not evolved at the rate they have in other industries" (Economist & Unit, 2005,p.4). The reasons behind this reluctance to embrace technology innovations include: the low efficiency of the manufacturing could be complemented by the high-profit margin of new drugs; the regulatory uncertainty of new technology or innovation; financial and time cost to make changes, etc. (Economist & Unit, 2005, p.4). Another obvious reason for the unwilling to invest in quality is due to the invisibility of the medical product quality to the end users (Yu, eta., 2017b). As to the patients, FDA approval means safety and officious; there is no easy way to discern the quality of a medical product. Therefore, no reward or incentive for the pharmaceutical company to go beyond the regulations or standards and invest in product quality improvement (Woodcock & Wosinska, 2013).

2.3 Progresses Made

To address the concerns or challenges describing as abovementioned, remediation has been taken to mitigate the issues, for instance, collect user fees from the industry besides the appropriation funding from the Congress, risk-based inspection concepts have been adopted and implemented, created super office to integrate both internal and external efforts, scientific and expertise-based oversight approach is under development, etc. These actions and progressions are described in detail in the following sections.

2.3.1 Risk-based Inspection Program

As discussed in the problem sections, severe harms to public health have been made due to the drug outsourcing and importation; however, the inspection frequency and an absolute number of foreign establishments are incommensurate to the introduced risk, and far lower compared to domestic inspections. GAO (2013) estimated that only 8% of the foreign establishments were inspected in the fiscal year 2007, although this portion has significantly increased (27%) for the year 2009 since the weakness in foreign establishment inspection was identified by GAO in 2008, however, the 11 percent of foreign establishments inspection per year still far below the rate of 42% for domestic inspections and seriously incommensurate with the safety risks caused by the drug importation. In the wake of series tragedies by drug importation, the FDA has allocated the resources to increase foreign inspections, open international offices and develop a prioritization model for inspections (United States Government Accountability Office, 2016). Till the fiscal year 2015, un-coverage percent of foreign inspections have dramatically curtailed from 64 percent in 2010 to 33%. However, the absolute number of not inspected foreign establishments are still remarkable, almost 1000 out of 3000 are still not inspected. Not to mention the efforts need to promote commensurate revisiting frequency as to domestic establishments (presently around every

2.5 years). While the FDA is doubted to have the sufficient capacity to fulfill this obligation in a short time, GAO has therefore made a reasonable suggestion to adopt a risk-based model to prioritize the surveillance inspections to both domestic and foreign establishments since 2008 (United States Government Accountability Office, 2008). Till 2012, the proposed risk-based concept has been aligned and enacted by FDASIA. The risk-based approach is mainly framed on three major factors: scores of facility and product, the time duration since the last inspection, also permits flexibility to fit in the logistics optimization for foreign establishment inspections, and free to make adjustment on the FDA's focus area or product when deems necessary (United States Government Accountability Office, 2013). The output of the model will, therefore, to generate a list of establishments with priority ranking to facilitate the FDA's decision making to allocate the resources for the surveillance inspection. The FDA further defines the major factors as follows: "the facility score includes information about the facility and its histories, such as the type of establishment (for example, a manufacturer or a laboratory), number of products produced at the facility, and inspection history." "The product score, meanwhile, captures information about a product itself, such as its therapeutic category (for example, an antifungal), its dosage form, and whether it is sterile." (United States Government Accountability Office, 2013, p.9).

2.3.2 The FDA Funding and Staffing

Since the enactment of user fees, FDA's funding and staffing have greatly augmented, it is reported by GAO that "Total funding increased from about $ 562 million in the fiscal year 1999 to about $ 1.2 billion in the fiscal year 2008, with user fee funding accounting for more than half of this increase." (States & Accountability, 2009, p.19). FDA's current funding and staffing are empowered by enactment and reauthorization of a series of user fees, starting from 2002. Prescription Drug User Fee Act, (PDUFA, first enacted in 2002 to promote new drug and biologic

product application review); Medical Device User Fee and Modernization Act (MDUFMA, first enacted in 2002, to support medical marketing evaluation); Animal Drug User Fee Amendments (ADUFA, first enacted in 2008, to facilitate animal drug review process); Animal Generic Drug User Fee Act (AGDUFA, first enacted in 2009, to support abbreviated applications for generic new animal drugs.); Generic Drug User Fee (GDUFA, first enacted in 2012 to fund abbreviated new drug application(ANDA), and sponsor surveillance inspections); Biosimilar User Fee Act (BsUFA, first enacted in 2012 to support biosimilar product application review); The user fees collect for the fiscal year 2017 for GDUFA is $356.5 million (U.S. Food and Drug Administration, 2017), $ 837.5 million for PDUFA (U.S. Food and Drug Administration, 2017), $28.8 million for BsUFA (U.S. Food and Drug Administration, 2017). The greatly augmented funding permits FDA to fill the staff vacancy, upgrade the information technology, optimize organizational infrastructure, innovate in the program, promote close interactions with the sponsor, etc. As a result, there are very positive amelioration in the efficiency and speed of the drug development and marketing process, rectification and modernizing of the drug safety program, and also strengthening in the benefit-risk model to facilitate scientific and robust regulatory decision making (SDBOR, 2017). The foreign inspections challenges have been significantly remediated by the enactment and reauthorization of GDUFA, since almost 80% of the API manufacturers of the generic drugs products are produced abroad. Nevertheless, the funding approach from the regulated industry instead of taxpayers put FDA in a disputable position; there has been accusing that FDA lost its justice and introduce drug safety concerns due to heavily rely on the funding of user fee and lean toward the industry (Olson, 2008). Evidence supported by Light, Lexchin, and Darrow (2013) that almost 90 percent of the new drug approved in the past 3 decades does not have extra benefits to patients than already marketed drugs, in fact, “these companies are mostly developing drugs that

are mostly little better than existing products but have the potential to cause widespread adverse reactions even when appropriately prescribed." (p.591). According to Light (2013), over the past 30 years, "Since the industry started making large contributions to the FDA for reviewing its drugs, as it makes large contributions to Congressmen who have promoted this substation for publicly funded regulation, the FDA has sped up the review process with the result that drugs approved are significantly more likely to cause serious harm, hospitalizations and deaths" (para.5). There is a crying need to have scientific, consistent expertise and risk-based oversight model to communicate the drug and company risk profile and therefore to guide drug approval, remediate drug safety concerns, and most importantly inform a scientific and expertise-based, consistent regulatory decision-making process.

2.3.3 OPQ Office Creation and Ongoing Efforts

Super office-Office of Pharmaceutical Quality (OPQ) is launched in 2015 within the department of FDA Center for Drug Evaluation and Research (CDER) to dedicate on product quality on a global scale; to bridge the gaps and disconnections between the drug review, surveillance inspections, to improve post market drug safety monitoring program; to underscore the importance and impact of knowledge and information on product and company to scientific and risk-based regulatory oversight (U.S. Food and Drug Administration, 2015).

To proceed the vision for the 21st -century manufacturing (U.S. Food and Drug Administration, 2004), and also respond with the questioning of the inability to fulfill the mission of protect public health by GAO, FDA white paper (2015) deeply dived and dig the deep root of the current product quality and safety concerns, the issues are found to stem from various sources, including outdated technology, data and knowledge disconnection existed in internal organizations, and inefficiently usage of the limited resources. In the same paper, among the proposed

remediation actions, FDA pointed out a need to transform the “product quality oversight from a qualitative to a quantitative and expertise-based assessment” (p.4), which to qualify and measure the product quality based on product knowledge, collect quality metrics to “manage quality of manufacturing processes and products within drug facilities” (p.5), inform and feedback from the prioritized inspections.

2.3.4 FDA Quality Metrics Pilot Program

On July 2012, the FDASIA signed into law, one of the provisions calls for a replacement of current biennial inspections to a risk-based inspection, to support this transformation, the FDA announces its intention to initiate a quality metrics program in early 2013(Brookings, 2014), and ask for public insights about the metrics selection. Quality metrics are a powerful instrument to lay the foundation of a quantitative measurement for regulatory oversight. The intention of the metrics program can be briefed in several keywords: to enable efficient regulatory oversight, risk-informed surveillance inspections, early alert of potential drug shortages and product recalls, encouragement and recognition of high performance. The program was first presented to the industry in 2015 in the form of draft guidance. Four mandatory quality metrics are required to be reported by certain establishments for certain covered drugs, the metrics to be collected include lot acceptance rate, product quality complaint rate, invalidated out-of-specification (OOS) rate and annual product review (APR) or product quality review (PQR) on time rate (Woodcock. Iyer & Viehmann, 2015). Unanticipatedly, the draft generated a disappointing response, the industry strongly argued that further studies and discussion should be done by the agency before posing this mandatory requirement (Howard & Sudhana, 2018). The FDA revised the draft guidance on quality metrics in 2016, modify the reporting from compulsory to voluntary instead, also intended to publish a list of establishments and group them into tiers based on the involvement degree of

the quality metrics voluntary program. The program “elicited nearly unanimous opposition from every corner of the drug manufacturing industry, despite the fact the FDA has made numerous changes requested by manufacturers since the concept was first broached, as a mandatory program, in 2015” (Barlas, 2017, p.446). Meanwhile, there is also a severe questioning of the agency’s legal authority and critics about the flaws of the program (Howard & Sudhana, 2018).

Quality Metrics Feedback Program has been initiated by FDA in Jul 2018 to address the aroused questioning and seeks to have an interactive dialogue with the stakeholders to reach a mutual alignment on the metrics program finally, companies are encouraged to the participant via Type C Formal Meetings and Pre-ANDA Meetings and Pilot Visit Program (Kux, 2018, p. 30749).

2.3.5 Associations Effort on Quality Metrics

To respond with the request of quality metrics program, handful organizations are making the efforts to help consolidate the quality metrics program, for instance, the international Society for Pharmaceutical Engineering (ISPE), Parenteral Drug Association (PDA), Brookings Institution, etc.

ISPE conducted two waves of pilot programs to answer the request of FDA’s quality metrics and Federal Register Notice (FRN), aside from the strategy and structure suggestions for the program to move forward, ISPE partnered with McKinsey & Company, and 103 sites from 46 companies, developed quality metrics proposals, and made a great contribution to the draft guidance on quality metrics issued by FDA in 2015. On wave 2 pilot program (International Society for Pharmaceutical Engineering, n.d.), ISPE explores further on company culture and process capability, also sought collaboration with PDA to refine on the culture measurement (Maria, 2018). The gist of the metrics of wave 1 and wave 2 pilots are displayed as in figures 2.2 and 2.3 as follows by the ISPE chairman Michael Arnold.

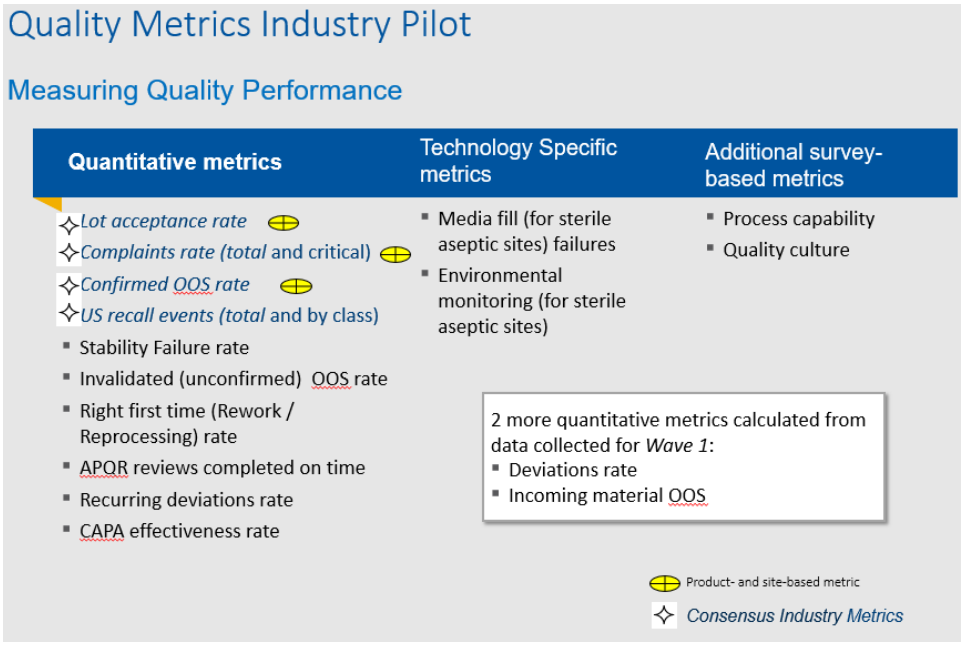


Figure 2.2 *ISPE Wave 1 Pilot Metrics (Michael Arnold, n.d.p.6)*

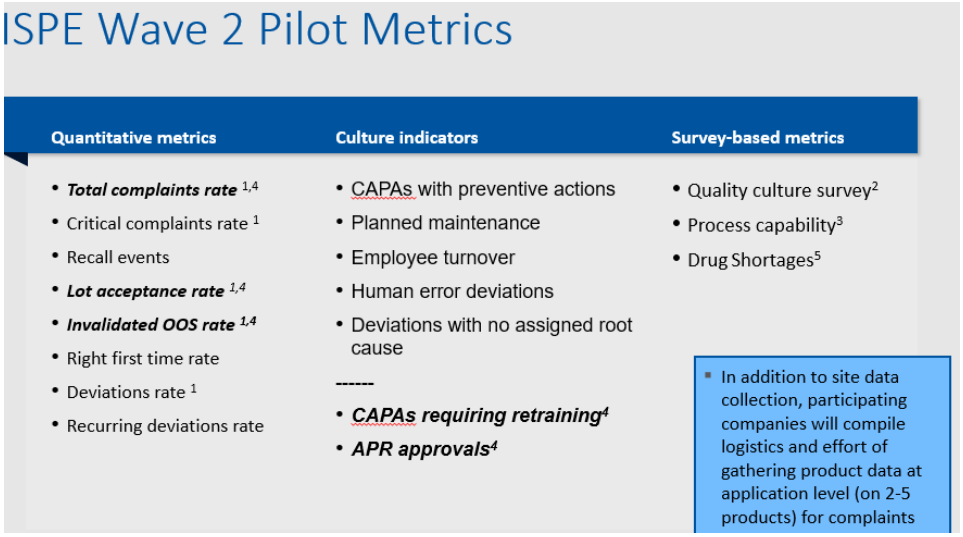


Figure 2.3 *ISPE Wave 2 Pilot Metrics (Michael Arnold, n.d.p.9)*

The Engelberg Center for Health Care Reform of the Brookings Institution also yields some insights of the quality metrics collection via cooperation with FDA and experts' representatives from the industries, the aligned metrics comprise of four indicators: Lot acceptance rate, product quality compliant rate, confirmed out-of-specification (OOS) rate and recall rate. The former 3

indicators are adopted in the FDA draft guidance on quality metrics. Additional thoughts are also proposed as included on following figure 2.4.

Table 2: Additional metrics proposed by stakeholders

• Corrective and Preventive Action (CAPA) effectiveness, recurring deviations, repeat non-conformance • Lead times for investigation (cycle times, ability to close) • Quality system effectiveness • Quality trending • Annual product quality review (on time performance) • Process capability (Cpk)/ Process Performance (Ppk) • Rework and reprocessing rate • Audit inspections • Unplanned equipment down time • Adherence preventive maintenance level	• Right second time • Training effectiveness • Lots on hold / Inventory on hold • % Quality Assurance (QA)/ Quality control (QC) staffing • Customer service measures Recall procedure • Supplier complaints • Supply chain metrics – Supply chain cycle time – Order fulfillment by line – Risk mitigation plans – Inventory (components, API drug product) – Supply chain adherence – Redundant capacity

Figure 2.4 *Additional Metrics Proposed by stakeholders (Brookings, 2014)*

2.4 Gaps

Benjamin Davies, MD (2017), thought FDA's quality metrics program as an absolute right move to address the drug shortages, however, he has doubted the program impact without the legislation endorsement. As discussed, according to Barlas (2017), the program has "elicited nearly unanimous opposition from every corner of the drug manufacturing industry" (p.446). The drawbacks of this metrics program to the industry includes: financial burden (aside from the expense from information and system construction, the minimum cost is estimated at about $285 million, per ISPE CEO, Bournnas, (p.446)), the extra workload due to the atypically data collection and calculation different from the industry normally does, the ambiguity of the definitions and calculation, concerns about the bad metrics consequences, etc (Barlas, 2017). David R, Senior

Vice President for Sciences and Regulatory Affairs from the Association for Accessible Medications (AAM), argues this quality metrics program may, on the contrary, deteriorate drug shortages, he states:

"We are concerned that the actions FDA is taking with its quality metrics program are more likely to increase drug shortages than reduce them. Specifically, the significant burden to report the data requested in the draft guidance must be factored into a company's decisions about continuation of products, may lead to the discontinuation of products that give poor metric results that increase the risk of more frequent inspections. It may also lead to the discontinuation of contract manufacturers and other suppliers that cannot or will not, meet metrics reporting requests. Firms may eventually move production capacity outside the U.S., especially scarce injectable capacity, in order to avoid FDA metrics reporting burdens." (p.447)

FDA has modified the program along the road to mediate the arousing concerns from the industry; nevertheless, Barlas foresees a cessation of the program regardless of voluntary or mandatory. Given the uncertain future and timing of the metrics program, further, the current plan only covers the company metrics, not for the product. There is a need to work on the quantitative and expertise-based assessment in alternative approach.

2.5 Chapter Summary

Medicinal product quality defects touch everybody's heart as it is a matter of life and death. FDA carries on the heavy burden as the safeguard to protect the public in the U.S. from defective drugs and assure the patients access to affordable high-quality, efficacious, and safer drugs.

For decades, the FDA has gained and continuously built up the public's trust by fulfilling its mission diligently; however, severe critics stemmed from various aspects also accompany along the journey. Due to the weakness in the agency's regulatory oversight framework, not optimized

utilization of limited resources, internal disconnection of information and data, challenges aroused with the technology advancement and global trade modernization, etc, intolerable high drug recalls, withdraws from the markets, and unsolved shortages crisis are still threatening the public health and trust in the FDA.

To respond to this safety concerns aroused by quality defects and work toward the 21st - century drug manufacturing vision, aside from replenishing manpower, augment the funding with user fees collection, innovate the infrastructure, etc, FDA also sought a transformation from qualitative measurement oversight to a one of quantitative and expertise-based. Quality metrics program, launched in 2015, is a fundamental instrument to inform the quantitative oversight model, augment the quality improvement, promote early alert of drug shortages, inform the risk-based inspection, recognize the high performer, therefore, to encourage the industry to invest in quality.

Nevertheless, despite all the collectively efforts by FDA, ISPE, PDA, and Brookings institutions, etc., the quality metrics program evoked unanimous opposition from the industries, mainly because of the doubts about whether it serves its intended purpose, the heavy financial and resource burden to collect the metrics, worries about the poor metrics consequences or even just the opposite exacerbate the drug shortages due to the burden aggravation.

Given the ubiquitous objection, the future of metrics program seems pretty dismal no matter voluntarily or mandatorily reporting. There is a need to develop a quantitative and expertise-based assessment in an alternative approach. Moreover, the current metrics collections are all almost site and company-centric, the metrics for products are not well studied.

CHAPTER 3. METHODOLOGY

The unclear future of FDA quality metrics on account of the ambiguous objection from the industry suggests another way out instead of collecting confidential data from companies, use public domain data to estimate the company's compliance and product quality, ultimately to feed the quantitative and scientific assessment. This study utilizes public domain data to explore the factors that may tell about the company's compliance status or risk of drug or serve as future further study inspiration. This chapter will start from the conceptual framework, depict the methodology structure and elements to guide the study, followed by detailed data collection procedures, the variables, and analysis method.

3.1 Conceptual Framework

The studies are primarily grouped into two parts, company-centric metrics study, and product-centric metrics study. To that end, conceptual scorecard frameworks for both company-centric and product-centric are generated to guide the further specific research questions.

3.1.1 Company Conceptual Framework

A robust, fit for purpose quality system and well implementation is essential and crucial to assure the quality of product delivered, it is easy to understand that it is a very complex task to have a precise risk profiling for a company due to the extreme complexity of the system and operation, while, unwind the complexity and mystery, we see three major pillars (figure 3.1) that hold tightly together to achieve the desired medical products, employee qualifications and engagement (education, training, experience, culture, etc.), environment (company quality system and culture microenvironment, authority macro regulation environment), and monitoring and

continuous improvement (inspections, recalls, refusals, drug shortages, warning letter, etc.). For each pillar, there would be both micro and macro layers. The microlayer for the employee is company level employee education, training, experience, and engagement. The macro layer of the employee would also be the corresponding national education attainment, continuous human development, and maturity of the society. The micro-regulation environment is the company pharmaceutical quality system; the macro regulation environment includes local and traded countries regulation intensity, public attitude and maturity of the regulation system. For the implementation, company corporate audit outcome (if any), company self-inspections, and noncompliance data (deviations, complaints, etc.) represent the micro implementation, authority's inspections, import refusals, even warning letters to serve as the macro signals of the company system performance. Studies by Richard Blundell, etc.al. found human capital was necessary for firm growth, productivity, and adaption to new technology, education attainment also have a positive impact on the likelihood of getting training, etc. Gallup researchers found the top quartile in employee engagement has lower quality defects by 41% compared to bottom –quartile units3 (Sorenson, 2013). Per Janet Woodcock, high-level quality drug is enabled by tightly regulated pharmaceutical manufacturing(Woodcock, 2004). Kishu also underlines the importance of the quality assurance system and their close interaction with employee and company continuous improvement (Manghani, 2011).

Figure 3.1 *Company Conceptual Framework*

3.1.2 Product Conceptual Framework

To the end user patient, medication risk could either from the drug product, medication errors or improper compliance; the patient side story will not be discussed in this study, product side risk would be mainly focused. Product risk can be intrinsic and extrinsic. The intrinsic risk here refers to the inherent risks, built on the biochemical properties, for instance, the molecule weight, solubility, permeability, stability, etc. The extrinsic risk here refers to factors that are associated with the processing and product control, formulation selection, how well of the process knowledge is understood and studied, etc. All these could eventually contribute to the drug product efficacy or safety in the patient via the 'IPO' process (Input (Product)-Process-Output (Customer Reaction), figure 3.2). This is in synergy with the ICH's Quality Target Product Profile (short for 'QTPP'), to trace quality back from clinical (ICH,2009).

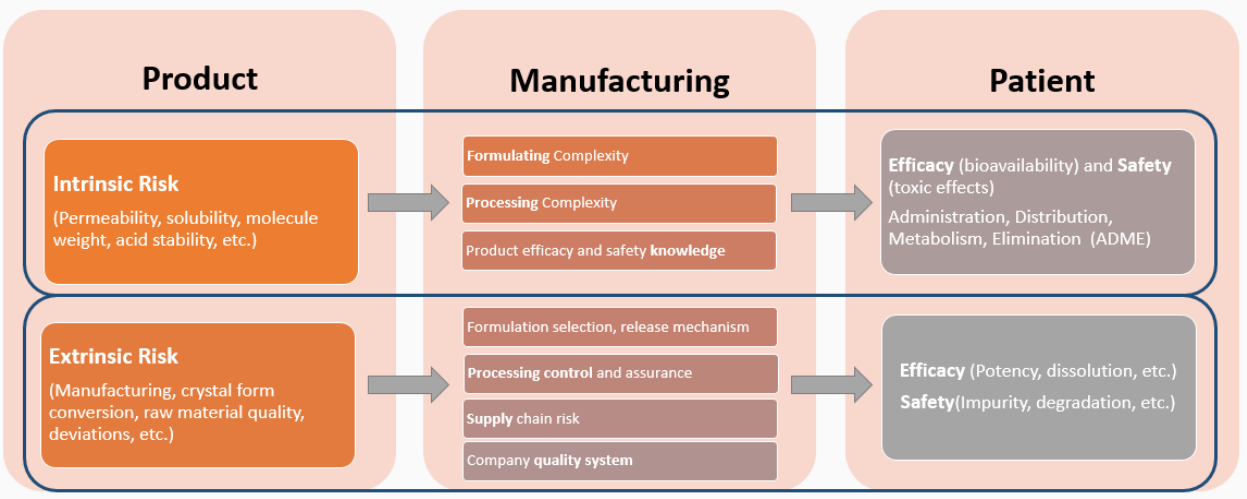


Figure 3.2 *Input-Process-Output Model of Drug Product*

Guided by the process flow along from the product nature to the end user, our conceptual scorecard tries to capture the full dimensions (Inherent-In Process-In System-In Vivo risk) from molecule properties to pharmacokinetics and pharmacodynamics effect (figure 3.3). These risks are grouped into 3 major categories, patient in vivo efficacy risks stem from the compound inherent risk (black box warning, therapeutic index, BCS class, etc.) of the product, and dosage associated variations (metabolism, transporting, etc.), production risk contributed by the product attributes that may augment or diminish production complexity and difficulty (dosage forms, release mechanism, sterility, etc.) and also the company quality system risk which from both internal and external supplier. This conceptual scorecard is scope to drug product mostly, biologics may also find most of the concepts still applicable, despite that the majority of biologics are administered parenterally.

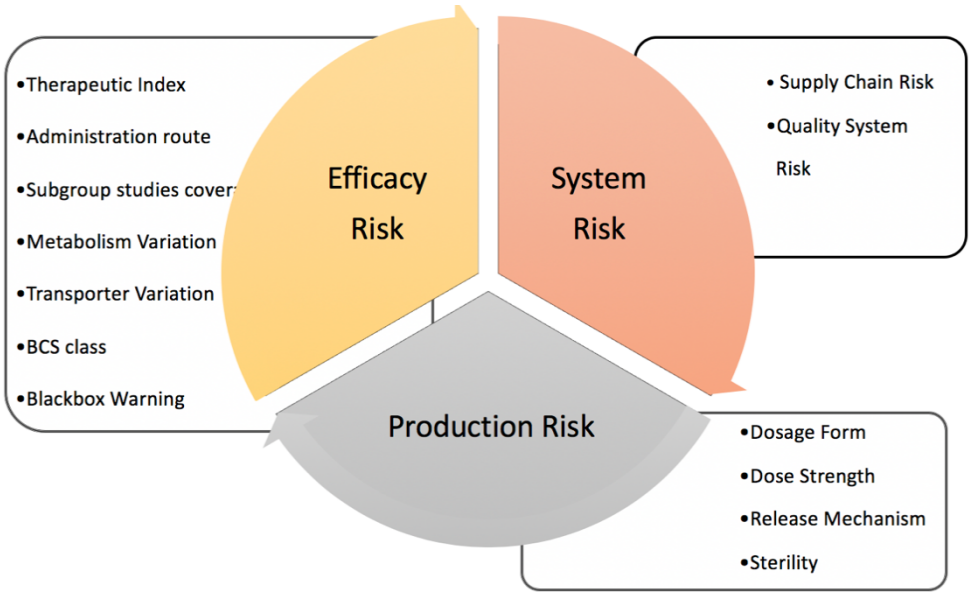


Figure 3.3 *Product Conceptual Framework*

3.2 Research Hypothesis

Guided by the conceptual framework, the research hypothesizes further developed into two groups, company-centric hypothesis and product-centric hypothesis.

3.2.1 Company-centric Hypothesis

3.2.1.1 Research question 1:

Is there a relationship between education index or education length and pharmaceutical regulatory compliance behavior, for those pharmaceutical companies who have business with EU and U.S.?

- Null hypothesis H_0:

  There is no relationship between education index or education length and pharmaceutical company regulatory compliance rate.

- Alternative hypothesis H_a:

There is a positive relationship between education index or education length and pharmaceutical company regulatory compliance behavior.

3.2.1.2 Research question 2:

Is there a relationship between local authority regulation intensity and pharmaceutical regulatory compliance behavior, for those pharmaceutical companies who have business with EU and U.S.?

- Null hypothesis H_0:

  There is no relationship between local authority regulation intensity and pharmaceutical company regulatory compliance rate.

- Alternative hypothesis H_a:

  There is a positive relationship between local authority regulation intensity and pharmaceutical company regulatory compliance behavior.

3.2.1.3 Research question 3-1:

Are historical inspection results good indicators of the companies' compliance state?

- Null hypothesis H_0:

  There is no relationship between historical inspection results (NAI%, VAI%, OAI%) with a future warning letter.

- Alternative hypothesis H_a:

  between historical inspection results (NAI%, VAI%, OAI%) with a future warning letter.

3.2.1.4 Research question 3-2:

Whether the companies with historical OAI result are more likely to receive another or more OAIs compared to the average?

- Null hypothesis H_0:

  The chance of getting an OAI result for companies with historical OAI result does not differ from the other companies.

- Alternative hypothesis H_a:

  The possibility of getting an OAI result for companies with historical OAI result is higher than the other companies.

3.2.1.5 Research question 4:

Is there any pattern of the warning ratio change along with the increased inspection times?

3.2.2 Product-centric Hypothesis

3.2.2.1 Research question 5:

What are the variable factors that would contribute to a considerable product efficacy variation?

3.2.2.2 Research question 6:

The processing attributes (dosage form: solid, solution, other forms; sterility requirement: sterile or not, release mechanism: immediate release, modified release; strength: low, medium, and high strength) which possess different manufacturing difficulty or complexity, whether individually will have relationship with the product recall associated with the manufacturing difficulty or complexity.

- Null hypothesis H_0:

There is no relationship between the individual processing attributes and the manufacturing difficulty or complexity associated product recall.

- Alternative hypothesis H_a:

  There is a positive or negative relationship between the individual processing attributes and the manufacturing difficulty or complexity associated product recall.

3.3 Research Question 1 Methodology

3.3.1 Introduction

This study aims to explore a general understanding of the relationship between education and regulatory compliance behavior for those pharmaceutical companies have business with the U.S. and EU. Both response and explanatory variables will be presented in numerical value.

3.3.2 Variables

The response variable of this study is the regulatory noncompliance rate of worldwide pharmaceutical companies with U.S. FDA and EU EMA inspection data, grouped by country region. The explanatory variable is the education length and education index in the corresponding country.

3.3.3 Population and Sample

The population of this study is the worldwide pharmaceutical companies that have business with the U.S. and EU. Countries that have total inspections amount on pharmaceutical companies from the U.S. FDA and EU EMA less than 10 inspections are not included in the sampling, initial proportion of the noncompliance rate was calculated, the worst proportion was thereafter used in the proportion sampling size equation: $n = p * (1 - p) * \frac{z^2}{m^2})$, wherein p is the noncompliance ratio, the worst sample proportion value (0.12) was used, z takes the value of 1.96, stands for 95%

confidence level, m takes default 0.10 as the margin error, 43 countries that have more inspections than the recommended sampling size n (41) were enrolled in the final samples.

3.3.4 Data collection

The noncompliance rate of a country was populated with the results of inspections from both the U.S. FDA (source: FDA data dashboard) and EMA database (EudraGMDP public database), the results of the inspections was sorted by the country for use. The inspection total numbers, and also the noncompliance report number from EMA, and warning letter number from the FDA for each country were collected. To have a general understanding of compliant behavior for medical field, the product type includes drug, biologics, and veterinary drug products. Food, cosmetics, or tobacco are excluded from the sampling scope. Nine years period data (2009 to 2017) were collected and averaged to leverage some lurking variables, for instance, the difference in inspection frequency and coverage (i.e., the inspection frequency of foreign inspection are not defined by United States until 2012 to adopt risk-based approach (GAO,2016), until 2015, 33% of foreign establishments have no FDA inspection history (the number of foreign establishments for no FDA inspection history is 64% in 2010), barriers of conducting foreign inspections (GAO,2016), etc. The equation for the noncompliance ratio of the selected country is:

$$NCR\ ratio = \left(\frac{\Sigma\#\ of\ (\ EMA\ NCR + FDA\ WL)}{\Sigma\#\ of\ (total\ EMA\ inspections + FDA\ inspections)}\right)$$ (where NCR stands for noncompliance report, WL stands for warning letter, and the ratio is calculated for each country in the samples.) The education length and education index data are directly obtained from United Nations public human development data for the sampled countries; education length took the average value of the schooling years from 2009 to 2017, where education index took the average value of the education index from 2009 to 2017.

3.3.5 Data Analysis

Correlation between the response and explanatory variables are sought, linear regression analysis was performed with statistic software SAS.

3.4 Research Question 2 Methodology

3.4.1 Introduction

This research question tries to find difference in the local authority regulation intensity influence on the pharmaceutical companies that have business with the U.S. and EU.

3.4.2 Variables

The response variable of this research question is country noncompliance ratio obtained in the research question1. The explanatory variable is the sample country's local authority intensity.

3.4.3 Data Collection

The noncompliance ratio from the research question 1 is also used the response variable in this study. As it is hard to give an objective value for each sample country in terms of the authority regulation intensity, therefore the stringent regulatory authority definition in WHO is adopted. National medicines regulatory authorities (NMRA) of ICH members, who are prior to the changes of ICH; ICH observers, who are also members of European Free Trade Association (EFTA), and authorities who have legal binding, mutual recognition agreement, are defined as stringent regulatory authorities (World Health Organization,2014).

3.4.4 Data Analysis

As the independent variable is categorical, and the dependent variable is continuous, SAS ANOVA test is applied for the analysis.

3.5 Research Question 3-1 Methodology

3.5.1 Introduction

This research intends to analyze the inspection history of the pharmaceutical companies, to check the past inspection results distribution (i.e., the ratio of the NAI, VAI, OAI for the historical inspections) relationship with the future warning letter probability.

3.5.2 Variables

The response variable of this study is a binomial data, whether the pharmaceutical company gets a warning letter or not. The explanatory variable is inspections result categories (NAI, VAI, OAI) distribution for the historical U.S FDA inspections.

3.5.3 Population & Sample

The population of this study is a drug manufacturer that is subjected to FDA regulation. To avoid other lurking variables, the business type of the company were also controlled, the samples were limited to drug manufacturers, other business types; for instance, standalone analyzer, packer, re-labeler, distributor, IRB, investigators, etc. has different business focus than drug manufacturers, consequently they were anticipated to have different system focus and operation complexity, and therefore excluded from this study. The drug manufacturer that is registered with U.S. FDA and has at least 3 FDA inspections will be enrolled in the sample (since the inspection distribution is assessed). Systemic random sampling is used for sampling.

3.5.4 Data Collection

The data used for this study are all observatory data from the public domain; no treatment or intervention is designed or conducted. The response variable data that whether a company gets a warning letter will be confirmed with FDA public data dashboard, compliance dataset by the identifier of company FEI number. As the variable studied was the ratio of the three variable

inspection outcomes, at least three inspection results were expected from each sampled company, as the estimated inspection periods are about every two years; therefore, the data collection period from 2012 up to 2018 was therefore set. The inspections outcome data were downloaded from the FDA data dashboard sorted by company FEI number, the company business type was followed and confirmed with the FDA's drug establishment and registration list website. With the successfully verified manufacturers, the inspection results count for each class was therefore collected. The study was grouped into two groups, warning letter group, no warning letter group. For the warning letter group, the inspection results before the warning letter issued are used. The ratio of each inspection outcomes are calculated with the following equations: $NAI\% = \left(\frac{\Sigma \#\ of\ NAIs}{\Sigma inspections\ within\ the\ duration}\right)$, VAI and OAI ratio were calculated in the same way. One hundred seventeen companies' data are collected.

3.5.5 Data Analysis

The response variable warning letter issuance is a binomial data, whether gets a warning letter or not, therefore a numeric value 0 will be assigned for the outcome of no warning letter, and value one was assigned for the fact that a company receives a warning letter. The ratio of the inspection results categories, (i.e., NAI%, VAI%, etc.) were calculated and presented in numeric values. Logistic regression analysis was performed with software SAS.

3.6 Research Question 3-2 Methodology

3.6.1 Introduction

In this study, we aim to check whether the companies with historical undesired OAI result are still more likely to receive another or more OAI results compared to the average.

3.6.2 Variables

This study compares the OAI reception possibility of the companies historically received OAI to the population companies who had at least two inspections result.

3.6.3 Data Collection

The primary source of data was the inspection data set downloaded from the FDA's data dashboard. Drug establishment was the studied objects. As the future inspection result beyond an OAI result or non-OAI result WAS sought, therefore, companies that with at least two inspections enrolled in the analysis, due to the massive data for business type confirmation (6265 establishments), the business type for this study was not further differentiated. The total count of the drug establishments which received OAI inspection results were collected. The population ratio of getting OAI results was calculated with the equation: $OAI\% = \frac{\Sigma\#\ drug\ establishments\ with\ OAI\ result}{\Sigma\#\ drug\ establishment\ with\ more\ than\ 1\ inspections}$. For the drug establishments that had recurred OAI results, the count of the drug establishments and the timing reoccurred were also collected, the recurring ratio was calculated with dividing the counts of establishments that have more than one OAI result, by the number of establishments that have inspections followed an OAI result.

3.6.4 Data Analysis

T-test with SAS between of the OAI occurring ratio between the historical OAI group and the population average was performed to understand the difference.

3.7 Research Question 4 Methodology

3.7.1 Introduction

This study tries to study the pattern of warning letter issuing rate change along with the increased inspection times.

3.7.2 Variables

This study tries to examine the response variation in warning letter issuing ratio at the increased inspection times (i.e., being inspected for 1, 2, 5 times, etc.)

3.7.3 Data Collection

Companies who received FDA inspections were obtained from FDA data dashboard. To control the lurking variables of different product type, this study only sampled from the drug establishments. The inspections data set were sorted by FEI number, replicate FEI number were removed to assure the sampling not biased. From the dataset, three thousand establishments were selected, these three thousand establishments were thereafter searching with FEI number against with the compliance data set sorted only with 'warning letter' for the action type (the compliance data set was also downloaded from FDA data dashboard). The establishment that yielded a positive result then followed by checking the total inspection times, and at which inspection the establishment received the warning letter. FDAzilla was used as the primary database for this study, for mainly, FDA inspection database does not specify the FEI number, the establishment is identified by the company name and together with the located city, however, this does not always distinguishable, and the database only support tracing back to year 2008, where is not sufficient for this study. FDAZilla is a platform that monitors FDA, claimed to have a most complete repository of FDA inspection data in existence, cited by major media like MSNBC, WSJ, and the Boston Globe, etc. (FDAzilla, n.d.). The inspection document MSNBC got and confirmed with FDAZilla was submitted for the FDA review; the authenticity was not denied by the agency (NBC News, 2011). Despite the agency's recent effort to update the inspections classification database to bring more transparency (FDA, 2018), the cross-check for the inspections with FDA inspection

database of the window 2008 to 2019 is not always successful, due to the limitations that the FDA database is not complete and not site specific.

3.7.4 Data Analysis

T-test of the warning letter issuing ratio along the increased number of inspection times is performed to understand whether there was change over the inspection times change.

3.8 Research Question 5 Methodology

This study aims to collect the variable factors that may contribute to a considerable product efficacy variation; literature review approach is adopted for this study.

3.9 Research Question 6 Methodology

3.9.1 Introduction

This study target on the relationship between the processing attributes that may contribute to different manufacturing difficulty or complexity, with the product recall associated with the manufacturing difficulty or complexity.

3.9.2 Variables

The explanatory variables include the four group processing attributes (dosage form: solid, solution, other forms; sterility requirement: sterile or not, release mechanism: immediate release, modified release; strength: low, medium, and high strength). The response variable of this study is whether there is product recalls associated with the processing difficulty or complexity.

3.9.3 Data Collection

The product was randomly sampled from the FDA orange book product index, all the active commercial dosage form for the sampled product under the selected products were collected from

drugs @ FDA. Information to collect included, dosage form (powder, solution, or others), sterility (sterile or not), release mechanism (immediate release, or modified release, etc.), and strength value. Three groups have been applied for the potency: low, medium, and high potency. The range for each group has been arbitrarily given <=5mg or mg/ml for low strength group, 5-20mg or mg/ml for medium strength group, and >20 mg or mg/ml for high strength group. Product recall data were thereafter confirmed with FDA enforcement report database searching with the part of the product names and confirmed with the matches. Each dosage form and strength were recorded separately for whether there is a corresponding product recall. Product recall in this study only referred to the recall pertinent to the product processing difficulty, for instance, product recalls due to dissolution failure, sub-potent, degradation impurity out of specification, sterility assurance failure, etc. Product recalls caused by noncompliance operations, labeling errors, mix-up, cross-contamination, etc., were not counted. Total 223 sets of products data were collected for the study.

3.9.4 Data Analysis

As the independent variables and dependent variables use categorical data, zero is given for negative choice, and one is given for positive choice. Logistic regression with SAS is used for the analysis.

3.10 Chapter Summary

Given the ubiquitous objection of the quality metrics program from the industry, to answer the calling for a quantitative and scientific evaluation for the company and product, our study approaches the goal with an alternative route by looking at publicly available data. We think three major pillars (employee qualification and engagement, micro, and macro regulation environment, system implementation and improving) work tightly together to enable the company's delivery of

a quality product. For the product quality, guided by input-process-output principle, we capture inherent, in process and in vivo risk for the product in the conceptual framework, as both the inherent and extrinsic risk all matters to the patients. Specific and detailed methodology for each hypothesis is further elaborated to consolidate our conceptual framework.

CHAPTER 4. ANALYSIS OF DATA

Aside from the literature review to identify the variable factors contribute to the product efficacy variations, the other research questions are analyzed quantitatively, correlations, or difference between two groups are sought with software SAS. Results analysis would be represented in two parts: company-centric study analysis and product-centric study analysis.

4.1 Company-centric Data Analysis

4.1.1 Employee Qualification & Engagement Pillar-Education

As depicted in our concept model, we expect employee qualification and engagement as one of the three major pillars (figure 3.1) plays a certain role in shaping the product quality by influencing the compliance behavior, wherein qualifications are typically empowered by education, training and experience as perceived by the regulators (International Conference on Harmonization Expert Working Group, 2000; US Food and Drug Administration, 2017). Education is a powerful instrument to enable a better society, have intricate direct and indirect effects, Mandela (2014) thought that 'education is the most powerful weapon which you can use to change the world'(p1), education is also perceived as 'a strong indicator of attitudes and wellbeing' (ESRC,2014, p1). Feinstein et al. (2006) suggested that 'substantial public significance of the potential role of education improving health' (p176). Professor Rindermann from Chemnitz University of Technology, author of the 'cognitive capitalism: Human capital and the wellbeing of nations,' stated that the high-quality education changes attitudes and behavior, strengthen thinking, and enable tackle of more complex tasks (Wai, 2018.). Blundell et al (1999), found that educated person was more likely to receive training, Botelho, A. et al. (2012), found the education and training have positive influence over the waste reduction compliance behavior, Potoski, M (2005)

observed more educated neighbor also influence the company's decision to join the ISO 14001. Acknowledging with the sophisticated networking of education, here we try to explore the association of the education (average years of schooling for over 24 years old adult for the estimation) with the compliance behavior.

The analysis suggests a strong correlation between education length or education index with the noncompliance rate (corr. coeff r = - 0.6; with p-value extreme small (<0.0001), both significant result), however, due to some data clustering, the normality of the model residual does not look good. To meet the regression model assumptions, both the dependent and independent variable have been transformed with logarithmic transformations (Benoit, 2011). After the transformation, the linear regression assumption has neem approximately met (Data distribution before and after transformation can be referred to appendix A), the significant analysis still shows significant results (p-value for both are smaller than 0.05, significant at 95% confidence level, table 4.1), the correlations suggested moderate negative relationship between the logged education length/education index with the logged noncompliance ratio (figure 4.1), which appears, the less educated country has higher noncompliance rate. Constrained by the data accessibility and complexity of a company major composition, the national education data may not estimate the pharmaceutical companies' education state well, considering the intricate networking effects of education in general (deepen learning, problem solvability, change attributes, compliance behavior in environment, training probability, etc.), it is still possible that general education together with its underlying intricate networking effects has a positive association on pharmaceutical regulatory compliance behavior as suggested by the study. Whether the effect is causality is beyond this study. If interested, the education distribution map of the globe based on 2017 length of schooling can be referred to Appendix B.

Table 4.1 *Education Length and Education Index Correlation with Noncompliance Ratio*

Correlation (p-value)	Education Length	Education Index
Noncompliance	-0.469 (0.0318**)	-0.469(0.0284**)

*Note:** 95% confidence level*

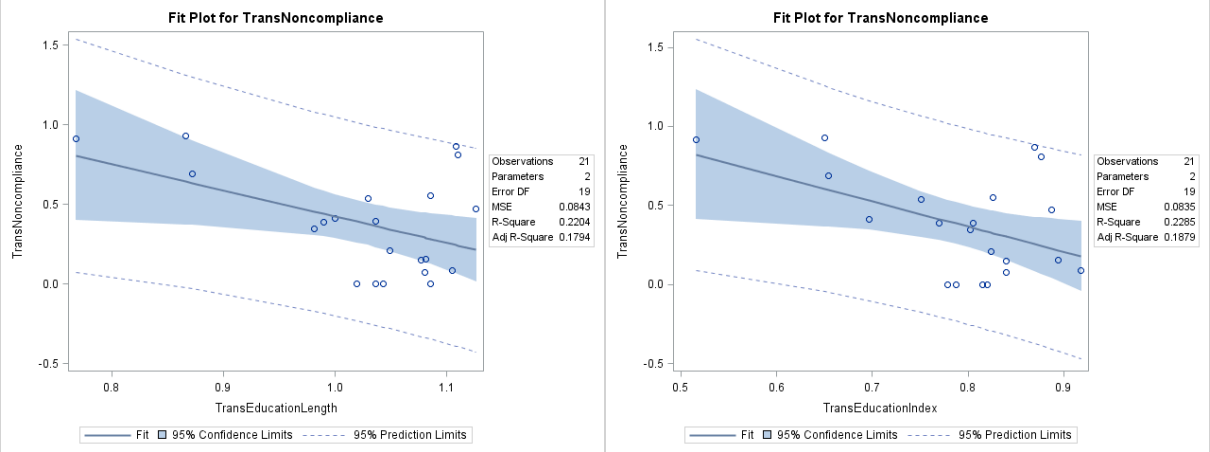


Figure 4.1 *Correlation Analysis for Education Length/Education Index with Noncompliance*

Constrained by the limitations (national education data is used to estimate the pharmaceutical field education data, which may differ from the national data) and assumptions (data from FDA data dashboard and EudraGMDP are complete and accurate)) discussed in chapter 1, the negative relationship of education length and education index relationship with the noncompliance behavior is served as reference for future exploration for pharmaceutical companies, for instance, employee education degree or employee continuous development for a specific company or a department, study their impact on the deviation or noncompliance performance or effect on training effectiveness or engagement, etc.

4.1.2 Macro Environment Pillar-Local Authority Intensity

Local authority regulating intensity and environment as a macro environment, also with less anticipated barriers of foreign inspections, may have some associations over the pharmaceutical

companies' compliance that involves the U.S. and EU businesses. We hypothesize that companies with non-stringent regulatory authorities are more likely to show worse compliance behavior.

The original dataset, unfortunately, was observed of three outliers, to better fit the assumptions, the noncompliance ratio also been log-transformed instead of removing the outliers unreasonably (The original dataset boxplot can be viewed in Appendix C). As indicated by the ANOVA analysis, sufficient evidence suggests a significant difference between the non-SRA authorities and SRA in terms of the log-transformed noncompliance ratio (figure 4.2). The SRA group has lower noncompliance ratio compared to the non-SRA. (P-value: <0.0001, less than 0.01, 99% confidence level).

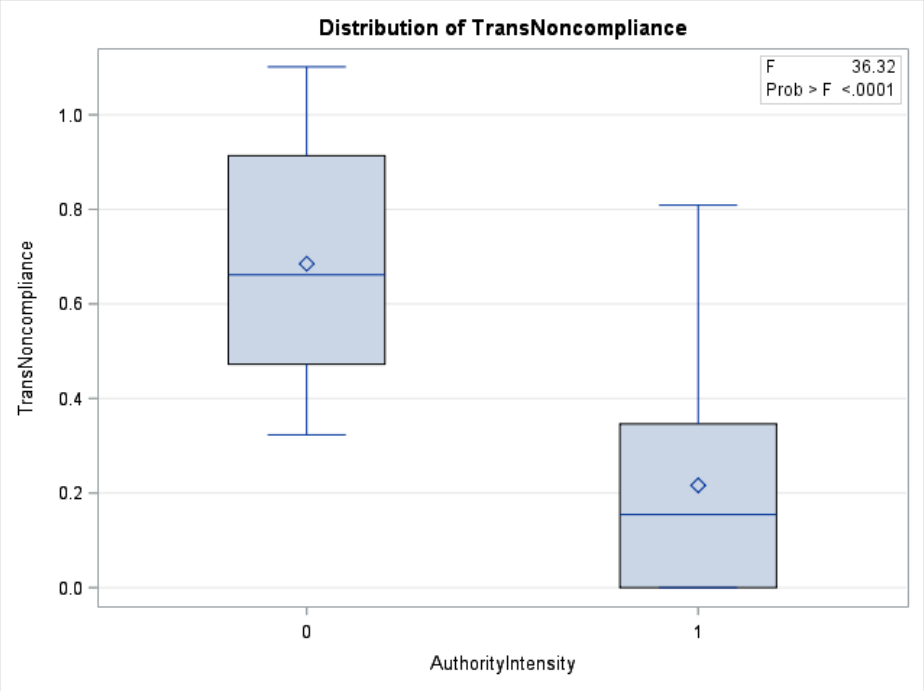


Figure 4.2 *Noncompliance Ratio Comparison between SRA and non-SRA Group*

Despite we have sufficient evidence to suggest that the noncompliance ratio of the companies has stringent local regulatory authorities significantly lower than the ones with non-stringent authorities, it should cautiously to infer the conclusion to individual company, due to the

limitations (the companies have business with the U.S. and EU may not be fully inspected) and assumption (the stringent definition is based on WHO definition, data from the FDA data dashboard and EudraGMDP are complete and accurate). This study serves as information for further future study, for instance, from a company view, this local authority intensity could be inferred to the mainstream quality system that a company follows. Companies that mainly compliant to rigorous international standards (i.e., ICH, etc.) may anticipate having more resistant and robust quality system than the other set of standards.

4.1.3 System Implementation and Improvement-Historical Inspection Result

Mediccinal products' quality is assured with a fit for purpose, and robust quality system, inspections of the system, and operations are a direct measurement of the quality assurance state. Ball (2015) found a positive correlation of VAI and OAI with company recalls in medical device sector, whereas NAI has presented negative correlation, the recall hazard increases by 52.2% for a company that receives an OAI result than an NAI result. Ball also observed the outcome of inspections may be influenced by the complacency, training, and experience of the investigator. One may also expect that corrective and improvement efforts would be put upon receiving a bad inspection result (e.g. OAI), thereafter the company compliance state is supposed to improve afterward, however, study of Macher identified that the company with bad or improving compliance reputation still has greater probability to receive a completely non-compliant result (Macher et al., 2011). Another study by Anand et al. (2012) claimed that "We determine that the tendency toward high process entropy is pervasive, even in an industry where product conformance is clearly critical and strict regulations exist. On average, in the absence of an external renewal, operational systems decay over time. This empirical result is especially surprising, given that it is likely that unobservable internal renewals occur with some regularity in this industry"

(Anand et al., 2012, p1701). In this study, we also try to confirm this finding with the public domain data and also check whether the inspection history may be a still good indicator for getting warning letter despite the acknowledged variables mentioned (inspection result representations of the compliance state, the state may change over time, etc.).

The result analysis suggests a significant effect of NAI% and OAI% ratio on future warning letter issuing, wherein the higher the NAI ratio is, the less probability drug manufacturer will receive a warning letter, the relationship is opposite for OAI ratio (table4.2, figure 4.3). However, insufficient evidence is in place to suggest an effect from VAI%. Further, in the case of OAI or two NAIs exist in the last three inspections, the warning letter probabilities are increased or decreased correspondingly (figure 4.4). This result should be very intuitive to the pharmaceutical field, as the inspection result of NAI very often suggests no objectionable conditions or practices during the inspections (FDA, 2019), which typically implies a favorable quality system and implementation, although this may not be necessarily true (as discussed earlier the investigator experience, training or complacency etc. may influence the inspection result). On the other hand, despite not every OAI result necessarily triggers a warning letter (13.6 % of establishments receive OAI (1163 out of 8552 establishments), 6.2% receives warning letter, refer to 4.1.4 section), or warning letter may be triggered by violations observed other than inspections (approximate 5.9%, see 4.1.4 section), while OAI results suggest regulatory and/or administrative actions are recommended (FDA, 2019), which means significant violations of the regulations are confirmed, correction need to be made. This confirms the hypothesis despite the known lurking variables (warning letter may not be triggered by inspections, inspection result may not represent the actual compliance state, the compliance state may change over time, etc.), the ratio of historical

inspection result classes (NAI and OAI ratio) still serve as a useful quality indicator for quality system.

Table 4.2 *Inspection Outcome Class Distribution and Inspection Pattern Correlation with Warning Letter*

correlation	Inspection Outcome Class Distribution			Last 3 inspection pattern	
p-value	NAI%	VAI%	OAI%	With OAI	2 NAIs
Warning	-0.49202	0.10681	0.69368	0.88044	-0.46950
letter	<0.0001**	0.2501	<0.0001**	<0.0001**	<0.0001**

*Note:** 95% confidence level*

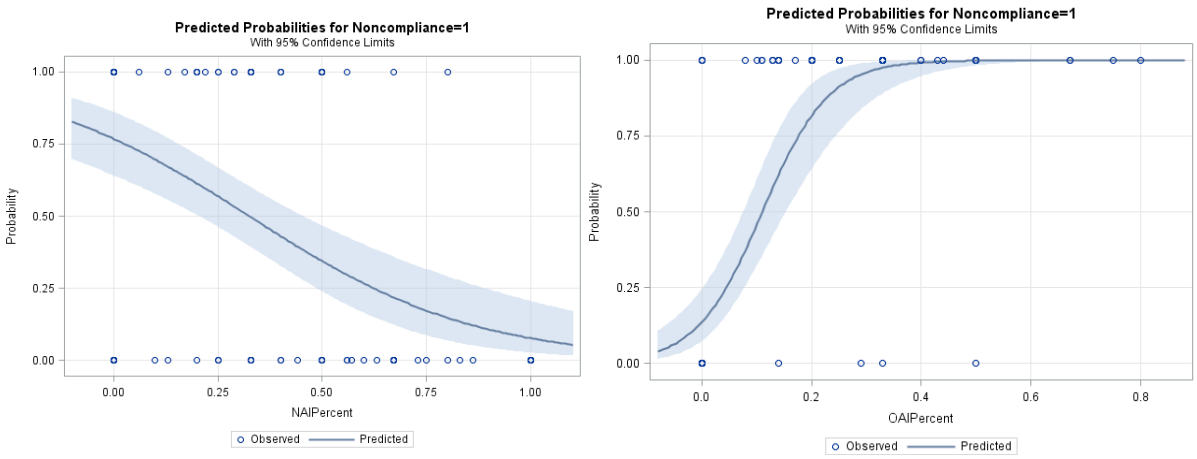


Figure 4.3 *Historical Inspection Outcome NAI, OAI Distribution Relation with Warning*

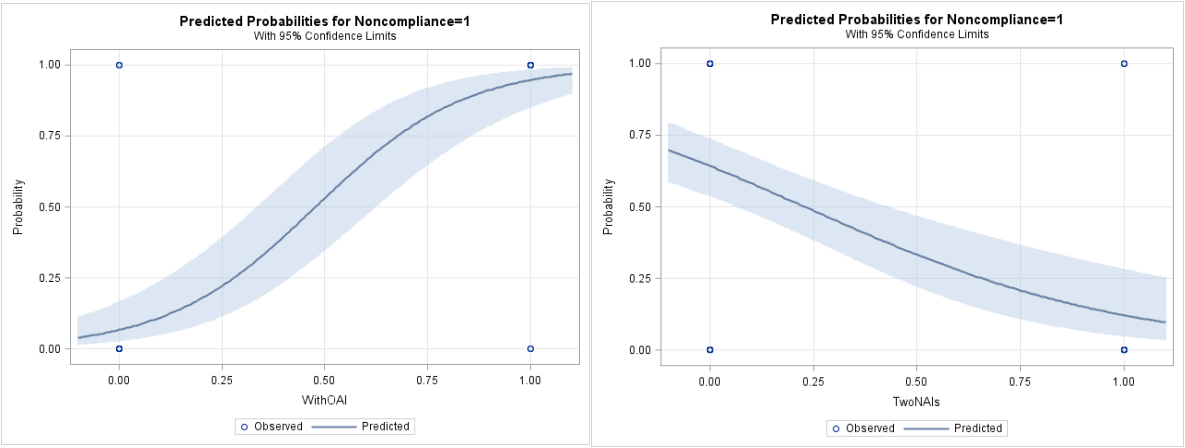


Figure 4.4 *Last 3 Inspections Patterns Relation with Warning*

For the historical OAI inspection result implications about future inspection result study, 6265 drug establishments have at least two inspections identified, among these establishments, 647 establishments are found to have OAI results (population ratio: approximate 14.1%). 1one hundred fifty-nine drug establishments are identified to have reoccurred OAI result followed historical OAI results (24.6%), which is significantly higher than the average population ratio (p-value: 7.26E-27, extremely small, very high confidence level). This finding aligns with Macher and Anand's observations, that is establishments with historical OAI result are more likely to receive another or more OAI result. Theoretically one may expect drug establishment would make an effort to correct and improve the compliance upon receiving an OAI result, the higher reoccurring OAI probability suggests there should be other factors hinder the company from getting better, maybe timing, financial and expertise resources limitation, etc. In this study, we further analyze the timing aspect, whether there may be a recovering phase for the establishments to reinstate the average compliance risk. The timing of the reoccurred OAIs pattern is analyzed in greater detail for this conjecture.

We observed that the timing of reoccurred OAIs followed OAI inspection result tend to cluster at the first four years (approximate 80.5%, figure 7). To control the possible bias by the

inspection frequency (one may expect that the number of companies inspected by multiple times is smaller in number than companies received only a couple of inspections), the absolute values are further normalized by taking into account the inspection frequency. The ten years-span are roughly taken as five times of inspections (2 years inspection interval is used), the absolute values are approximately normalized by the numbers that establishments received at least two, three, four and five times respectively. The ratios are thereafter adjusted by a factor that sums the five inspections ratio into the total 24.6%. Normalized reoccurring OAI data suggests that after two inspections (approximate 4 years), the probability of getting an OAI result (10.96%) drops back to the average population probability (10.3%), in other words, averagely it takes drug establishment approximate four years to recover from the OAI state.

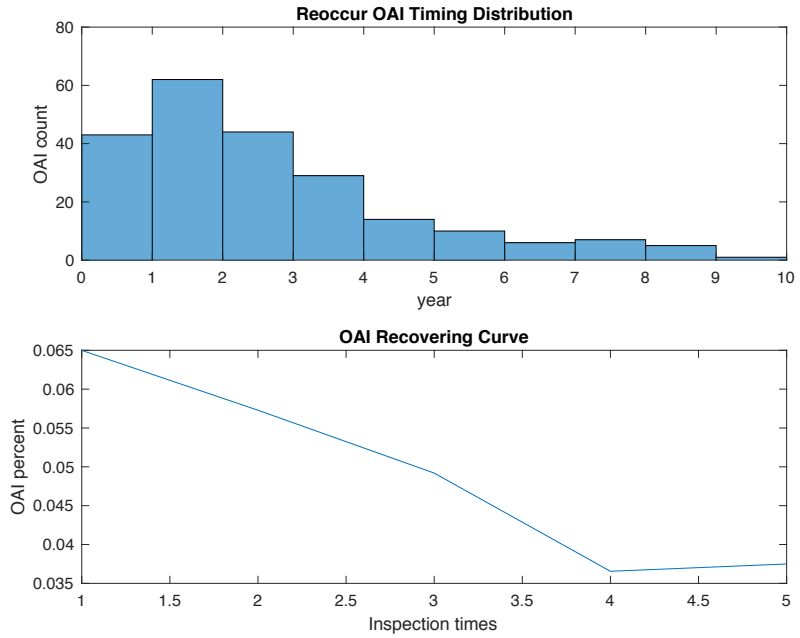


Figure 4.5 *Reoccur OAI Inspection Timing Distribution and Recovering*

Suspect hidden possible factors that delay or even hinder the companies to recover soon from the OAI state may be: 1) The company system (maybe human capital limitations, or financial

support, or weak system, etc.) is not sufficient to enable a good compliance status, 2) The company's ability to reinstate compliance state is limited once there is compliance state drifting 3) The companies' operations way too complex and bulky, which delay the recovering. For the 3rd suspected factors, the amount of the products produced at the company will be a good start, however, due to the data accessibility, the product numbers at a specific site are not able to be attained, as the orange book data published by FDA does not allow distinguishing from the company site or even a company. For the 1st factor, the historical inspection results are examined to understand the company compliance status (the same method for the historical inspection results are adopted), the companies find hard to restore compliance state are observed to have higher historical OAI ratio (0.533%) than the rest (0.40%) (p-value:0.0104), which suggests that the companies are long lingering around the dangerous zone (OAI state) for whatever reasons (i.e. Lack of competent human capitals, or short of financial support), it's hard for the companies to have a breakthrough improvement. For the 2nd ability to recover from an OAI with a drifting state, the companies' CAPA effectiveness are intended to be examined. Repeated 483 observations ratio are measured to understand the CAPA effectiveness, however, the 483 citations published by FDA are not complete, are therefore not feasible for the data analysis (FDA, n.d.). 483 observations from FDAZilla FDAdatabase are used for the exploring (unfortunately, despite FDAzilla is more complete than the FDA public citations databases, it is still not complete), higher recurring of the deficiencies (the total 483 observations number is collected by searching with the company FEI number, the repeated observations would be added up, and divided by the total number of 483 observations) were observed for the companies not recovering soon (t-test, p-value: 0.006539), however, it is strongly suggested to bear in mind that due to the incomplete of the inspection citations data, this observations only serves as inspiration for future rigorous study. This also

brings another point that in spite of FDA has made tremendous efforts to bring the transparency; there is still a need to step further, the public deserves the right to access the necessary data to make an informative decision other than entirely rely on FDA's regulatory oversight.

4.1.4 System Implementation and Improving-Warning Pattern Analysis

Regulations for pharmaceutical sectors has rooted a century ago (stemmed from the first Pure Food and Drug Act of 1906), it has continuously developed and involved with the advancement of technology, scientific knowledge or in the wake of series of tragedies (Elixir sulfanilamide disaster, 1937; sulfathiazole tragedy, 1941; chloramphenicol incident, 1952; Thalidomide tragedy, 1962 (Commissioner, n.d.);). To be an active part of the competition landscape, establishment need to understand the regulations well and execute effectively and continuously. A learning journey for the company to get acquainted and grow the experience of regulations is expected. We hypothesize the companies who never been inspected before might possess higher compliance risk compared to those who have routine inspections. Authority inspections, as one of the two major instruments (inspections, and market approval) that the FDA utilized to exert oversight (Yu et al., 2015), the direct measurement of the compliance state, is used to represent the compliance risk.

Among the 3000 randomly selected establishments, 187 of the establishments were identified to receive warning letters (about 6.2%); 11 of the 187 (5.9%) establishments' warning letter were confirmed not being triggered by inspections (e.g., product review, website review, etc.), therefore were excluded from the analysis. Eight establishments (4.5%) received two warning letters, in these cases, both warnings were counted separately. The number and percent of the warning letters mainly cluster at the first three inspections (about 70%, figure 4.6).

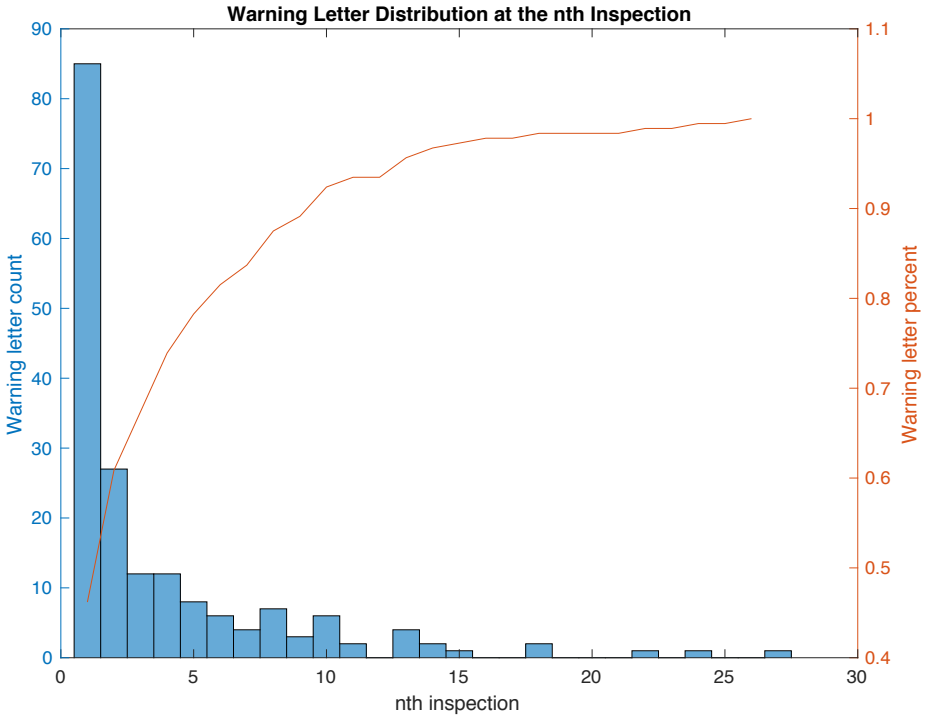


Figure 4.6 *Drug Establishment Get Warning Letter at the Nth Inspection*

The absolute value may be misleading, as the probability of drug establishments being inspected for the nth time (the inspection times ranges from one to forty-two in this study) may not be equal; therefore, the data is normalized with the inspection times. The normalized distribution is calculated with the following formula $Kth\% = \mathrm{X}/\sum_k^n \mathrm{y}$, where the X is the count of the warning letter at Kth inspection, y is the inspection counts of not less than K times. With the normalization, the distribution still suggests that there is a significant higher (figure 9) chance to receive warning letter at the first time than 2nd (p-value: 0.0005, very high confidence level >99.999%), and 3rd of inspections (p-value: 0.0009, very high confidence level >99.999%), compared to the 2nd to 4th inspections, the p-value is 0.000142, which suggests the first time inspections have a higher warning risk compared to those who received 2 to 4 times, this observation also aligns with the observation from the FDA most recent published report on pharmaceutical quality (FDA, 2019),

where the FDA observed that the inspection score for manufacturers never been inspected are lower (the score is 7.6 for sites received two or inspections, compared to score of 6.0 for those initially inspected). Difference between the 4^{th}, 5^{th} ,6^{th}, and 7^{th} are not observed (p-value: 0.911). A higher ratio of 8^{th},9^{th} and 10^{th} are then followed (p-value:0.005, confidence level >99.99%). The compliance pattern somehow resemble the Robert Feldman's CRIC cycle (Crisis-Response-Improvement-Complacency), a bad start, followed up stabilizing stage, then elevated risk (whether complacency involved is not known), however, it should be noted that due to the limited positive number at the greater inspection times, the statistic inference of the later elevated risk may not be valid (8 warnings, statistically, at least 10 should be ensured for the statistical inference.. Widely used average smoothing method (Pollard, 1979) is used to remove the noise and show the general trend (smoothed percent, the bottom of figure 4.7).

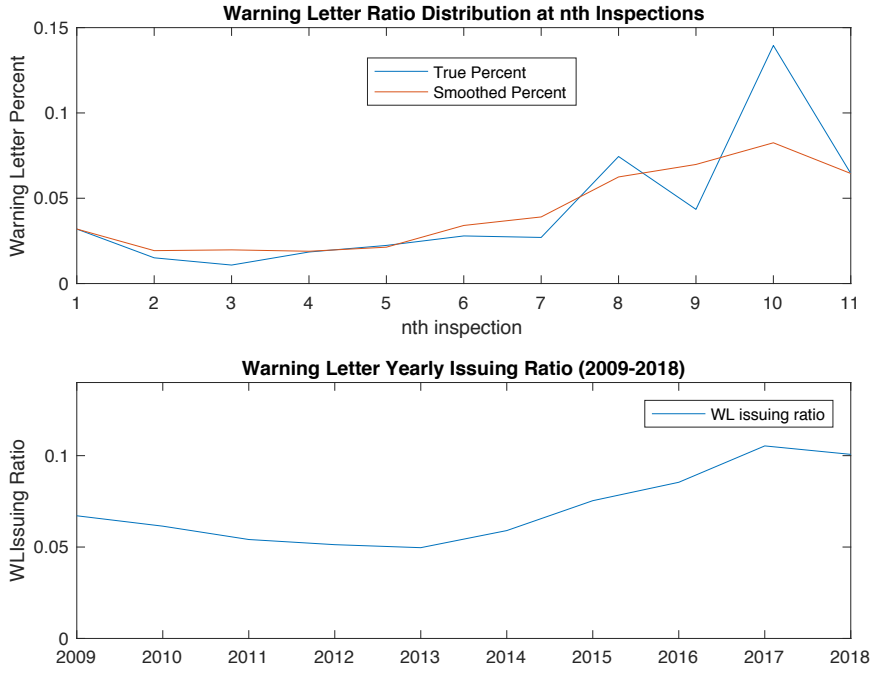


Figure 4.7 *Warning Risk Along with Increased Inspection Times*

To confirm the warning letter ratio distribution are not lurked by the yearly warning letter issuing rate, annual warning letter issuing ratio from 2009 to 2018 also populated by dividing the warning letter issues number by the total inspections number for the physical year, coincidently, correlation between the n^{th} inspection warning letter issuing ratio and yearly warning letter issuing ratio is observed, very strong correlation with smoothed percent (corr. R=0.899, p-value: 0.0004), strong correlation with true percent value (corr. R=0.67, p-value: 0.03). However, the distribution of the warning letters at the n^{th} (figure 4.8) does not show apparent progression in the year, which suggests the distribution ratio at the n^{th} inspections does not influence by the annual warning letter ratio.

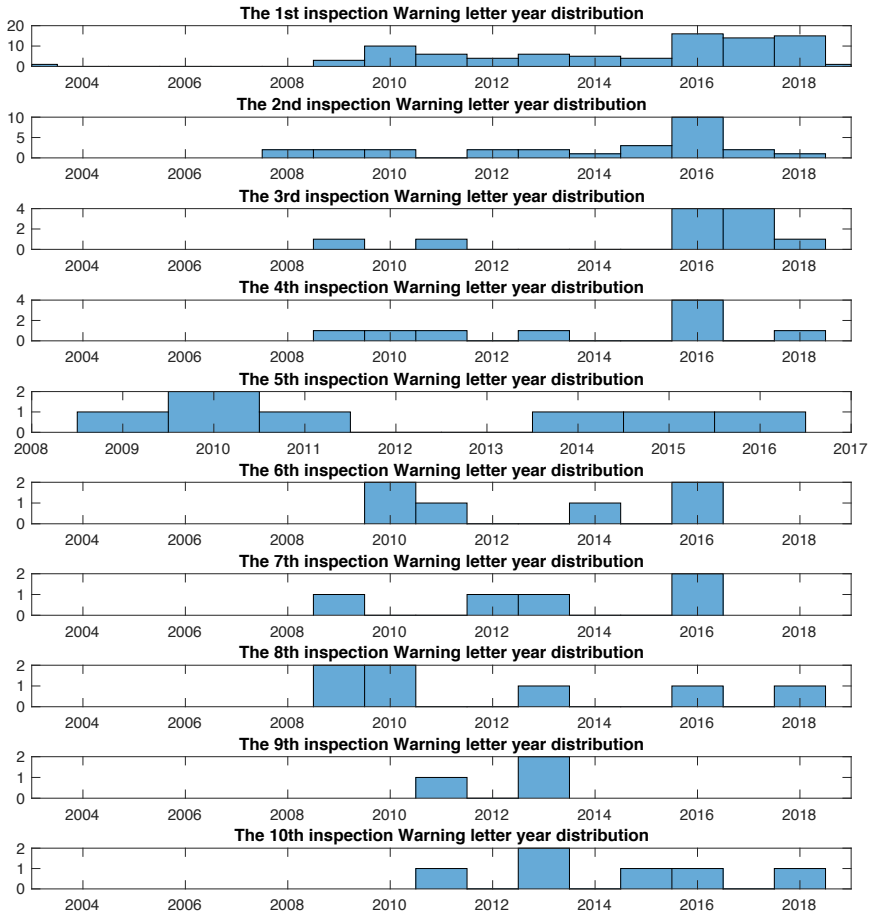


Figure 4.8 *Date Distribution of the Warning Letter Issued at the N^{th} Inspections*

The compliance journey represent four major stages: bad start, improvement, stable and complacency, resembles the CRIC cycle in the majority, as limited by the resources, whether this journey would start over another similar cycle upon emerging ubiquitous violations revealed (e.g., data integrity, etc.) or drastically modified regulation, is not understood. This compliance journey curve is suggested for further study reference since the primary data are not being able to verify at this moment and the periodicity of the cycle is not able to be checked.

4.1.5 Company Warning Letter Prediction Model

In this study, we populate the historical inspections of a drug manufacturer, collect the NAI, VAI and OAI counts between 2012 to 2018 years, if warning letter is confirmed, the inspection results will scope to the time before the warning letter issuing date. Shallow neural networking with gradient descent optimization method is used for the modelling. Total of 331 dataset are collected for the modeling, the data are therefore split into three groups, training-validation-testing, with the percent of 75%-15%-15%, after tuning of the hyperparameters, three layers are used (with nodes of 5:5:1), stages stepwise learning rate are tuned (learning rate: stage1: 0.0945, stage 2: 0.105, and stage 3: 0.118) , L2 norm regulations are also explored for better generation (lambda=0.115), decision boundary of 0.285, with the tuned hyperparameters, the modelling have pretty decent prediction of warning letters (figure 4.9), around 93% accuracy for both validation and testing dataset, over 70% precision and 90% recall (specificity). Still, historical inspection results are lagging indicators, a good model to predicate an OAI result may benefit the companies better in the sense of prevention, by saving the financial and time expense to correct the mistakes.

Table 4.3 *Drug Manufacturer Warning Letter Prediction Model Performance*

Data Set	Accuracy	Precision	Sensitivity	F1 Score
Training data	93.5065%	80.7018%	92.000%	0.859813
Validation data	94.0000%	72.7273%	100.00%	0.842105
Testing data	93.5065%	71.4286%	90.9091%	0.800000

4.2 Product-centric Data Analysis

4.2.1 Literature Review for Efficacy Variation Risk

To exert the intended drug therapeutic effect, active moiety needs to reach the target site of action. Bioavailability, calculated as the percent of drug or desired metabolite enters the systemic circulation, is often perceived at the practical level as the available drug proportion reaches the target site. The factors that are influential of bioavailability are generally grouped majorly into three categories: physiochemical factors, physiological factors, and formulation factors (Rosenbaum, 2016; Gibaldi,1991).

4.2.1.1 Physiochemical Factors

Manifold physiochemical factors that are inherent to the nature of the drugs have an effect on the drug absorption, and therefore affect drug bioavailability (Nada, 2018), includes, but not limited to: Solubility, permeability, Pka (precipitation effect, not readily be absorbed), Particle size and distribution (help to shape the solubility and dissolution), polymorphism forms (typically amorphous dissolves faster than crystals), hygroscopicity (affect particle size, polymorphs, stability, etc.)

To start the absorption process, drug needs to be dissolved first in body fluid to allow diffusion across the membrane and reach the target action site. Therefore, among the factors above-mentioned, solubility and permeability are perceived as the most influential physicochemical

factors to the extent and rate of absorption (Song, Zhang & Liu, 2004). Biopharmaceutical classification system (BCS) has increasingly been widely accepted for assessing the solubility and permeability of drug and adopted by the FDA in 1995 (Davis, 2005) to estimate drug absorption.

Drugs exhibiting poor water-soluble properties are more likely to have incomplete absorption as the residence time at the absorption site may not be sufficient, thus tends to have highly variable and as well as low bioavailability. On the other hand, a drug of BCS class 1 (highly soluble and highly permeable) prone to be invariant to pH and site, consequently, has higher bioavailability and more resistant to the alter in dissolution caused by other factors (table 4.4, 4.5).

Table 4.4 *BCS* Classification *Implications for Solid Oral Dosage Forms*

BCS Class	Solubility	Permeability	Absorption
I	High	High	Well absorbed
II	Low	High	Well absorbed Many displays variable absorption
III	High	Low	Variable
IV	Low	Low	Poorly absorbed

Note: reference from (Davis, 2005; Shodhganga,.n.d.; Khadka et al., 2014; Chakraborty, Bhattacharjee, Dutta, & Mukhopadhyay, 2016)

Table 4.5 *BCS* Classification *Implications for Extended Release Drug Forms*

BCS Class	Solubility	Permeability
Ia	High and site independent	High and site independent
Ib	High and site independent	Dependent on site and narrow therapeutic window
IIa	Low and site independent	High and site independent
IIb	Low and site independent	Depend on site and narrow therapeutic window
Va: acid	Variable	Variable
Vb:basic	Variable	Variable

Note: reference from (Amren, 2014)

4.2.1.2 Physiological factors

Administered drug is susceptible to physiological barriers more or less, the extent and complexity associated with the administration route. The physiological barriers for a particular administration route are combinations of various factors. Membrane physiology (Nada, 2018; Bauer, 2006), regional blood flow (Bauer, 2006), drug-protein and tissue-binding (Bauer, 2006), body fluid volume (Bauer, 2006), biotransformation (Nada, 2018), biological barriers, stress, disorders, age, sex, genetic phenotype (Nada, 2018; Bauer, 2006), etc., to name a few. These physiological factors play a particular role influencing the drug absorption, distribution, metabolism or elimination, and therefore impact the drug therapeutic effect.

- Absorption:

  Drug absorption can be markedly altered by a number of factors, physicochemical factors we discussed earlier (e.g. dissolution, permeability, particle size, polymorphism, etc.), and multiple physiological factors, includes, but not limited to, drug transport processes across the biological membrane, gastrointestinal physiology (gastric emptying rate, intestinal motility, drug stability in the GI tract, GI tract pH, blood flow, food effect, age, disorders, etc.) (Qiu, Chen, Zhang, Liu & Porter, 2009). Most cases, gastric emptying and gastro-intestinal motility often accompanied with the increased absorption of drug (Nimmo, 1976), food and diet (high fat, high protein, etc.) may play complicated effect on drug absorption by interference of the transporters, alter the blood flow and impact bioavailability (Gu et al., 2007).

  Majority of the drug across the membrane through the passive transport path, driven by the difference gradient in the active moiety concentration. No saturable or capacity variation associated with this path. On the other hands, active transport, which are carrier-mediated transport against the concentration gradient more likely susceptible to

factors that inference with the transporters, e.g., drug-drug interactions, drug-food effects, genetic variation introduced expression difference in influx and efflux transporters (Chen, Li, Brown, Cheatham, Castro, Leabman, Urban, Chen, Yee, Choi, Huang, Brett, Burchard, 2011; Ayrton & Morgan, 2001) . Passively reabsorption also occurs in many drugs in the distal renal tubules; this process bears similar influences as the gastrointestinal absorption (Qiu et al., 2009).

- Distributions

Once absorbed into the bloodstream, drugs are ready to distribute throughout the body and organs. Drug plasma proteins binding may reduce the net transfer by limiting freely circulated drugs, this process is generally reversible and rapidly process. Tissue binding may generate localized drug concentration based on affinity. Regional blood flow also has an effect of the drug distribution. Disease states is observed to influence the apparent volume of distribution, e.g., chronic liver disease may generate lower the plasma drug concentration because of the lower serum albumin concentrations (Bauer, 2006; Qiu et al., 2009).

- Metabolism

A Drug that susceptible to metabolism often subject to a highly variable biotransformation process, notably, the hepatic first-pass effect phenomenon also guts metabolism (Qiu et al., 2009) for the oral dosage form. Rectal also subject to varying degrees of the first-pass effect, for other administration routes, which circulates in the system may, therefore bypass the liver first-pass effect (Qiu et al., 2009). While liver and gut metabolisms are not the only site metabolism taking place. High variability of the metabolism process may be contributed by the number of factors, e.g., enzyme

induction or inhibition (Susa &Preuss, 2018) depot binding (Susa, et al.,2018), age (McLachlan & Pont, 2012; Blanchard & Keith,1986), sex (Blanchard et al.,1986), disease status (Bauer, 2006), environment, diet and nutritional status (McLachlan et al., 2012), genetic phenotype (may be accountable for 20 to 95 percent of patient variability) (Zanger & Schwab, 2013; Belle & Singh, 2008; Sim, Reisinger, Dahl, Aklillu, Christensen, Bertilsson & Ingelman,2006).

- Eliminations

Drug elimination happens simultaneously with the distribution, mainly through kidneys. Liver and lungs may also exert drug elimination, excretion via other paths other than urine and feces also observed for some compound, e.g. bile, exhalation, sweat, or milk, etc (Qiu et al., 2009; McLachlan et al., 2012). Kidney and liver functional impairment may be problematical to metabolize the compound and promptly remove the compound from the body (McLachlan et al., 2012). The bioavailability variable factors from physiological aspects are summarized in the table 4.6.

Table 4.6 *Physiological Factors Contribute to Bioavailability Variation*

Absorption	Distribution	Metabolism	Elimination
GI emptying rate, intestinal motility, GI tract pH, blood flow, food effect, age, disorders, etc. transport processes (genetic variation, drug-drug and drug-food interactions, Detc.	Tissue binding, regional blood flow, disease state, volume of distribution	Administration route, depot binding, age, sex, disease state, environment, diet and nutritional status, genetic phenotype (may be accountable for 20-95% patient variability)	Kidney and liver impairment

Reference: (Nada, 2018; Bauer, 2006; Nimmo, 1976; Gu et al., 2007; Chenet al., 2011; Ayrton et al., 2001; Qiu et al., 2009; Susa, et al.,2018; McLachlan et al., 2012; Blanchard et al.,1986; Zanger et al., 2013; Belle et al., 2008; Sim et al.,2006).

4.2.1.3 Formulation factors

Drug bioavailability may change considerably between various dosage form, ingredients selection, formula, release mechanisms, etc. (Bauer, 2006; Qiu et al., 2009). As the vehicle of the active moiety to exert the therapeutic effect, a drug needs to be administered and delivered to the site of action, thus how the drug is delivered is very vital to the pharmacological effect (Perrie & Rades, 2012).

- Dosage forms

Intravenously injected drug goes directly to the systemic circulation, there is no fraction loss due to the physiochemical (e.g., poor membrane penetration, etc.) or physiological factors (e.g. first pass effect, age, sex, disease, etc.), therefore can enable higher accuracy of the dose (Tsume, Mudie, Langguth , Amidon, G.E., & Amidon, G.L., 2014). While the dominant administration route today is still oral administered (estimated to be about 90 percent of the drug) (Qiu et al., 2009). Formulation changes can considerably alter the drug's bioavailability (Chakraborty, Bhattacharjee, Dutta, & Mukhopadhyay, 2016). The bioavailability between dosage forms generally follows the rule: Solutions > Emulsions > Suspensions > Capsules > Tablets > Coated Tablets > Enteric-coated Tablets > Sustained Release Products (Qiu et al., 2009), while the bioavailability order for the common oral dose drug follows this order: solution > suspension > capsule > tablet > coated tablet (Bauer, 2006);

Physiological factors may also compound the bioavailability together with the physicochemical factors, e.g., the gastric residence time may vary considerably inter and intra patients, for solid drugs restrained by the poorly dissolving or weak

penetrating, the reside time at the absorption site may not be insufficient, in this cases, oral bioavailability prone to be highly variable (Shodhganga, n.d.) (table 4.7).

Table 4.7 *Administration Route Impact of Bioavailability*

Route	Bioavailability	Variation Factors
Oral	Varies greatly (2 to 5 folds differences can occur, depend on the dosage form.) Most variable absorption pattern	Gastric emptying time Intestinal motility Food effect Intestinal metabolism and transport Hepatic metabolism
IV	Most reliable	Bypass most of the absorption barriers
Inhalation	Very rapid and complete, effective, predictable	Larger surface and minimal barrier for diffusion
Rectal	Incomplete and erratic Absorption very variable Highly variable	Variability stemmed from the suppository
Sublingual (buccal)	Most promising alternative route for enhancing the bioavailability	Not undergo liver first pass effect, goes to systemic circulation directly. Depends on the residence time, and buccal area.
Topical	Predictable response	Local absorption

Reference: (Bauer, 2006; Qiu et al., 2009; Perrie & Rades, 2012; Tsume et al., 2014; Qiu et al., 2009; Chakraborty et al., 2016; Shodhganga, n.d.)

- Release mechanisms

Another approach to differentiate drug delivery system other than dosage forms, is by drug release mechanism, immediate release (IR) and modified release (MR) or controlled release (CR). Different from immediately release after administration (IR), MR is designed to offer an enhanced drug therapeutically effect or better patient compliance. This enhancement may be achieved by control the exposure time of drug, alleviate the obstacles of physiological barriers, more precise targeting of action, etc. (Siepmann, Siegel, Ronald & Rathbone 2012).

Therefore, despite the advantages of controlled release (e.g. dose dumping, less flexibility inaccurate dose adjustment, poor in-vitro in-vivo correlation, increased potential for first pass clearance, patient variation, not permit prompt termination of therapy, etc.), modified release is perceived to have a superior performance than conventional IR dosage form, reduce the variability of drug performance, and enhance a better patient compliance (Miller, Krauss & Hamzeh, 2004; Shargel, Yu & Pong,1999).

4.2.1.4 Guided questions for assessing efficacy risk

Despite the fact that tremendous efforts have been made in multidisciplinary science, how drug exactly works remains unknown (Gottfredson, Najaka, & Kearley, 2003). Based on the above review, we formulated a series of questions to help in assessing the compound therapeutic risk.

- What is the administration route of the drug?
- What is the release mechanism of the drug?
- If it is administered other than IV, what is the BCS class? Is it a narrow therapeutic index drug?
- Is the compound a prodrug?

  Is the drug susceptible to metabolism?

  What is the extent of metabolism?

  If subject to metabolism, is the hepatic impairment, age (e.g., infant, elderly, etc.), pregnancy, drug &food effect, sex, races, etc. studied?
- What is the mainstream transport path for the compound?
- If the dominant transport is active transport, is there known genetic variation?

  Is the genotype required for the treatment?

Is the interference of drug, food, diet, age, race, etc. studied?

- What is the mainly excretion pathway?

  Is the renal or hepatic impairment studied if main via kidney and extensively metabolized?

4.2.2 Manufacturing Risk

Product recall process comprises three major stages, events met recall situation occurs, appropriate recall decision is made, and the recall event is conducted. For the stage 1, we hypothesize that the processing difficulty and complexity will have a positive effect on product recalls associated with processing, e.g., low potency, sterility requirement, modified release, or product forms other than powder, solutions (e.g., suspension, cream, gel, etc.) may have higher processing nonconformance chance. We understand that lurking variables exist that might aggravate or mitigate the nonconformance caused by the complexity (stage 1), for instance, sound and efficient knowledge management (Calnan, Lipa, Kane & Menezes, 2018), quality system effectiveness and robustness (FDA, 2018), or early detection, etc. Ideally, for stage 2, recall decision making should be very direct and straightforward, the recall decision should be made promptly once a recall events are met, the reality is there is no clear cutoff as a recall decision boundary, the criteria that' the product presents a risk of illness or injury or gross consumer deception' (CFR,21) provide some space for the recall decision, which George ball (2015) found may dependent on the situational factors (whether the defects are detectable or not, root cause identified or not, etc.) or dispositional factors (gender, cognitive reflection test score, etc.), we acknowledge there may be some or even similar confounding factors that impact drug recalls decisions. Ball also found the responsiveness timing to close a recall is also observed to be a predictor for the future recall (stage 3). Stage 3 is beyond the discussion of this study, so will not

be further studied here. In spite of the potential variables discussed, we hypotheses associations might still stand between the product recall possibility related to the processing variables with the processing variables.

Among the four groups processing variables, dosage form, sterility requirement and potency all identified to associate with the product recall pertinent to processing difficulty (table 4.8). Wherein, powder and high potency has strong negative relationship with the processing difficulty associated product recall, product of solid form, and with high potency has lower recall probability (figure 4.9). Other dosage forms (other than solid and solution), sterile, low potency are observed to have a strong positive relationship with the product recall probability, the product with these properties tend to have a higher likelihood of product recall that associated with the processing difficulty (figure 4.9). However, insufficient evidence in place to support there is an association between the release mechanism with the associated recalls, besides the confounding factors discussed earlier, this not significant effect in part might because the majority of the occasions, modified release accompanies with the non-sterile and solid product attributes, which may undermine the associations. The observed relationship between the processing variables and the probability to have process difficulty associated recall should be read cautiously, as of the built-in limitations of judgmental call for the product recalls, and the potential being influenced by lurking variables that alter the compliance state (process control, product knowledge, quality system), or variables in recall decisions making step (gender, CRT of the manager, etc.).

Table 4.8 *Processing Factors Significance Test Results*

Odds ratio (p-value)		Recall
	Powder	0.324 (0.0008**)
Dosage form	Solution	2.068 (0.0767)
	Others	3.264(0.0114**)
Sterility requirement	Sterile	3.378(0.0009**)
	Low potency	2.384(0.0056**)
Potency	Medium potency	0.861(0.6524)
	High potency	0.520(0.0282**)
Release mechanism	Immediate release	1.369 (0.3251)
	Modified release	1.108(0.7547)

*Note: **95% confidence level*

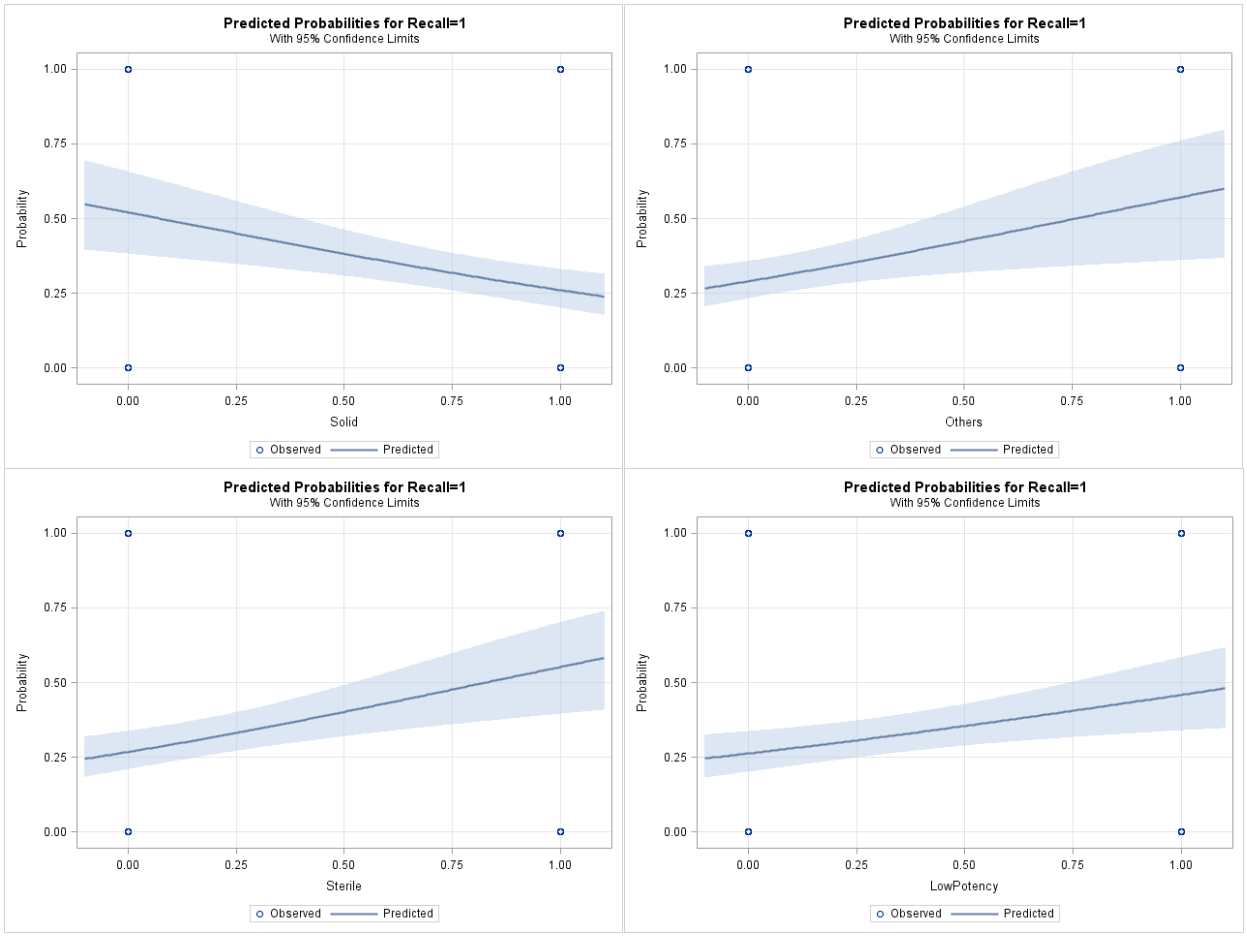
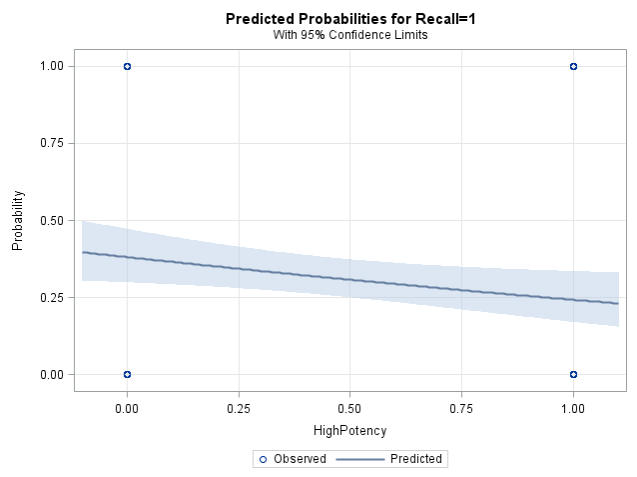


Figure 4.9 *Product Attributes Associations with the Pertinent Product Recall*

Figure 4.9 Continued



4.2.1 Product Attributes Associated Recall Prediction Model

Four categories of product attributes (dosage forms, release mechanism, dose strength, sterility, fixed combination) have been collected as the input features to feed the neural networking modeling (five layers are selected, 10;5;5;5;1), same as company warning letter model, gradient descent optimization was also used for training the model, 233 sets of data are used, split into three groups: training (75%), validation (15%), and testing (15%) (table 4.9), with the tuning of the hyperparameters, the stages stepwise learning rate are tuned with the value of 0.132 for stage 1, 0.190 for stage 2, 0.384 for stage 3, l2 norm regulations of lambda (0.189) are explored for better generate prediction, decision boundary of 0.30, with the tuning of the hyperparameters, the modeling have about 74% accuracy. The model prediction result may somehow confirm our discussion in the product attributes analysis (section 4.2.2) that there might be some lurking variables behind the scene, for instance, reasonable product control, defects detection, or robust quality system, or influence over decision of making recalls, etc. A refined design of the modelling input features, for instance, to incorporate the quality system indicators may work better for the

prediction. Further, the model only works for the product attributes associated recall; a general product recall model would benefit better for any interested parties.

Table 4.9 *Product Attributes Associated Recall Prediction Model Performance*

Data Set	Accuracy	Precision	Sensitivity	F1 score
Training Set	74.0260%	55.00%	71.7391%	0.622642
Validation Set	81.8182%	71.4286%	83.3333%	0.769231
Testing Set	74.0260%	58.2090%	76.4706%	0.661017

4.3 Chapter Summary

Employee, regulation system and system implementation are the major pillars that hold the company tightly together to enable the good quality product delivery. Education as the very powerful instruments to promote a better society has been observed with considerable intricate effects, with the associated effects we also observed a positive association of education with the regulatory compliance behavior, however this conclusion should be read with the context of this study limitations and assumptions that the national education data can have a rough estimation of the pharmaceutical companies education state, serve as further future study inspiration. Local authority regulation intensity also observed to have positive influence over the regulatory compliance behavior for those pharmaceutical companies have business with U.S. and EU. In spite of other compounding factors, historical inspection results still serve as a good indicator of the future warning letter reception, which are further demonstrated by our warning letter prediction model, where with the historical inspections results alone, the model is able to have about 93% accurate prediction. Companies with historical OAI result also are observed to more likely to receive one or more OAIs, and it approximately take the company about 4 years in general to drop back the average risk. There is also observed pattern of the warning letter issuing pattern along the

increasing in inspections times, which resembles Robert Feldman CRIC (crisis-response-improvement-complacency) cycle, wherein we saw crisis-improvement-stabilizing-complacency, however, whether this pattern is repeatable or will be started over upon significant medication or ubiquitous emerging violations (i.e. data integrity, etc.) are not known at this moment, this study serves as inspiration of future more rigorous study.

Product risk comprises of inherent, in processing and finally patient in vivo risk, understand the hidden risk behind the physiochemical (BCS class, etc.), physiological (genetic phenotype, gender, pregnancy, elderly, disease state, etc.), formation (dosage forms, release mechanisms, etc.) will give privilege to assess the product risk. Acknowledge the possible confounding variables of product recall, we do see possible associations between the product attributes correlations with the associated product recall, higher strength, solid product appears lower recall risk, oppositely, low strength, sterile and other dosage forms rather than solid and solution, appears a higher recall risk, however, this association may be undermined by good product control and quality system, or influence in recall decision, moreover, this factors not absolutely isolated from each other, therefore, in our product recall prediction model, we combine all the four studied product attributes plus the fixed combination, establish a product attributes associated recall prediction model, the model somehow also support the hidden variables that compromise the associations, with about 74% accuracy and sensitivity, wherein precision only with 58%. Refinement with the input features incorporating the quality system and generalize to broader product recall may benefit the interested parties better.

CHAPTER 5. SUMMARY, CONCLUSIONS, AND RECOMMENDATIONS

5.1 Executive Summary

Poke cloud and mist to see blue sky, we see two threading of quality risk on the medical products, product carried on risk and company system operation risk. For each thread, we build a conceptual framework to illustrate the overview of the compliance and risk profile, perform factor analysis and model part of the risk.

5.1.1 Company-centric Analysis and Modeling

It is easy to understand by the pharmaceutical field that estimates or precisely profile the company compliance risk is an extremely complex task , unwind the complexity, we perceive employee qualification and engagement, law and regulation environment, and system implementation and continuous improvement as the three major pillars to directly depict or indirectly imply about the overall compliance state and risk for a company, each pillar comprise two levels, the micro company level, and macro national environment level; These three major pillars intertwines and interacts at two layers to shape the company compliance state. The compliance risk is afterward incorporated into the medical products.

Education, training, and experience are powerful instruments for employee qualification. In this study, we examined the education association (not causality effect) with compliance behavior and observed a positive relationship between the log-transformed country warning ratio with the national education length and education index. We acknowledged that the study bears the limitation to have a precise estimation of the employee education data over pharmaceutical companies (complex human resources background), still, it is possible that the education and its intricate associated effects may have a positive relationship with the compliance behavior

(education may alter attitudes, training possibility, compliance behavior observed in waste reduction, higher awareness to promote the neighborhood facilities' voluntary regulation by the ISO 140001,etc.) .

Companies local authority regulation environment as the macro environment of the companies are expected to influence the company's compliance behavior; our study found a compliance behavior difference over the varied local regulation intensity; companies with stringent local regulation are observed to have relatively higher compliance behavior than the one with non-stringent local regulation.

FDA inspections as one of the two principal regulation oversight instruments have been long served as direct measurement of the establishments' compliance state. Despite there may be confounding factors (investigator' complacency, training, and experience, company's compliance state may change over time, etc.), we still see a strong correlation between the historical inspection results with the future warning. The higher ratio of NAI result, the lower risk of warning, on the opposite, the higher the OAI ratio is, the higher risk of warning, which should be very intuitive to the pharmaceutical field. We also confirmed the observations that companies with historical OAI result are more likely to receive one or more OAI result (Macher, et al and Anand et al), we further examined the recurring OAI pattern, and found it might roughly take establishments about 4 years to recover from the OAI state, for those did not recover as expected, we saw the establishments were long lingering around the dangerous zone (OAI result), for whatever reason (human expertise, financial support, complex operations, etc.), the establishments do not have a strong robust quality system, it's quite challenging to make a breakthrough improvement and correcting the state. We also tried to examine the difference of the correction action and prevention action effectiveness by looking at the repeated 483 observations ratio, higher repeating ratio was observed for those

establishments who did not recover as the general population; however, the conclusion should be read with the context of the study limitations that the primary source data were not be able to be verified at the moment.

Warning pattern along the increasing inspection times are observed to somehow resemble the Robert Feldman's CRIC circle (Crisis, Response, Improvement, Complacency, where the companies never been inspected have a higher warning risk (1^{st}), immediate improvements are observed with reception of more routine inspections (2^{nd}-3^{rd}), the compliance risk seems to stabilize for the 4^{th}-7^{th} inspection, an elevation risk for since 8^{th} inspection are observed; however, whether this elevation associated with the growth in compliancy as the CRIC or caused by noise due to the data statistical limitation is not well known. The beneath reasons for the warning risk along with the increasing inspection times are not examined, or whether the circle is repeated or started over because of significant prevalent violations, data integrity for instance, or massive modifications of the law or regulation, etc. are not understood due to the data limitations.

As a further verification of our finding that historical inspections result could serve as useful indicators of compliance state, we use historical inspection results solely build a warning letter prediction model with shallow neural network, with the tuned hypermeters, the prediction model has a decent performance, possess about 93% accuracy, over 70% precision, and more than 90% sensitivity.

5.1.2 Product-centric Framework and Modeling

Guided by the input-process-output model, we see inherent, in processing and patient in vivo risk factors when considering product quality. This inherent-in processing-in vivo concept shapes our conceptual framework into three principal components, patient efficacy risk, manufacturing risk, and quality operation and supply risk.

End user's risk matter considerably to us, as the nature of the special mission of medicinal products, it is a matter of life and death. The variable factors that may contribute to the drug products can be mainly categorized as physiochemical, physiological, and formation factors. We look at some of the exemplary factors, for instance, BCS for physiochemical factors, ADME variable factors for physiological factors, dosage administration, and release mechanism for the formation aspect. Based on the literature review, we developed a series of guiding questions to aid in the efficacy risk evaluation.

Product attributes (dose forms, strength, sterility, release mechanism) that could contribute to varying complexity and difficulty in production are hypothesized to have some influence over the risk of product recalls. Acknowledging that there might be considerable confounding variables that might comprise the associations (i.e., good process control, robust detection system, influential factors over product recall decision making, i.e., manager gender, CRT result, quality defects visibility, etc.), we still observed possible associations. Products with higher strength, and solid forms tend to have lower product associated recall risk, on the opposite, the sterility requirement, lower strength, and dosage forms other than solid, or solution are prone to have a higher recall risk. However, the conclusion should be read with the limitations (might be judgmental call of the product recalls) and taking into considerations of the confounding variable discussed.

With the dosage forms, sterility requirement, release mechanism, dose strength, and fixed-dose combination as the input factors, we build a product recall prediction model with neural network, the model seems to agree with our discussion very well, that there may be associations with the product attributes with the associated recall, yet, there also existed confounding variable factors. The considered product attributes alone does not explain very well of the product recall, with the tuned hyperparameters, the prediction model possesses an overall 74% accuracy and

sensitivity, wherein precision is only about 58%, we anticipate the aforementioned confounding factors and companies quality system risk might contribute to the variation in product recall that the model does not explain.

5.2 Recommendations

As our study is mainly focused on the macro level, the data for the study are observatory data obtained from public domain. Restrained by the data accessibility, the data may not be particular for the study intention, this limit a rigorous study to some extent. In this sense, this study mainly serves as an inspiration for more rigorous and in-depth research, for instance, education and training of employee in a department, and their association with the deviations, company most stringent quality system with the compliance behavior effect over the other quality systems, CAPA effectiveness with the OAI occurrence, etc.

For the modeling of the risk, earlier alerting prediction (i.e., OAI or drug shortages, etc.) other than too late (warning letter) may benefit the industry and the authority more. For the recall prediction, other input factors should be considered for a better prediction (i.e., companies quality system risk, brand or generic, decision making influence factors, etc.).

5.3 Chapter Summary

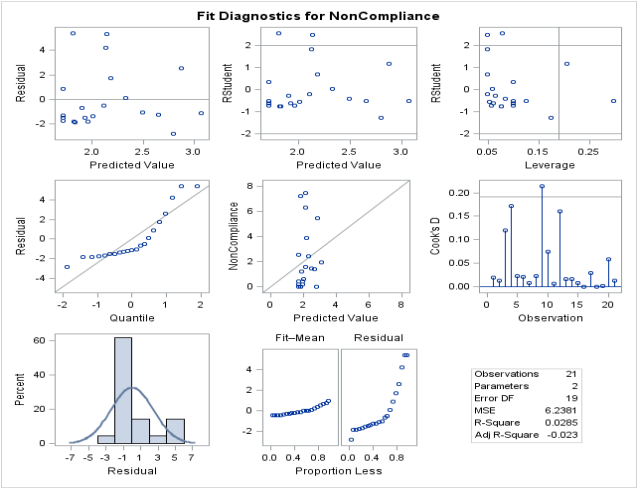
Our study mainly responds to the need of estimating and quantifying the medicinal product and company quality risk, meanwhile, to answer the unmet need of informing the quality of medicinal product to other interested parties than FDA, i.e. physicians, patients, group procurement organizations, etc. Given the ubiquitous oppositions aroused from the industries against FDA quality metrics program, we approach this need from public data aspect, and try to explore the possible impact factors. In this study, we first conceptualize the framework for both

company and product-centric study, further analyze the selected factors guided by the framework. Supported by the factor analysis results, we build a decent warning letter prediction model with historical inspection results, and product recall prediction model to capture the processing risk of the product.

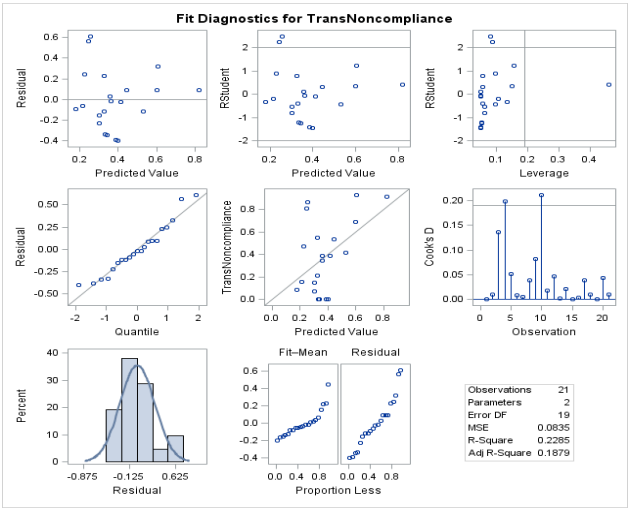
As the complexity of the risk profiling for a company or a product, we acknowledge our study only explore small proportion of the big picture, further thorough and in-depth research is needed to answer the need to quantify the company and medicinal product quality risk.

APPENDIX A. ASSUMPTION CHECK FOR DATA FOR EDUCATION STUDY

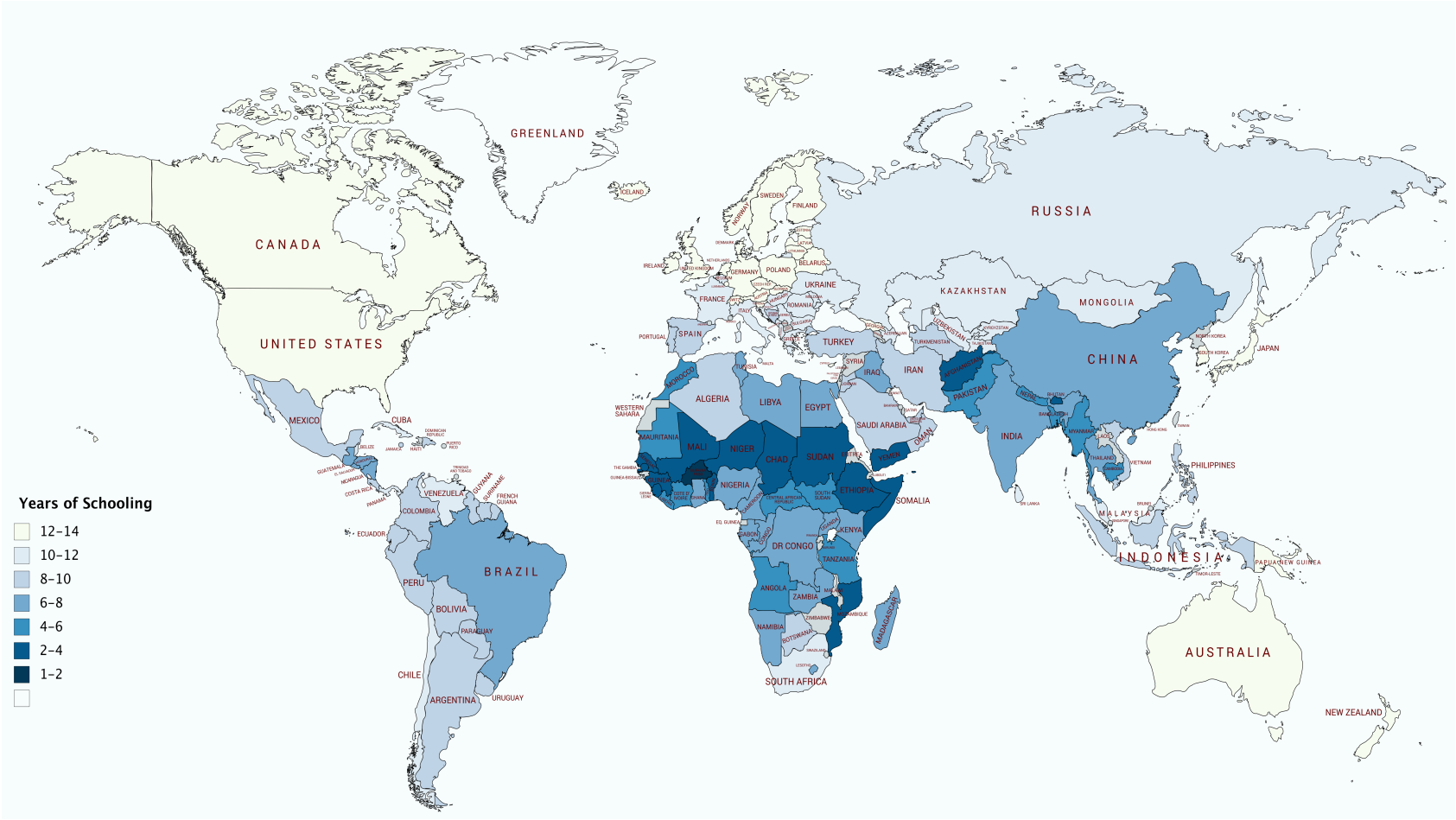
As suggested by the below figure, the untransformed data does not have reasonable normality; this violates the assumptions of the linear regression analysis; therefore log-transformation are applied for better distribution.



With log-transformation of both input and output data, the variance of the data and normality of the residues (showing as follows) all get a better fitting for the linear regression analysis as the following figure.



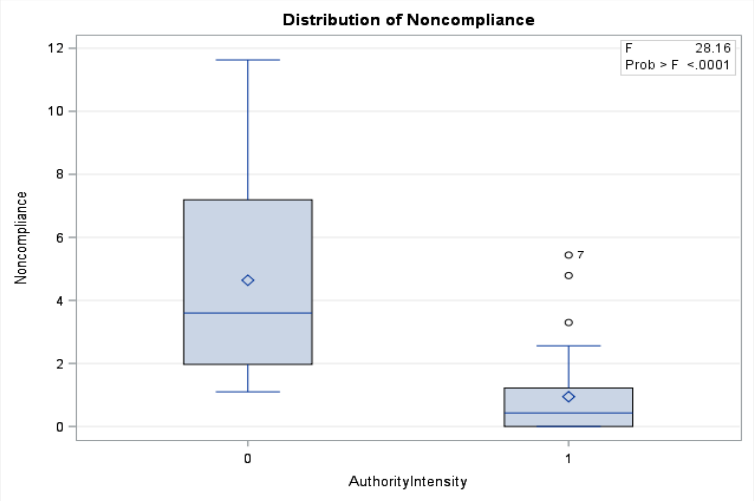
APPENDIX B. GLOBAL YEARS OF SCHOOLING MAP



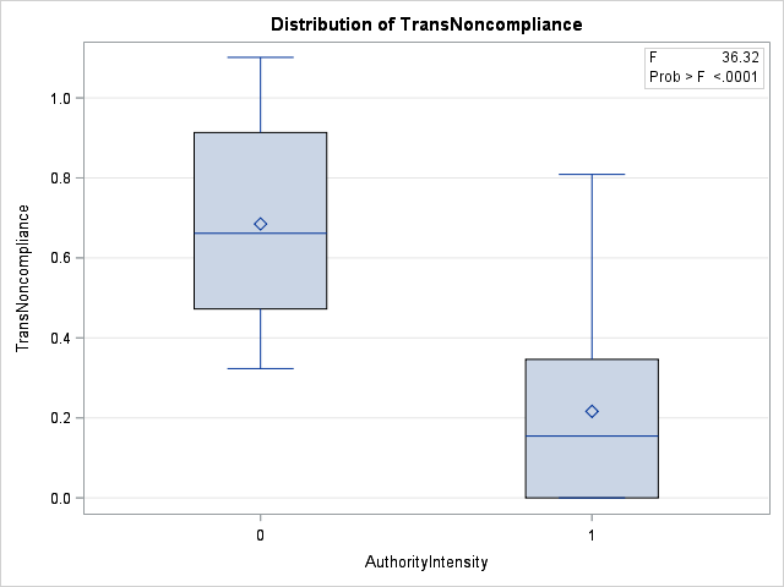
Note: The map is built based on the years of schooling of global 2017 from United Nations public data.

APPENDIX C. ASSUMPTION CHECK FOR LOCAL AUTHORITY INTENSITY STUDY

As the figure suggests, there are three outliers for the group SRA, as the underlying reason for the outlier cannot be determined, it is not appropriate to remove these outliers, to fit the analysis assumptions better, noncompliance data has been log transformed.



With the log-transformation as described in the study, there are no longer outliers as following figure displayed.



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