RISK ASSESSMENT OF GMP INSPECTION OF OVERSEAS PHARMACEUTICAL MANUFACTURERS BASED ON PIC/S DESKTOP INSPECTION

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A Thesis Submitted in Partial Fulfillment of the Requirements
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การประเมินความเสี่ยงของการตรวจประเมิน จีเอ็มพี สถานที่ผลิตยาในต่างประเทศโดยอาศัยการตรวจสอบเฉพาะเอกสารตามแนวทางพีไอซี/เอส

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วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาเภสัชศาสตรมหาบัณฑิต
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Thesis Title	RISK ASSESSMENT OF GMP INSPECTION OF OVERSEAS PHARMACEUTICAL MANUFACTURERS BASED ON PIC/S DESKTOP INSPECTION
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วรานนท์ ชีวาจร : การประเมินความเสี่ยงของการตรวจประเมิน จีเอ็มพี สถานที่ผลิตยาในต่างประเทศโดยอาศัยการตรวจสอบเฉพาะเอกสารตามแนวทางพีไอซี/เอส. (RISK ASSESSMENT OF GMP INSPECTION OF OVERSEAS PHARMACEUTICAL MANUFACTURERS BASED ON PIC/S DESKTOP INSPECTION) อ.ที่ปรึกษาหลัก : อ. ภญ. ดร.วฤณ ฐิตาภิวัฒนกุล, อ.ที่ปรึกษาร่วม : ผศ. ภญ. ดร.นฤพร สุตัณฑวิบูลย์

การตรวจประเมิน จีเอ็มพี สำหรับสถานที่ผลิตยาในต่างประเทศ ใช้ระบบการตรวจประเมินจากเอกสารที่กำหนด โดยสำนักงานคณะกรรมการอาหารและยา (อย.) ซึ่งทำการประเมินมาตรฐานวิธีการผลิตยาจากเอกสารเป็นหลัก โดยไม่ได้ตรวจประเมิน ณ สถานที่ผลิตยาเหมือนการตรวจสถานที่ผลิตยาในประเทศ ผลการตรวจประเมินจึงอาจเป็นข้อสงสัยในคุณภาพและความน่าเชื่อถือ นอกจากนี้ยังไม่มีการศึกษาการประเมินความเสี่ยงของระบบการตรวจประเมินนี้ในประเทศไทย รวมถึงมีงานวิจัยที่เกี่ยวข้องกับเรื่องดังกล่าวอย่างจำกัด งานวิจัยนี้มีการนำเอาหลักการการบริหารจัดการความเสี่ยงตามแนวทางขององค์กร The International Council for Harmonization Q9 (ICH Q9) โดยใช้เครื่องมือ Failure Mode and Effects Analysis (FMEA) สำหรับศึกษาการประเมินความเสี่ยงและหาแนวทางในการควบคุมความเสี่ยงของระบบการตรวจประเมินด้วยเอกสารของประเทศไทย การดำเนินการศึกษาประกอบด้วย 5 ขั้นตอน คือ การจัดตั้งคณะทำงานประเมินความเสี่ยงและการวิเคราะห์ข้อมูลที่เกี่ยวข้องกับการตรวจประเมิน จีเอ็มพี และข้อมูลปัญหาคุณภาพยาตั้งแต่ปี พ.ศ. 2559-2561 การระบุความเสี่ยงด้วยหลักการวิเคราะห์ช่องว่างของกฎหมายและขั้นตอนการปฏิบัติงาน สำหรับการวิเคราะห์ช่องว่างของกฎหมายมีการศึกษาเปรียบเทียบระบบของประเทศไทยกับต่างประเทศคือ ประเทศสิงคโปร์ มาเลเซีย ออสเตรเลีย องค์การอนามัยโลกและองค์กร Pharmaceutical Inspection Co-operation Scheme (PIC/S) ถัดมาเป็นการวิเคราะห์ความเสี่ยงและการประเมินความเสี่ยงโดยใช้การระดมสมองจากคณะทำงานประเมินความเสี่ยงร่วมกับการใช้เครื่องมือ FMEA และ Risk priority number (RPN) และสุดท้ายเป็นการลดความเสี่ยงโดยเสนอแนวทางในการลดความเสี่ยงสำหรับความเสี่ยงทุกข้อ การตรวจสอบวิธีการลดความเสี่ยงโดยการนำมาปฏิบัติจริงและการประเมินความเสี่ยงซ้ำ ผลการศึกษาพบว่าความเสี่ยงที่ส่งผลกระทบกับคุณภาพและความน่าเชื่อถือของระบบการตรวจประเมินด้วยเอกสารที่มีคะแนน RPN สูงที่สุดคือ การตรวจประเมินมาตรฐานวิธีการผลิตยาจากเอกสารสำหรับสถานที่ผลิตยาประเภท Non-PIC/S หรือ Non-WHO prequalification (RPN = 100) และการไม่มีข้อกำหนดในการประเมินจุดสำคัญของเอกสารแต่ละประเภทในขั้นตอนการตรวจประเมิน (RPN = 80) ซึ่งจัดเป็นความเสี่ยงสูงโดยเป็นความเสี่ยงที่มาจากการวิเคราะห์ช่องว่างของกฎหมายและการวิเคราะห์ขั้นตอนการปฏิบัติงานตามลำดับ เนื่องจากสถานที่ดังกล่าวมีมาตรฐานจีเอ็มพีที่แตกต่างกันในแต่ละประเทศ รวมทั้งถูกตรวจประเมินด้วยหน่วยงานกำกับดูแลด้านยาที่แตกต่างหลายระดับ ในขณะเดียวกันการไม่กำหนดจุดสำคัญในการประเมินเอกสารอาจทำให้การตรวจประเมินไม่ครอบคลุมทุกประเด็นสำคัญและมีผลการตรวจประเมินที่แตกต่างกันได้ แต่อย่างไรก็ตาม หลังจากการปรับปรุงมาตรฐานวิธีการปฏิบัติงานในการตรวจประเมิน สามารถทำให้ระบบการตรวจประเมินมีคุณภาพมากขึ้นและคะแนน RPN ลดลงมาอยู่ในระดับที่ยอมรับได้ ผลการศึกษานี้สามารถทำให้ อย. จัดการและลดความเสี่ยงลงได้เพื่อปรับปรุงระบบการตรวจประเมินสถานที่ผลิตยาในต่างประเทศของประเทศไทยให้มีคุณภาพที่ดียิ่งขึ้นและมีการพัฒนาอย่างต่อเนื่องต่อไป

สาขาวิชา	เภสัชอุตสาหกรรม	ลายมือชื่อนิสิต .....
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KEYWORD: Desktop inspection / GMP clearance / Overseas pharmaceutical manufacturers / The Pharmaceutical Inspection Co-operation Scheme (PIC/S) / Risk assessment / ICH Q9

Waranon Cheewajorn : RISK ASSESSMENT OF GMP INSPECTION OF OVERSEAS PHARMACEUTICAL MANUFACTURERS BASED ON PIC/S DESKTOP INSPECTION. Advisor: Varin Titapiwatanakun, Ph.D. Co-advisor: Asst. Prof. NARUEPORN SUTANTHAVIBUL, Ph.D.

Good manufacturing practice (GMP) inspection of overseas manufacturers is regulated under desktop inspection by Thailand Food and Drug Administration (Thai FDA). The desktop inspection system is verified mainly by document without on-site inspection like for local manufacturers. The inspection results may thus cause certain gaps in terms of quality and reliability. In addition, none has reported the risk assessment of desktop inspection system in Thailand and the limited research articles investigated these gaps. This work utilized the quality risk management (QRM) of International Council for Harmonization Q9 (ICH Q9) guideline with Failure Mode and Effects Analysis (FMEA) tool to study risk assessment and risk control of GMP desktop inspection system of overseas pharmaceutical manufacturers in Thailand. The study design consisted of 5 steps. First, pre-assessment step was to set up a risk assessment team and data analysis of desktop inspection and drug quality defect situation over three years in 2016 – 2018. Next, risk identification step was performed by analysis of regulation gap and routine workflow. The regulation gap was analyzed by comparing Thai regulations against five globally-selected countries/organizations, namely; Singapore, Malaysia, Australia, World Health Organization (WHO) and The Pharmaceutical Inspection Co-operation Scheme (PIC/S). Followed by risk analysis and risk evaluation step, brainstorming based on team discussion, along with using FMEA tool and risk priority number (RPN) were conducted. Finally, risk reduction step described all the risk mitigation approaches, verified by implementation and re-assessment. The results showed that the most potential negative effects on the quality and reliability of the desktop inspection system with highest RPN values were desktop inspection pathway for non-PIC/S or non-WHO prequalification certified manufacturers (RPN = 100) and lack of stepwise approach in document review (RPN = 80) that were analyzed as the high-risk level based on the regulation gap and workflow analysis, respectively. Such overseas manufacturers tended to have various GMP standards based on their own quality system criteria and be inspected by different levels of the authorized inspectorate. Meanwhiles, lack of this stepwise can lead to missing critical points and difference in inspection results. Nevertheless, after implementation, stepwise procedures justified the quality of inspection results and reduced RPN value and risk level to acceptable level. This work can be very useful for the Thai FDA to manage and minimize all potential risks for continual quality improvement of the desktop inspection system for overseas pharmaceutical manufacturers in Thailand.

Field of Study:	Industrial Pharmacy	Student's Signature .....
Academic Year:	2019	Advisor's Signature .....
		Co-advisor's Signature .....

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CHAPTER I

INTRODUCTION

1.1 Background and rationale

Drug product or medicinal product is one of the most important components for human living. It is widely accepted that a number of patients recover from disease by the good quality of drug product. Nevertheless, if the product has poor quality, it will be strongly harmful to patients. Consequently, the medicinal product needs to be registered and regulated by drug regulatory authority. In Thailand, The Thai Food and Drug Administration (Thai FDA) acts as the national regulatory authority under the Ministry of Public Health.

Drug registration system of imported products, regulated by the Thai FDA consists of three main steps. Firstly, companies/licensees submit an application for importing medicine product to supply in Thailand then an import license will be granted to the company after assessment by the Thai FDA. Secondly, licensees submit an application for good manufacturing practice (GMP) inspection of overseas pharmaceutical manufacturers which is evaluated by GMP inspector. The approval of GMP inspection will be granted to licensee if such manufacture complies with GMP standard. Finally, licensees submit their drug dossiers according to the ASEAN common technical dossier (ACTD) for registration processes. After approval, the marketing authorization will be granted to the licensee and thus imported product can be distributed in Thailand (1-3).

GMP inspection system of an overseas pharmaceutical manufacturer is regulated under the desktop inspection system according to the Pharmaceutical Inspection Co-operation Scheme (PIC/S) that is verified by document-based only. The system is conducted by GMP Inspectorate Unit of Post Marketing Control Division under the Bureau of Drug Control, Thai FDA. Regulation of the desktop inspection has been enforced on all imported pharmaceutical products for supply in Thailand since October 1, 2012 (4). Thai FDA use the desktop inspection system for overseas manufacturers because of many limitations to conduct an overseas on-site inspection. For examples, the number of overseas manufacturers tend to increase

due to economic growth and advance technology of supply chain and transportation system, whereas the inspection resource, especially number of inspectors, is another concern (5). Meanwhiles the risk of danger may occur during on-site inspection such as travel safety, health problem, security of each country. Lastly, redundant inspections from their own local regulatory authority and Thai regulatory authority may occur, further consideration should be taken (6).

A list of required documents for inspection (such as GMP certificate, GMP inspection report, corrective action and preventive action (CAPA) report, site master file or photos of buildings, production and quality control area, machine/ equipment) could reflect the GMP compliance status of manufacturers (3). However, the inspection results may cause certain gaps in terms of quality and reliability. It is questionable that document verification is adequate and can replace an on-site inspection. In addition, none has reported the risk assessment of desktop inspection system while risk assessment concept has been reported in pharmaceutical quality guidelines.

According to The International Council for Harmonization (ICH), it describes the approach to manage pharmaceutical quality systems as quality risk management (QRM) Q9 guideline and related tools (7). The QRM element categorizes into three steps; risk assessment, risk control and risk review that are used to assess the potential risks affecting the quality of processes or products. This risk management approach widely applies to routine work, not only in the pharmaceutical industry but also in drug regulatory department.

The desktop inspection system in Thailand is a complicated system and has many steps of inspection. The inspection results may thus cause certain gaps in terms of quality and reliability. Consequently, QRM principle should be applied to assess the risks that potentially have negative effects on the quality and reliability of the desktop inspection results, leading to continual quality improvement of the desktop inspection system for overseas pharmaceutical manufacturers in Thailand.

1.2 Objectives of study

1) To study risk assessment of GMP inspection of overseas pharmaceutical manufacturers based on desktop inspection system as required in Thailand according to quality risk management (QRM) in ICH Q9 guideline.

2) To evaluate potential failures of each risk, risk level and risk reduction measures.

1.3 Expected benefits

1) Risks that affect the quality and reliability of desktop inspection results, risk levels and risk reduction approaches can be understood.

2) The Thai FDA was informed about risk reduction measures which should be revised in inspection regulation to improve reliability of desktop inspection system.

3) Overseas regulatory authorities, local and overseas pharmaceutical manufacturers and licensees can understand and access to information of desktop inspection system for overseas pharmaceutical manufacturers as required in Thailand.

CHAPTER II

LITERATURE REVIEW

The literature review of this study was conducted to collect the related information for data analysis that mentioned and used in the research. Several sources were examined for literature review e.g. Thailand and international's law and regulation, Thai FDA database, guideline from official website, textbook, journals, standard procedure, official news, etcetera. The study review was separated into five parts as follows.

2.1 GMP standard in Thailand

GMP is a system to guarantee which the products are constantly manufactured and controlled in accordance with quality standards. The design system of the pharmaceutical manufacturing process should minimize the involved risks that unable to eliminate throughout quality testing of the finished product (8). Manufacturing activity is an important and that necessarily requires a qualified person to operation because that process directly impacts quality of products. Consequently, Thai FDA has adopted the principle of GMP following the World Health Organization (WHO) guideline to implement all of the domestic manufacturers since 1978 (9). The GMP certificate was issued by Thai FDA for such manufacturer that complied with the GMP standard as a voluntary implementation mode (9).

Until 2003, the GMP standard was enforced as a national legislation to all domestic manufacturer (10, 11). This regulation was described the basic GMP principle into five chapters; the premises of production area, machine and equipment, the production process of a general non-sterile product, sterile product and active pharmaceutical ingredient (API). In 2011, Thai FDA had adopted an internationally recognized standard as the PIC/S GMP for improvement and enhancement of Thailand's pharmaceutical industry (9, 12). Because these were arrangement to apply a member of ASEAN Listed Inspection Service and PIC/S (13, 14) and that was enhanced GMP inspection system to comply with the global standard (15).

After Thai FDA became a 49th PIC/S member in August 2016, that was updated GMP regulation correlated to lasted version of PIC/S GMP guidance (16). Currently, GMP regulation using PIC/S guideline version 2015 (17) and scope cover another product, not only modern medicine but also traditional medicine and API.

Together these studies provide history and development of GMP standard in Thailand. This is beginning with non GMP requirement, voluntary implementation and law enforcement following an internationally recognized standard as PIC/S GMP.

2.2 GMP inspection system in Thailand

Inspection system was adopted PIC/S inspection procedure due to the accession to PIC/S member of Thai FDA (18) and that applied WHO inspection process as well (19). The reviews were separated into six sections as follows.

2.2.1 Type of inspection

1) Routine inspection: This is a full inspection of all components on GMP standard for evaluated of GMP compliance status. For example, when the manufacturer is initial or newly established, site change or renew inspection following the annual plan.

2) Follow-up inspection: This is a follow-up system that made to monitor the implementation of corrective action and preventive action plan from the previous inspection. An inspection will perform at a manufacturing site, for example, to follow up HVAC system installation, renovation of the production area.

3) Concise inspection: The selected of GMP requirements will adopt for concise inspection. The selective area of the manufacturing site shall conduct for concise inspection as well. For example, in case of an additional the new production building.

4) Special inspection: Special inspection or surprise visit may be necessary to undertake point checks following the quality defected products as complaints or recalls. It will immediately be taken without notification to the manufacturer and that focus on the defected issued or specific area for investigation.

2.2.2 Inspection process

GMP inspection processes is importance step that directly impact to the quality of inspection results (20). Overview of inspection processes is shown in figure 1.

Figure 1 Overview of inspection processes

1) Pre-inspection

Pre-inspection process were grouped into three activities which prepared at Thai FDA office. The beginning activity was preparation of annual inspection plan which considered frequency of inspection. Three factors used to define the frequency were; 1) complexity of manufacturing site (e.g. non-sterile or sterile site), 2) criticality of products (e.g. non-essential or essential products) and 3) level of GMP compliance which consider to the number of GMP deficiencies from previous inspection (21). The final plan included the scheduled and responsible lead GMP inspector for each inspection.

Next, lead inspector was set up the inspection team comprising of sufficient personnel (number of inspectors and days for inspection) and that covered scope of inspection (e.g. production areas, quality assurance, quality control, production supporting systems). In principle, there used 2 – 3 inspectors but taking more days in the inspection. In addition, subject matter expert (SME) was needed when performed an inspection of the specific site such as vaccine or blood product plants.

Lastly, lead inspector called team inspection for a meeting and assigns responsibility to each inspector. Besides, reviewing the documents was reviewed to prepare detailed inspection e.g. previous inspection report, site master file, complaint and recall reports or critical process parameters of each dosage form (18, 22). Each inspector had to prepare aide-memoire for inspection following the PIC/S guideline e.g. aide-memoire inspection for 1) utilities system (23), 2) quality control laboratories (24) and 3) APIs site (25), etcetera.

2) Inspection

Inspection activity starting when inspection team arrived the manufacturing site, lead inspector conducted the opening meeting. This meeting covered topics of inspection objective, GMP guideline, scope and agenda. Then, manufacturer made a brief presentation about the manufacturing site and updated of a significant change from the last inspection. After that, team had conducted the inspection. Inspector gathered data and evidence by; observe the operation, ask questions/ interview or review documents/ records. When found GMP deficiencies, inspector was informed to manufacturer's staff and written down into inspection note form.

Interestingly, the inspection will be followed the site tour to overview of manufacture facilities and equipment. Manufacturing processes was checked the critical steps that would be demonstrated the success of production as a whole, checking whether the critical steps were controlled and followed up according to GMP requirements. Another, check to ensure that manufacturer staffs follow the approved and updated operating procedures. There was focused on the highest risk activities, reviewed problems and deviations from routine activities (18, 19). Documents review were followed the example guideline. An example of significant documents should be reviewed e.g. manufacturing formula and records, specifications of raw materials, packaging materials and finished products, quality defected report, training records, relevant validation data, records of laboratory and quality assurance department. On the last day, the team will be prepared a closing report and conducted the final closing meeting. The closing meeting covered the following objectives, discuss findings, list of GMP deficiencies and conclusion.

3) Post-inspection

The related activities were separated into three steps; CAPA evaluation, formal report preparation and issuance of GMP certificate. First step was CAPA report evaluation which related to inspection team and inspected manufacturer. Such manufacturer was prepared CAPA report that comprising root cause investigation, correction, corrective action, preventive action and timeframe for operation. Lead inspector will be evaluated and provided an opinion of whether the plan is an appropriate plan. Then, CAPA report was verified by QSM before approval. The approval of the GMP compliance statement and issue of GMP certificate is carefully considered the accomplishment of CAPA. It should demonstrate the effectiveness to prevent potential risk that may affect with quality of products.

Next, inspection team was considered GMP deficiencies and carefully prepared official GMP inspection report by following standard format. The proper report should provide a brief of GMP activities, findings, deficiencies both strengthens and weakness, any medicinal product samples are taken, inspector's summary and conclusion (26). The report was comprised main three parts; 1) general administration information, 2) finding and evaluation results and 3) GMP compliance conclusion of inspected site. Then, final report was verified by QSM and sent to the director for approval. Finally, GMP certificate was issued by Thai FDA for such GMP compliance manufacture also published on Thai FDA website (27).

Table 1 Summary of GMP inspection report

Item	Topic/Detail
Inspected site	Name and full address
Activities	For example; manufacture of API, Finished product (FG)
Inspection date	Date, month, year
Inspector	Name of the inspector
References	PIC/S GMP standard
Introduction	Brief description of site, activities, major changes since previous inspection

Findings and deficiencies	9 chapter of PIC/S GMP guide: quality management, personnel, premises and equipment, documentation, production, quality control, contract manufacture and analysis, complaints and product recall, self-inspection and related annexes.
List of deficiencies classified	Details and level of deficiencies (critical, major, other deficiency)
CAPA evaluation	Conclusion result of CAPA evaluation
Summary and conclusions	Comply or non-comply with PIC/S GMP guide or any other concern

2.2.3 GMP deficiency

GMP deficiency is the deviation of finding or observation from a GMP standard that founded during a regulatory inspection period. Deficiency levels were the critical, major and other deficiency that correlated PIC/S classification guidance (28).

1) Critical deficiency as a serious deficiency which has contribute to a potential risk and harmful to the people and/or veterinary patient. The misrepresentation, falsification drug products, engaged in fraud that made by manufacturer are included this deficiency. In addition, combination of many deficiencies leads to the quality system failure can classify to this deficiency as well.

2) Major deficiency as a deficiency may produce a product which does not comply to specification. Example, it does not ensure effective implementation of GMP requirements, major deviation, failure of releasing products for sale or combination of several other similar deficiencies.

3) Other deficiency as a deficiency unable to grouped as either major or critical deficiency, but demonstrates a deviation from GMP standard or inadequate information to categorize it as a both of deficiencies above.

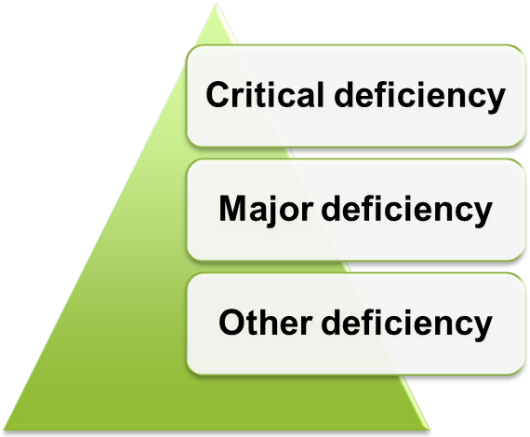


Figure 2 Summary of classification of GMP deficiencies

2.2.4 GMP Certificate

GMP Certificate is the important document that indicated the manufacturer is capable of drug manufacturing by following GPM standard. The validity was defined in three years after the inspection date. Example of certificate was shown in Figure 3 and Figure 4. Listed of GMP compliance manufacturer was published on official website of the Thai FDA (27).

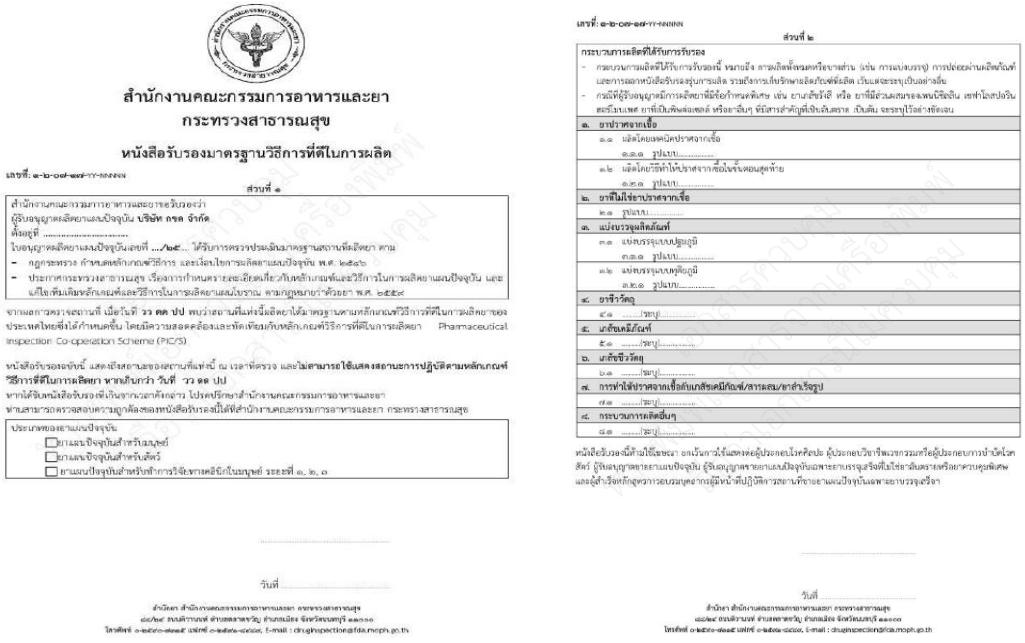
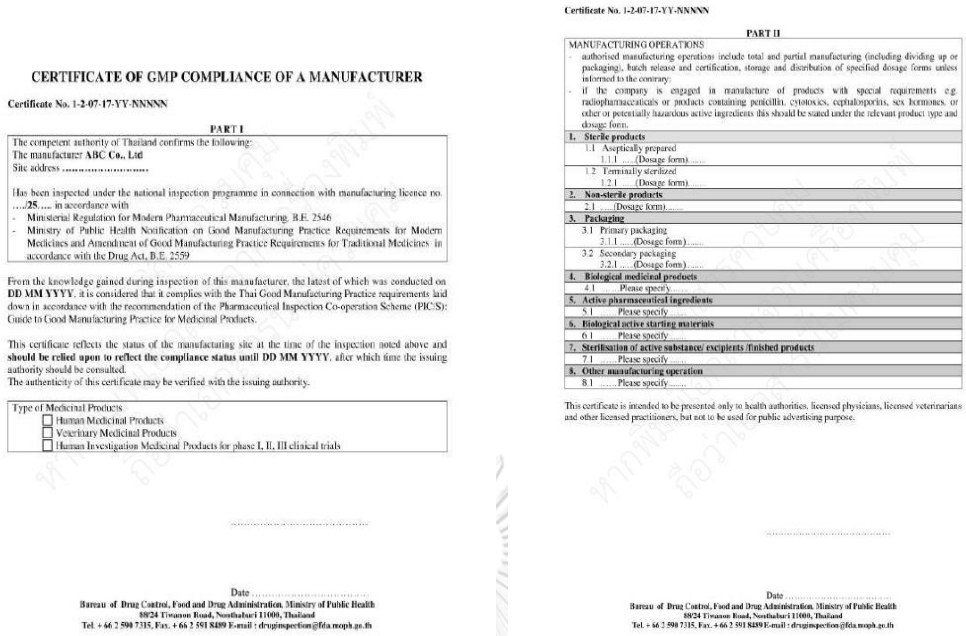

สำนักงานคณะกรรมการอาหารและยา
กระทรวงสาธารณสุข
หนังสือรับรองมาตรฐานวิธีการที่ดีในการผลิต

Figure 3 GMP certificate (Thai version)



CERTIFICATE OF GMP COMPLIANCE OF A MANUFACTURER

Certificate No. 1-2-07-17-YY-NNNNN

PART I

The competent authority of Thailand confirms the following:
The manufacturer **ABC Co., Ltd**
Site address .....

Has been inspected under the national inspection programme in connection with manufacturing licence no. .....**25**..... in accordance with
- Ministerial Regulation for Modern Pharmaceutical Manufacturing, B.E. 2546
- Ministry of Public Health Notification on Good Manufacturing Practice Requirements for Modern Medicines and Amendment of Good Manufacturing Practice Requirements for Traditional Medicines in accordance with the Drug Act, B.E. 2559

From the knowledge gained during inspection of this manufacturer, the latest of which was conducted on **DD MM YYYY**, it is considered that it complies with the Thai Good Manufacturing Practice requirements laid down in accordance with the recommendation of the Pharmaceutical Inspection Co-operation Scheme (PIC/S): Guide to Good Manufacturing Practice for Medicinal Products.

This certificate reflects the status of the manufacturing site at the time of the inspection noted above and **should be relied upon to reflect the compliance status until DD MM YYYY**, after which time the issuing authority should be consulted.
The authenticity of this certificate may be verified with the issuing authority.

Type of Medicinal Products
- ☐ Human Medicinal Products
- ☐ Veterinary Medicinal Products
- ☐ Human Investigation Medicinal Products for phase I, II, III clinical trials

.....

Date .....
Bureau of Drug Control, Food and Drug Administration, Ministry of Public Health
88/24 Tivanon Road, Nonthaburi 11000, Thailand
Tel. + 66 2 590 7335, Fax. + 66 2 591 8489 E-mail : druginspection@fda.moph.go.th

Certificate No. 1-2-07-17-YY-NNNNN

PART II

MANUFACTURING OPERATIONS
- authorised manufacturing operations include total and partial manufacturing (including dividing up or packaging), batch release and certification, storage and distribution of specified dosage forms unless informed to the contrary;
- if the company is engaged in manufacture of products with special requirements e.g. radiopharmaceuticals or products containing penicillin, cytotoxics, cephalosporins, sex hormones, or other or potentially hazardous active ingredients this should be stated under the relevant product type and dosage form.

1. Sterile products	
1.1 Aseptically prepared	
1.1.1 .....(Dosage form).....	
1.2 Terminally sterilized	
1.2.1 .....(Dosage form).....	
2. Non-sterile products	
2.1 .....(Dosage form).....	
3. Packaging	
3.1 Primary packaging	
3.1.1 .....(Dosage form).....	
3.2 Secondary packaging	
3.2.1 .....(Dosage form).....	
4. Biological medicinal products	
4.1 .....Please specify.....	
5. Active pharmaceutical ingredients	
5.1 .....Please specify.....	
6. Biological active starting materials	
6.1 .....Please specify.....	
7. Sterilisation of active substance/ excipients /finished products	
7.1 .....Please specify.....	
8. Other manufacturing operation	
8.1 .....Please specify.....	

This certificate is intended to be presented only to health authorities, licensed physicians, licensed veterinarians and other licensed practitioners, but not to be used for public advertising purpose.

.....

Date .....
Bureau of Drug Control, Food and Drug Administration, Ministry of Public Health
88/24 Tivanon Road, Nonthaburi 11000, Thailand
Tel. + 66 2 590 7335, Fax. + 66 2 591 8489 E-mail : druginspection@fda.moph.go.th

Figure 4 GMP certificate (English version)

2.2.5 GMP inspector

The GMP inspector who is a qualified person to be responsible for conducting GMP inspection. Inspector was properly qualified and consistently controlled by the qualification system. These was four levels as follows;

1) Lead GMP inspector, who was qualified person together with leader in GMP inspection and appointed by director of the Bureau of Drug Control.

2) GMP inspector, who was qualified person and appointed by director of the Bureau of Drug Control to conducts GMP inspection by following duties assigned by lead inspector.

3) Trainee, who was a person during qualification process to be an inspector level.

4) Observer, who was a person that intends to observe GMP inspection and was authorized by lead inspector.

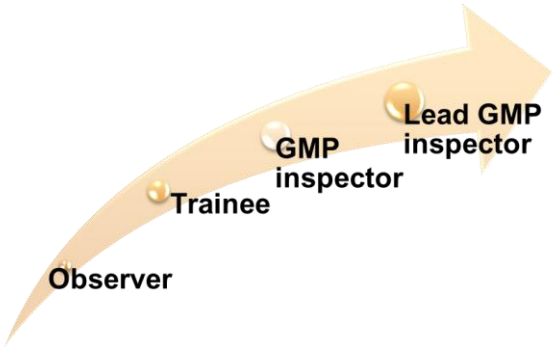


Figure 5 Summary of GMP inspector levels

Some specific inspection, subject matter expert (SME) was needed to performing. The SME who had specific knowledge or expertise in the organization, procedures, activities or matters that were to be inspected e.g. SME from the national control laboratory (NCL) of Thailand when perform inspection of biological manufacturer. In addition, related person with inspection system was quality system manager (QSM), who was a qualified person and responsible to verified inspection result before approval.

2.3 GMP desktop inspection of overseas pharmaceutical manufacturers

GMP desktop inspection is one of many inspection types which evaluate manufacturer GMP compliance by document-based only, without undertaking an on-site inspection. The desktop inspection approval will grant to inspected site if there are acceptable GMP evidence demonstration.

In Thailand, GMP desktop inspection system of an overseas pharmaceutical manufacturer is regulated by GMP inspectorate unit of Thai FDA. Every importing licensee that intends to register imported drug product in Thailand must be submitted GMP desktop inspection application of their foreign manufacturer before submitting drug dossiers to registration (2). In case of desk assessment results is unaccepted of GMP compliance and inequitable with local manufacturer, drug registration and distribution in Thailand cannot be performed. Consequently, evaluation and approval process of desktop inspection is one of critical steps of drug registration cycle.

Many factors are considered to implement the desktop inspection instead of on-site inspection, for example, to reduce the need for redundant inspections from their own authority (6), to make proper of limited inspection resources as an inspector (5), increasing number of overseas pharmaceutical manufacturers that will be inspected (29) and to avoid additional costs of company due to a certain amount of inspection fees. Accordingly, it was regulatory best practice to use the desktop inspection for prioritizing inspection activities.

2.3.1 First GMP desktop inspection regulation in Thailand

First desktop assessment was launched as named "Thai FDA notification on GMP accreditation of an overseas (non - domestic) manufacturer" since October, 2012 (4). PIC/S GMP standard was adopted to assess GMP compliance of overseas manufacturers similar to domestic manufacturers. The required documents adapted from the GMP desktop assessment guideline of the Health Sciences Authority (HSA) of Singapore (4). Furthermore, in case of the desktop inspection results still questionable in terms of quality and GMP conformity and non-equivalent to local manufacturer, an on-site inspection can be taken by the Thai FDA.

The foreign manufacturer can be categorized into two groups; 1) PIC/S manufacturer and 2) non-PIC/S manufacturer.

1) The "PIC/S manufacturer" is a manufacturer located in PIC/S country, located outside PIC/S country but have been inspected by PIC/S member or located in ASEAN country and have been inspected by ASEAN Listed Inspection Service. The required documents for inspection was GMP certificate, GMP inspection report and site master file.

2) The "non-PIC/S manufacturer" is a manufacturer located outside the PIC/S country and never been inspected by PIC/S member. The set of the required documents was different that depend on manufacturer types. Many additional documents from type 1 (above) were required, for examples, manufacturing process related procedure (e.g. personal qualification, training program, premise and equipment, documentation control system or main activities of production and quality part), documents recorded (e.g. batch production record, validation protocol and report, qualification of supporting system).

2.3.2 Current GMP desktop inspection regulation

After the Thai FDA became the PIC/S member in 2016, desktop inspection was revised by following an international guideline. The system improvement and enhancement were main objectives. Therefore, second desktop regulation was announced in the name “Thai FDA notification on GMP clearance of overseas pharmaceutical manufacturers” since June 2017 (3). The standard for assessment was similar (PIC/S GMP guideline) but listed of required documents were changed. Categorization of foreign manufacturers divided into three groups; 1) MRA or PIC/S manufacturer, 2) certified by PIC/S or WHO PQ certified manufacturer and 3) non-PIC/S manufacturer.

1) The “MRA or PIC/S manufacturer” is located in PIC/S member country or located in the jurisdiction of ASEAN country and have been inspected by ASEAN Listed Inspection Service under the ASEAN sectoral mutual recognition arrangement for GMP inspection (MRA). Required documents were four; GMP certificate, GMP inspection report, CAPA report and GMP/Quality agreement between a licensee and overseas manufacturer.

2) The “certified by PIC/S or WHO PQ certified manufacturer” is located outside PIC/S country but have been inspected by PIC/S member or inspected WHO prequalification team. One additional document from type 1) was site master file.

3) The “non-PIC/S manufacturer” is located outside PIC/S country and never been inspected by PIC/S member or inspected WHO PQ team. Many additional documents from type 2) were required. Because such manufacturing site was not fully implemented PIC/S guidance as a law lead to strict inspection more than the previous both types. Examples of documents were quality manual, regulatory action details last five years, batch processing records and batch analysis record, standard operating procedure of release product for supply, validation master plan and process validation report, local GMP guideline and listed of documentation/ picture of manufacturing process.

Because desktop inspection was required many documents, definition and explanations was concluded for more understanding as example below.

- Site Master File (SMF) is a quality document that provides information of the manufacturer's operations, facilities and quality management system. Important information are name and site address, overview of all activities following GMP requirements, cross contamination controls strategies for high-risk products and other documents e.g. the list of an operation plant and equipment of production and quality control laboratory department.

- GMP/Quality agreement is the official contracts whereby provide information of the roles and responsibilities between the related overseas manufacturing site and Thai's licensees in relation to the important aspects of GMP activities and imported products. The main aspects are cover all of the correlated activities e.g. manufacturing process, production area, quality control and quality assurance that impact to quality, efficacy and safety of products. Additionally, these are obviously describing the role of every related manufacturing site e.g. validation activities, stability study, complaints and recall management, release product for supply process, testing methodology and change control system management.

- Release product for supply procedure is document that provides information about how the authorized person at the manufacturing site conducts the release of a medicinal product for sale. Each batch has been manufactured and checked for compliance with the requirements of the marketing authorization and GMP requirement.

- Validation master plan (VMP) is document which defines further detail information of the qualification and validation operation of the manufacturer. The VMP use to verify the scope, status and activity of qualification and validation for its operations. Besides, its usage to check appropriately qualified and validated and have a suitable re-validation schedule. VMP should provide information on at least the following; 1) validation policy, 2) briefly of processes, machine/equipment, facilities and systems to be validated, 3) documentation control to be used for protocols and reports, 4) planning and scheduling and 5) change control management.

- Product Quality Review is another document that provides details of the effectiveness of controls and processes on the quality of products and that consistent the existing manufacturing activities of drug products. It also shows the data on deviations to product license and customer complaints.

- Regulatory action details last five years describe additional information about the foreign manufacturing site's compliance history lasted five years e.g. quality defected as serious complaints and recall reports, warning letters, suspension and revocation of GMP certificate or product license, which caused by the overseas manufacture and taken by their own regulatory authority.

Taken together, these results suggest that desktop inspection is an important system and critical step to verify the GMP conformity of an overseas manufacturer before drug dossier evaluation. The questionable and reliability of inspection results might occur from any related parties because this inspection conducts only the required documents. To deeply analysis of this points is highly recommended to fulfill this questionable and improvement of inspection system.

2.4 The Pharmaceutical Inspection Co-operation Scheme (PIC/S)

2.4.1 Introduction and history

The Pharmaceutical Inspection Co-operation Scheme (PIC/S) is an organization which a non-binding arrangement and unofficial co-operative among national regulatory authorities in the field of GMP for human or veterinary's drug products. At the beginning, these were established in 1995 for any regulatory authority having a comparative of GMP inspection system. Currently, PIC/S consists of 53 participating authorities (PA) coming around the world including Thailand (30).

2.4.2 Objective of organization

The objectives were to harmonizing the inspection system by developing the standards as common requirements in the field of GMP and that provide the training program for inspectors. In addition, it was accommodated collaboration and networking among participating authorities including the global organizations contribute to increasing of the reliability and mutual confidence. It can be reflexed in the organization's mission that was "To lead the international development,

implementation and maintenance of harmonized GMP standards and quality systems of inspectorates in the field of medicinal products" (31). The achievement of goals should be performed and continuously maintained the development and promoting of the harmonization on GMP standards and guideline documents such as inspector training program, re-assessment of the PIC/S member and networking among regulatory agencies and international organizations.

2.4.3 How to access PIC/S member

The accession process to PIC/S member has to be assessed the regulatory authority before accepted for membership. The assessment processes are undertaken to examine that the drug regulatory authorities have managements and competence necessary to adopt and maintain a GMP inspection system comparable to another current PIC/S member. Several systems will involve and examine during the assessment process, not limited to, GMP inspection system, quality system of inspectorate unit, legal requirements, inspector training strategies and site visit for evaluation of GMP inspection system (32).

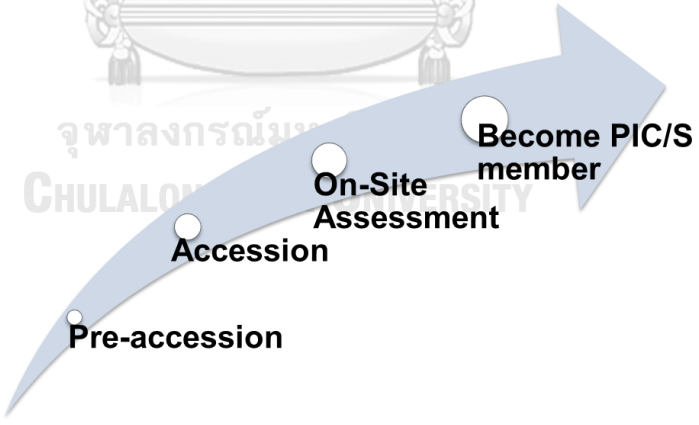


Figure 6 Summary of the accession to PIC/S member

As shown in the figure, the accession steps can explain in main two steps are the pre-accession and accession process that include an on-site assessment and become the membership process.

1) The pre-accession step is a voluntary step for performed gap analysis and self-evaluation. It is advantage to providing the proper option for interested authorities that may unable to meet the accession's requirement. Before submitting, such authority should ensure that the introduced of the quality system following the PIC/S guidance and PIC/S GMP guidance are fully implement within its own inspectorate unit. The interested authority must have the inspection resources for attending PIC/S activities particularly the annual committee meeting and related seminar. The required documents for submission are the questionnaire and the audit checklist following PIC/S format. Additionally, the regulation gap analysis between the PIC/S GMP requirements and their own GMP requirements is recommended to analyze before submission (33, 34), .

2) The accession step is an important step. The PIC/S secretariat will provide all appropriate required documents like questionnaire and the audit checklist that comprising regulatory requirements, GMP standards, inspection resources and performance, enforcement powers, alert and crisis systems, analytical capability and quality management system (20, 35). After receipt application, PIC/S will set up a rapporteur and co-rapporteurs to leading of the accession evaluation. Next, the on-site visit is conduction for assessment (e.g. inspection system, inspection practice and to observe inspection practice of inspectors at local manufacture site). Lastly, the team will be prepared on-site assessment report to PIC/S committee for evaluation and make final decision. After accepted to membership, the secretariat will inform to the applicant and officially publish on PIC/S website (36). Currently, PIC/S consist of 53 participating authorities coming around the world (Europe, Africa, America, Asia and Australasia) (36).

Thai FDA became the PIC/S member from August 2016 in order of PIC/S' 49th participating authority (16). Begin, the application was submitted in March 2015. The documents assessment was performed in view of its accession to PIC/S, followed by an on-site assessment in March 2016. The assessment team comprised four delegates from PIC/S committee (Mr Jacques Morenas from France, Mr Boon Meow Hoe from Singapore, Ms Gaye Camm from Australia and Ms Shanti Marlina from Indonesia). The scope of assessment covered both modern and traditional medicinal

products. After accession processes, the assessment results report was accepted and officially became the member by PIC/S committee meeting at Manchester, the United Kingdom since August 2016 (15, 16).

Table 2 List of PIC/S participating authorities

No.	Participating authorities	Country	Accession
1	National Institute of Drugs	Argentina	January 2008
2	Therapeutic Goods Administration (TGA)	Australia	November 1995
3	Austrian Agency for Health and Food Safety (AGES)	Austria	November 1999
4	Federal Agency for Medicines and Health Products	Belgium	February 1997
5	Health Canada	Canada	January 1999
6	Taiwan Food and Drug Administration (TFDA)	Chinese Taipei	January 2013
7	Agency for Medicinal Products and Medical Devices of Croatia	Croatia	January 2016
8	Pharmaceutical Services (CyPHS)	Cyprus	July 2008
9	State Institute for Drug Control	Czech Republic	January 1997
10	Institute for State Control of Veterinary Biologicals and Medicines (ISCVBM)	Czech Republic	July 2005
11	Danish Medicines Agency (DKMA)	Denmark	November 1995
12	State Agency of Medicines (SAM)	Estonia	January 2007
13	Finnish Medicines Agency (FIMEA)	Finland	January 1996
14	French National Agency for Medicines and Health Products Safety (ANSM)	France	February 1997
15	Agency for Food, Environmental & Occupational Health Safety	France	January 2009
16	- Federal Ministry of Health (BMG) - Central Authority of the Laender for Health	Germany	December 2000

	Protection regarding Medicinal Products and Medical Devices (ZLG)		
17	Greek National Organization for Medicines (EOF)	Greece	January 2002
18	Pharmacy and Poisons Board of Hong Kong (PPBHK)	Hong Kong SAR, China	January 2016
19	National Institute of Pharmacy and Nutrition (NIPN)	Hungary	December 1995
20	Icelandic Medicines Agency (IMA)	Iceland	November 1995
21	National Agency for Drug and Food Control (NADFC)	Indonesia	July 2012
22	Iran Food and Drug Administration (IFDA)	Iran	January 2018
23	Health Products Regulatory Authority (HPRA)	Ireland	February 1996
24	Institute for Standardization and Control of Pharmaceuticals (ISCP)	Israel	January 2009
25	Italian Medicines Agency (AIFA)	Italy	February 2000
26	Directorate General for Animal Health and Veterinary Medicinal Products (DGSAF)	Italy	January 2020
27	- Ministry of Health, Labour and Welfare (MHLW) - Pharmaceuticals and Medical Devices Agency (PMDA)	Japan	July 2014
28	Ministry of Food and Drug Safety (MFDS)	Korea	July 2014
29	State Agency of Medicines (ZVA)	Latvia	January 2004
30	Office of Healthcare (AG)	Liechtenstein	November 1995
31	State Medicines Control Agency (SMCA)	Lithuania	July 2009
32	National Pharmaceutical Regulatory Agency (NPRA)	Malaysia	January 2002
33	Medicines Authority Malta (MAM)	Malta	January 2008

34	Federal Commission for the Protection Against Sanitary Risks (COFEPRIS)	Mexico	January 2018
35	Health and Youth Care Inspectorate (IGJ)	Netherlands	November 1995
36	Medicines and Medical Devices Safety Authority (MEDSAFE)	New Zealand	January 2013
37	Norwegian Medicines Agency (NOMA)	Norway	November 1995
38	Chief Pharmaceutical Inspectorate (CPI)	Poland	January 2006
39	National Authority of Medicines and Health Products, IP (INFARMED IP)	Portugal	January 1999
40	National Agency for Medicines and Medical Devices (NAMMD	Romania	November 1995
41	Health Sciences Authority (HSA)	Singapore	January 2000
42	State Institute for Drug Control (SIDC)	Slovak	January 1997
43	Agency for Medicinal Products and Medical Devices (JAZMP)	Slovenia	January 2012
44	South African Health Products Regulatory Authority (SAHPRA)	South Africa	July 2007
45	Spanish Agency of Medicines and Medical Devices (AEMPS)	Spain	January 1998
46	Medical Products Agency (MPA)	Sweden	February 1996
47	Swiss Agency for Therapeutic Products (SWISSMEDIC)	Switzerland	February 1996
48	Food and Drug Administration (Thai FDA)	Thailand	August 2016
49	Turkish Medicines and Medical Devices Agency (TMMDA)	Turkey	January 2018
50	State Service of Ukraine on Medicines and Drugs Control (SMDC)	Ukraine	January 2011
51	Medicines & Healthcare Products Regulatory Agency (MHRA)	United Kingdom	June 1999

52	Veterinary Medicines Directorate (VMD)	United Kingdom	January 2014
53	U.S. Food and Drug Administration (US FDA)	U.S.A	January 2011

2.4.4 PIC/S GMP requirements

GMP requirements for medicinal products have been adopted due to many reasons such as to help the removal of technical barriers to trade in drug products, to encourage uniformity approval decisions and to ensure the quality assurance of manufacture still maintaining of the high standards. PIC/S guideline is categorized into main two parts and the annexes.

Part I covers principles and requirements for the manufacturing sites of finished products (FP) which cover nine chapters. Part II covers the GMP standard for active pharmaceutical ingredients (API) used as starting materials which comprise nineteen sections. Both parts are mandatory mode for each manufacturer type (FP or API site). Lastly, the annexes describe the information on specific areas of process that consist of twenty related annexes. Many annexes will concurrently be adopted by some manufacturing processes. For example, part I plus annex 1 (specific requirements for sterile medicinal products) are applied by the sterile manufacturer. Likewise, part I plus annex 9 (requirements for liquids, creams and ointments products) are adopted by the non-sterile manufacturers that produced the liquids and semi-solid dosage forms (37).

Table 3 Conclusions of PIC/S GMP elements

Topics	Conclusions
Part I: GMP principles for the manufacture of medicinal products	Chapter 1 - Pharmaceutical quality system - Principle and pharmaceutical quality system - Good manufacturing practice for medicinal products - Quality control - Product quality review - Quality risk management
	Chapter 2 – Personnel - Principle and general - Key personnel - Training - Personnel hygiene - Consultants
	Chapter 3 - Premises and equipment - Principle - Premises (general, production area, storage areas, quality control areas, ancillary areas) - Equipment
	Chapter 4 – Documentation - Principle and required GMP documentation - Generation and control of documentation - Good documentation practices - Retention of documents - Specifications - Manufacturing formula and processing instructions - Procedures and records

	Chapter 5 – Production - Principle and general - Prevention of cross-contamination in production - Validation - Processing operations, intermediate and bulk products - Starting materials, packaging materials and finished products operations - Rejected, recovered and returned materials - Product shortage due to manufacturing constraints
	Chapter 6 - Quality control - Principle and general - Good quality control laboratory practice (documentation, sampling, testing, on-going stability program, technical transfer of testing methods)
	Chapter 7 - Outsourced activities - Principle and general - The contract giver, the contract acceptor and the contract
	Chapter 8 - Complaints and product recall - Principle, personnel and organization - Procedures for handling and investigating complaints and recall including possible quality defects - Investigation and decision-making - Root cause analysis and corrective and preventative actions - Product recalls and other potential risk-reducing actions
	Chapter 9 - Self - inspection - Principle and inspection requirements

Part II: GMP for active substances used as starting materials	1. Introduction
	2. Quality management
	3. Personnel
	4. Buildings and facilities
	5. Process equipment
	6. Documentation and records
	7. Materials management
	8. Production and in-process controls
	9. Packaging and identification labelling of APIs and intermediates
	10. Storage and distribution
	11. Laboratory controls
	12. Validation
	13. Change control
	14. Rejection and re-use of materials
	15. Complaints and recalls
	16. Contract manufacturers (including laboratories)
	17. Agents, brokers, traders, distributors, re-packers and re-labellers
	18. Specific guidance for APIs manufactured by cell culture/fermentation
	19. APIs for use in clinical trials
The related annexes	Annex 1: Manufacture of sterile medicinal products
	Annex 2: Manufacture of biological medicinal substances and products for human use
	Annex 3: Manufacture of radiopharmaceuticals
	Annex 4: Manufacture of veterinary medicinal products other than immunological
	Annex 5: Manufacture of immunological veterinary medical products

	Annex 6: Manufacture of medicinal gases
	Annex 7: Manufacture of herbal medicinal products
	Annex 8: Sampling of starting and packaging materials
	Annex 9: Manufacture of liquids, creams and ointments
	Annex 10: Manufacture of pressurized metered dose aerosol preparations for inhalation
	Annex 11: Computerized systems
	Annex 12: Use of ionizing radiation in the manufacture of medicinal products
	Annex 13: Manufacture of investigational medicinal products
	Annex 14: Manufacture of medicinal products derived from human blood or plasma
	Annex 15: Qualification and validation
	Annex 16: Qualified person and batch release
	Annex 17: Real time release testing and parametric release
	Annex 18: GMP guide for active pharmaceutical ingredients
	Annex 19: Reference and retention samples
	Annex 20: Quality risk management

Overall, PIC/S GMP requirement is an internationally recognized standard that applied by worldwide drug regulatory authorities. For Thailand, PIC/S GMP is the national legislation and enforcement to all of local manufacturers. Therefore, overseas pharmaceutical manufacturers that intend to supply the products in Thailand should comply to this requirement as well.

2.5 Quality risk management (QRM) of ICH Q9 guideline

2.5.1 Introduction and principle

The QRM guideline (Q9 section) is established by the ICH organization that comprising three regulatory authorities (EU., Japan and USA.) and their industry association since 2005 (38). The QRM established based on two principles; 1) the evaluation process of the potential risk should consider on scientific base and ultimately relate to consumers protection and 2) the level of risk should appropriately define from the level of effort and formality.

Table 4 Summary of the QRM elements

Structure and details of the QRM Q9 guideline	
Introduction	
Scope	
Principles of quality risk management	
General quality risk management process	Responsibilities
	Initiating a quality risk management process
	Risk assessment
	Risk control
	Risk communication
	Risk review
Risk management methodology	
Integration of quality risk management into industry and regulatory operations	
Definitions	
References	
Annex I: risk management methods and tools	Basic risk management facilitation methods
	Failure mode effects analysis (FMEA)
	Failure mode, effects and criticality analysis (FMECA)
	Fault tree analysis (FTA)
	Hazard analysis and critical control points (HACCP)
	Hazard operability analysis (HAZOP)
	Preliminary hazard analysis (PHA)

	Risk ranking and filtering
	Supporting statistical tools
Annex II: potential applications for quality risk management	Quality risk management as part of integrated quality management
	Quality risk management as part of regulatory operations
	Quality risk management as part of development
	Quality risk management for facilities, equipment and utilities
	Quality risk management as part of materials management
	Quality risk management as part of production
	Quality risk management as part of laboratory control and stability studies
	Quality risk management as part of packaging and labelling

QRM Q9 elements are cover the principles, general process, methodology and tools for applications. This guidance provides principles of risk that focus on the possibility of occurrence of harm and the severity of that harm to products/processes. The methodology and tools for implementation are define and that can adapt to many pharmaceutical quality aspects (7) such as research and development process, manufacturing activities, distribution, GMP inspections and drug dossier evaluation processes. The implementation focus on safety, quality and efficacy of medicinal products and the stakeholders as manufacturers are considered to protect of the patient by reducing the risk. The effectiveness of QRM can further ensure the quality standard of products by control potential risks and any quality problem during manufacturing processes. Besides, QRM very use full to make the decision when the quality problem is occurred in term of the manufacture and drug regulatory authority's perspective.

2.5.2 General process of QRM

QRM is a systematic process which covers the activities of assessment, control, review and communication of risks that related to quality of product throughout product life cycle. Responsibilities persons comprising the interdisciplinary people that consist of specialists from the reasonable areas and a variety of functions of their organization. Before start QRM process, the data might cover the defined problem, background information analysis, study team resources and timeframe of operation. QRM activities comprised of three steps; risk assessment, risk control and risk review (7).

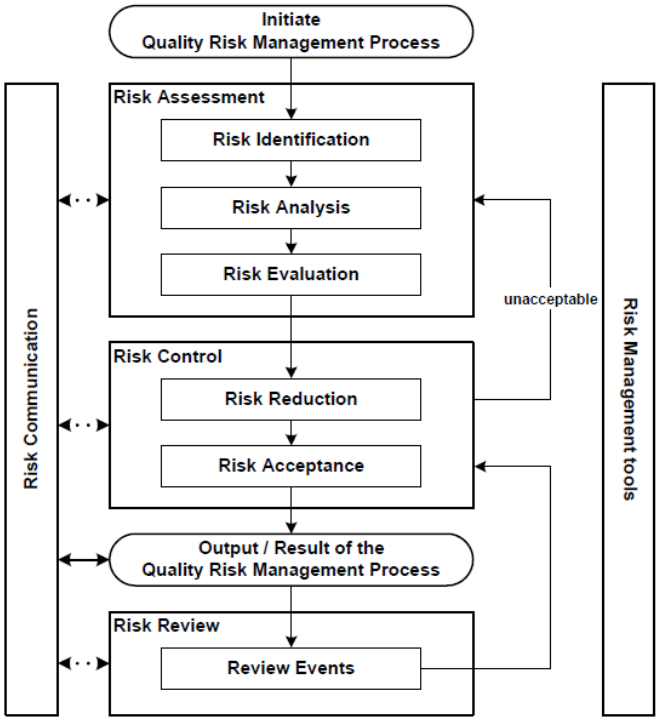


Figure 7 Overview of a standard quality risk management process (7)

1) Risk assessment, it is the first step that comprises of three processes; risk identification of hazards, risk analysis and risk evaluation correlated with those hazards. The appropriate of problem representation or proper risk question is recommended for beginning lead to well-organized and easily selected of QRM tools. The common questions can be used for defined the risk, for examples, “what might

go wrong?", "what is the likelihood (probability) it will go wrong?" or "what are the consequences (severity)?" (7).

Firstly, risk identification uses to find possible harm to the quality of the medicinal products or lead to the questionable problem. Identified risks may be coming from the background data analysis like historical data, theoretical analysis, informed opinions and stakeholder's interest. Secondly, risk analysis is performed to analyzes identified risks and can concurrently use QRM tools for analysis, for example, FMEA tool that considers the three factors of the probability, severity and detectability of each risk. Lastly, risk evaluation is performed to evaluate the identified risk. Likewise, the quality tools can be used e.g. the risk priority number (PRN) which use to define risk level by calculate the three factors from FMEA. Both of the qualitative description or quantitative estimate of risk is output of risk assessment performance.

2) Risk control, the objective of this step is to minimize the risk shift to an acceptable level. Thus, risk reduction approach should suggest for implementation. Several principles may use for consideration of the optimal level of risk control e.g. 1) benefit-cost analysis, 2) reduce or eliminate risks, 3) the suitable balance among risks, benefits and resources or 4) considering and controlling the new risk that might occur from the initial risk mitigation actions.

Risk control activity comprise of risk reduction and risk acceptable. Risk reduction emphasizes on processes for mitigating action or avoidance the exceeded from an acceptable level of the risk. Risk reduction actions are taken to reduce three factors of the risk (occurrence, severity and detectability). Next, risk acceptable is a decision process to accept the risks. the acceptable level shall depend on several parameters and should be determined on a case-by-case by the QRM team. The residual risk after risk reduction implementation will consider making a decision to accept the risk.

3) Risk review, after assessed and reduced the risk, the quality management process to monitor or review the risk events should be continuously implemented to take into account new information and experience. The frequency of the review activity should consider the risk level and maybe determine by the QRM team. The re-assessment of risk acceptance decisions maybe includes the risk review as well.

In addition, risk communication is involved all of step. It is a process for sharing information about risk between the QRM team and other relative functions/departments. The result from each QRM activities (e.g. identified risk, risk level, risk reduction) should be suitably communicated and documented to relevant persons. Besides, many tools are recommended to use concurrent with the QRM processes. For example, general techniques are usually used to managing data and serving to make a decision such as flowcharts, process mapping, check sheets or cause and effect diagrams (as known in term of the Ishikawa diagram or fishbone diagram). In addition, FMEA tool is widely used in field of pharmaceutical quality (39). This tool use to evaluate the identified risk by consider in three factors (occurrence, severity and detectability). Once the identified risk and that related failure modes are established by the QRM team, risk mitigation action can be used to reduce, eliminate, monitor or control those potential failures. This tool is suitable for complex process/system that can break down the analysis of the complexation system into controllable and easily steps e.g. manufacturing process of biological manufacturer or GMP inspection system of the national regulatory authority.

2.5.3 Implementation of QRM in the pharmaceutical industry and regulator

The implementation of QRM concept are dynamic and might variously apply throughout many phases of medicinal products life cycle as follows.

2.5.3.1 Pharmaceutical development

The research and development phase can be applied for operation such as new drug development that used the principle of quality by design (QbD) paradigm. Risk assessment may be applied to the screening study steps of the quality target product profile (QTPP) and critical quality attributes (CQA) for identifying the potential risk. Formulation stage such as finding starting and packaging material, formulation and process development can be used for assessing and controlling the

potential risk to cause failure. In addition, scale-up process might facilitate and ease by the applied of QRM principles (40).

An example, FMEA tool was used to identify the potential risk of the formulation and process parameters identification of lyophilization. Several aspects may be harmed and impacted to quality of lyophilized products which can be analyzed by the assumption of three factors (occurrence, severity and detectability) and risk priority number (RPN). Results of the potential risks from lyophilization were the suspension preparation, freeze-drying process and formulation process. The highest RPN value was the formulation process (RPN = 75 value) due to source of API used might be affected to the dissolution time by the variety of the particle size and crystallinity. Risk reduction was proposed to mitigation the risk e.g. the design of experiments (DoE) for product understanding and design space development study (41).

2.5.3.2 Pharmaceutical manufacturing activity

Refer to PIC/S GMP guideline, the QRM principle is specifically described in chapter I and annex 20 (37) to apply in each manufacturing activities e.g. receiving of starting and packaging material, production process, quality control, quality assurance, supporting systems and finished products management system. An example of research, it can be applied QRM for identified and analyzed the potential risk in manufacturing process that affect to the quality of drug products e.g. continuous manufacturing process of powder-to-tablet manufacturing, continuous direct compression step by three feeders (API, excipient, and lubricant) (42). In addition, process validation can be applied to operation by the QRM concept as well. This activity was no longer a one-time operation but covered all of the related quality activities throughout the product life cycle that, not limited to, the research and development step, scale-up activity and the commercial process. Therefore, potential risks can be mitigated and controlled to an acceptable level by QRM, lead to meet the product specification and quality attribute of commercial products (43, 44).

2.5.3.3 Pharmaceutical distribution

Distribution system is important phase of the pharmaceutical product life cycle because that might affect quality of products in particular of the environment control e.g. temperature and humidity. Consequently, distributer should maintain a principle and processes of QRM concerning their distribution activities. Many quality processes as a change control system, deviation management, corrective action and preventive action or outsourced activities agreement should apply this guidance for the appropriate management (45). The QRM guideline can be useful to identify the harm with potential risk and mitigation action of distribution system contributes the improvement of system e.g. avoided quality defected of products (complaint, recalls) and regulatory actions.

For example, risk assessment and FMEA tool was applied to assess the risk of logistics and distribution of pharmaceutical products. The background information analysis and questionnaire tool were prepared for information. Calculation of three factors (occurrence, severity and detectability) and risk priority number were used to evaluate potential risk. Results, five risks were identified and the highest PRN value was degradation of a product caused by the exposure of high temperature. The risk reduction activities has proposed for implementation such as ensuring environmental control and storage conditions in the transportation agreements, a show of transportation instructions on product containers, automatic data loggers (temperature measurement) and set up the notification and alert system for temperature excursions (46).

2.5.3.4 Regulatory GMP inspection system

Apart from pharmaceutical industry implementation, QRM can be applied by the drug regulatory authority. Many regulatory activities are implementing the principle in routine work especially the GMP inspection system that is example below.

- GMP inspection process, is a complex process and relates to many parties/persons. QRM principle can be very useful to facilitate the GMP inspection and that widely implement by drug regulatory authorities due to many requirements of GMP guideline (e.g. WHO and PIC/S guideline) that difficult to fully apply within the

limited time of inspection period (47). Most regulators agreed that a good risk assessment system should let regulatory authorities have a better targeted prevention and not just compulsion measures throughout the inspection period (48). It can be applied by GMP inspector to prepare information for inspection. The critical processes and quality problem are identified by QRM principle to prioritize inspection and to emphasize inspection areas. In addition, many documents can be applied the QRM concept for identify the potential risk e.g. change control records that indicate the significant change, product quality review, non-conformance report, out of specification report that demonstrates quality problem.

- Frequency of inspection, it can apply the risk assessment principle to define the inspection frequency. Many factors are involved to consider base on this principle; (i) complexity of the site, (ii) criticality of the medicinal products produced, and (iii) GMP compliance status. Those factors will consider to define the frequency for inspection (e.g. every 1 - 3 years). The frequency can adjust to add or reduce inspection times base on risk assessment evaluation (21).

CHAPTER III

METHODOLOGY

This chapter described the methodology to study risk assessment of GMP inspection of overseas pharmaceutical manufacturers based on desktop inspection system as required in Thailand by applying data analysis and brainstorming methods. This work utilized the quality risk management of ICH guideline Q9 with risk management methods and tools to evaluate the GMP desktop inspection system in the scope of overseas pharmaceutical manufacturers by carrying out in five steps; 1) pre-assessment, 2) risk identification, 3) risk analysis, 4) risk evaluation and 5) risk reduction as described in Figure 8.

Figure 8 The overview of study design

3.1 Step 1: Pre-assessment

3.1.1 Set up risk assessment team

The risk assessment team consisted of five interdisciplinary persons that work in the GMP inspection unit, drug product registration system and the Post-marketing Control Division under Bureau of Drug Control of the Thai FDA and have at least three years of qualified experience as the following;

1) Delegate from GMP inspection of overseas pharmaceutical manufacturers sub-committee under drug committee of drug act B.E. 2510, who has comprehensive scientific knowledge in the field of GMP inspection and work in a role of consultancy for GMP regulation of overseas pharmaceutical manufacturers.

2) Delegate from drug quality defect working group, who has responsibilities to consider the quality defect of imported products such as product complaints, product recalls.

3) Lead GMP inspector who has responsibilities to lead the GMP inspection team, conduct on-site and desktop inspection, verify inspection result and give an advice to junior inspector.

4) Reviewer from the drug registration unit who has responsibilities to review and evaluate drug dossiers (ACTD).

5) Delegate from manufacturers licensing unit who has responsibilities to consider a license issue of import licensees.

Brainstorming with team based discussion were mainly used for all assessments in the following parts (39, 49). Decision maker of the team was the author that made appropriate and timely quality risk management decisions.

3.1.2 Data analysis

Data analysis was performed by collecting the statistical data of the GMP desktop inspection situation and drug quality defect (complaints and recalls of imported product) in Thailand over the last three years in January 2016 – December 2018 as supportive data for risk analysis and evaluation. The information resources were from Thai FDA database.

3.1.2.1 GMP desktop inspection situation: The study analyzed the trend of overseas pharmaceutical manufacturers approval by focusing on in the three main topics of;

1) Number of manufacturers in GMP desktop inspection system

2) Number of manufacturers categorized by type of manufacturer (membership of PIC/S or non-PIC/S member)

3) Number of manufacturers categorized by dosage forms (non-sterile, sterile and biological manufacturers)

3.1.2.2 Product quality defect: The study analyzed the statistical data of complaints and recalls of the imported products in five topics of;

1) Number of complaints and recalls

2) Number of complaints and recalls categorize by type of manufacturer (membership of PIC/S or non-PIC/S member)

3) Number of complaints and recalls categorize by dosage forms (non-sterile, sterile and biological manufacturers)

4) Number of complaints and recalls categorize by causes of defect

5) Number of recalls categorize by type of recalls (voluntary and mandatory recalls)

3.2 Step 2: Risk identification

Risk identification was conducted and analyzed based on regulation gap and routine workflow that directly related to the quality and reliability of desktop inspection results.

3.2.1 Risk identification by regulation gap analysis

The regulation gap analysis was performed by comparing the Thai regulations against five globally-selected countries/ organizations under four criterias; 1) the national regulatory authority/ international organizations, 2) implemented the desktop inspection system, 3) regulation/guideline available on the official website and 4) various sources of guidelines representing region and global inspection systems (50). Five selected countries/organizations were 1) Health Sciences Authority (HSA) of Singapore (51), 2) National Pharmaceutical Regulatory Agency (NPRA) of Malaysia (52), 3) Therapeutic Goods Administration (TGA) of Australia (53), 4) World

Health Organization (WHO) (5) and 5) The Pharmaceutical Inspection Co-operation Scheme (PIC/S) (54). Sources of information was searched from the official website as at the date of search. The scope of regulation gap analysis was focused on three main aspects; 1) objective, principles and scope, 2) implementation and supervision and 3) regulatory contents (50). The regulation gaps and weakness of desktop inspection systems were identified and reported.

3.2.2 Risk identification by workflow analysis

The scope was to analyze the whole process of the current desktop inspection system used routinely, starting from document submission, evaluation and approval. In addition, many persons, relating with the workflow such as, licensees, Thai FDA officer, GMP inspector and the director were analyzed. Documents used in the workflow such as desktop inspection standard operating procedure (SOP), and manual of document preparation for licensee were used for analysis.

3.2.3 Risk identification by national and international GMP inspectors

The results of potential risk from regulation gap and workflow analysis were used for this section. Interview of ten GMP inspectors with the criteria of working in the GMP inspectorate unit of Thai FDA and having at least three years of GMP inspection experience were used. Researcher encouraged inspectors to talk and share opinions regarding the potential risk, additional risks, along with suggesting a risk reduction approach by asking the question and one to one interview. Next, those potential risks and risk mitigation approaches were asked at least three representatives of the selected countries/organizations in section 3.2.1. The official electronic letter was sent via electronic mail (e-mail). List of questions used for interview was validated by the risk assessment team as follows;

- Do you agree with the potential risk? Why?
- What are the comments or suggestions about the potential risk?
- What is the weakness of the desktop inspection system implemented in Thailand?
- What is the additional risk that you concern? Why?
- What is the potential failure mode and their consequences of the suggested risk?

- What are the propose risk reduction strategies of each risk?

After national and international GMP inspector interview, researcher and risk assessment team were brainstormed and discussed to summarize the identified risks which were used in the followings steps; risk analysis and evaluation.

3.3 Step 3: Risk analysis

3.3.1 FMEA tool

Risk analysis was conducted by using the FMEA tool, considering three main factors of occurrence (O), severity (S) and detectability (D) as defined below and classified quantitatively or qualitatively in Table 5, Table 6 and Table 7, respectively.

- O is the probability of the hazard failure

- S is the measure of the possible consequences of a hazard

- D is the ability to discover or determine the existence, presence, or fact of a hazard

The ranking scores were vertically determined in the rating scale of 1-5 by the risk assessment team and were assessed in the order of O among all identified risks for the first, S for the second and then D for the last to obtain the most appropriate values for each risk. In addition, the O value was considered under the results of data analysis (pre-assessment step in section 3.1.2). The S and D values were judged in the perspective of potential failure mode and consequence based on the interdisciplinary team's experiences which have different background and work covering a wide range of drug quality responsibilities. In contrast to O and S values, the D value was assessed reversely which means the higher detectability, the lesser is considered as risk rankings (39, 55), . In this method, risk assessment team ranked the number that was considered to reflect the frequency of each risk.

Table 5 Occurrence (O) ranking of failure modes for FMEA (39, 55)

Rank	**Criteria**
1	Nearly impossible or failure highly unlikely e.g. 1 in 150,000
2	Low/relatively low or few failures likely e.g. 1 in 15,000
3	Medium number of failures likely or moderately high e.g. 1 in 400
4	High number of failures like or repeated failures e.g. 1 in 20
5	Very high or extremely high or failure almost certain e.g. 1 in 3

Table 6 Severity (S) ranking of failure modes for FMEA (39, 55)

Rank	**Criteria**
1	Very low effect on product or system performance
2	Small effect on product performance or minor negative impact on the product
3	Product performance is degraded. Comfort or convince functions may not operate. Possible product complaint, product batch rejection, rework/reprocessing.
4	Product is inoperable with loss of primary function. The system is inoperable. Possible multiple product complaint.
5	Failure is hazardous, and occurs without warning. Non-compliance with statutory regulations. Product recall required.

Table 7 Detection (D) ranking of failure modes for FMEA (39, 55)

Rank	**Criteria**
1	Controls or design of control have a very high probability to detect potential cause of failure or subsequent failure mode.
2	Has moderately high effectiveness the design control for detect a potential cause of failure or subsequent failure mode.
3	Has moderately low effectiveness the design control for detect a potential cause of failure or subsequent failure mode
4	Has lowest effectiveness or remote chance the design control for detect a potential cause of failure or subsequent failure mode.

5	Design control will almost certainly does not detect the existence of a potential cause of failure or subsequent failure mode or there is no system control.

3.4 Step 4: Risk evaluation

3.4.1 Risk priority number

Risk assessment team evaluated the identified risks, quantified as risk priority number (RPN) which was calculated by multiplication of occurrence, severity and detectability values (equation 1).

RPN = Severity x Occurrence x Detection (O x S x D) (equation 1)

The RPN was used to categorize risk level for setting measures in risk reduction step. Risk level was grouped using the quality risk matrix of Nirmal Kumar and Ajeya Jha (46) (Fig 9): low risk (0-20 RPN score), medium risk (21-60 RPN score) and high risk (61-125 RPN score).

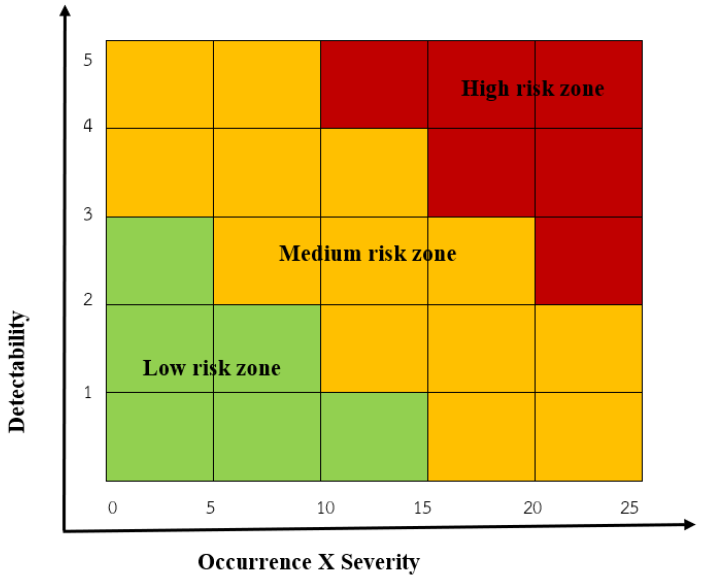


Figure 9 The quality risk matrix

3.5 Step 5: Risk reduction

Risk reduction strategy was examined by author and the risk assessment team by brainstorming based on interdisciplinary team experience and the interview results from national and international GMP inspectors. Risk mitigating approaches were proposed for all of the identified risks. To verify the feasibility of this risk assessment study, selected solutions of the highest RPN value were implemented in routine work before re-assessment. The new practices implementation period was approximately four weeks. Re-assessment was considered using FMEA tool as in section 3.3.1 by risk assessment team. New PRN values were defined by rating O, S, D values and scoring as RPN (equation 1).

CHAPTER IV

RESULTS AND DISCUSSION

The results and discussion were described based on the principles of quality risk management Q9 to assess the risk of desktop inspection system and separated into four part: (4.1) pre-assessment (4.2) risk identification (4.3) risk analysis and risk evaluation (4.4) risk reduction.

4.1 Pre-assessment

4.1.1 Set up the risk assessment team

The risk assessment team consisted of five interdisciplinary people (7) working in the division of GMP inspection and drug product registration system from Thai FDA and having at least three years of qualified experience, namely; (i) the delegate from GMP inspection of overseas pharmaceutical manufacturers sub-committee under drug committee of drug act B.E. 2510, having ten years' experience (ii) the delegate from drug quality defect working group, having seven years' experience (iii) lead GMP inspector, having eight years' experience (iv) reviewer from the drug registration unit, having four years' experience and (v) the delegate from manufacturers licensing unit, having five years' experience. Brainstorming with team-based discussion were mainly used for all assessments in the following parts; identifying risks with failure mode consequences/effects, ranking the risk priority number value and re-assessing the risk level after implementation of risk reduction approaches (39, 49).

4.1.2 GMP desktop inspection situation

GMP desktop inspection perform by GMP inspectorate unit of Bureau of Drug Control, Thai FDA. Therefore, all the information resource of this study was collected from Thai FDA desktop inspection database. The data collection was conducted between January 2016 – December 2018, consecutively, to analyze the inspection situation trends. The reason of the chosen time period is to match with the current regulation which was implemented in 2017 and used for regulation gap analysis in risk identification section (the following section). Data collection of GMP desktop inspection of overseas pharmaceutical manufacturers is a good representative of the past and present situations which can be useful for performing

risk analysis and risk evaluation steps in the aspect of ranking the occurrence and severity score rationally. The results were reported in terms of number of overseas manufacturers under GMP desktop inspection during 2016-2018, number of overseas manufacturers categorized by type of manufacturer and by dosage form.

4.1.2.1 Overview of GMP desktop inspection

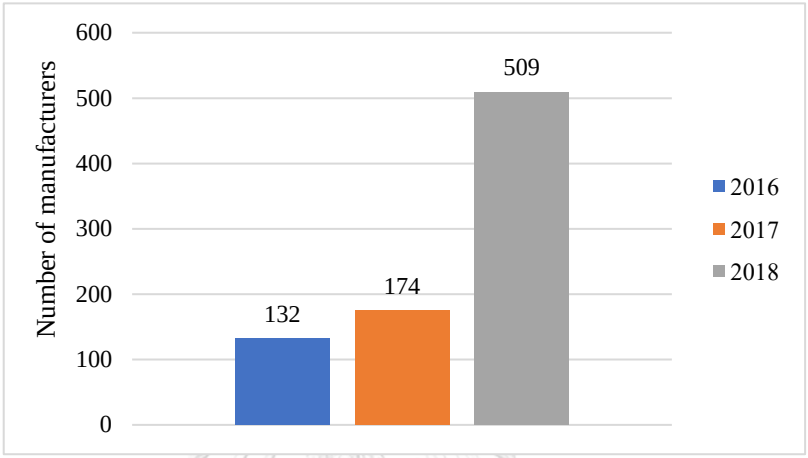


Figure 10 Number of overseas manufacturers under GMP desktop inspection during 2016-2018

Licensees have submitted application continuously to the Thai FDA for inspection as shown in Figure 10 from the increasing number of overseas pharmaceutical manufacturers. It was clear that the number of manufacturers increases significantly from 2016 to 2018, more than three-folded from 2016, suggesting that the number can be continuously increasing due to an economic growth, thus the strict and effective regulation enforcement for all imported pharmaceutical products will be required. In addition, there was a Thai FDA notification in 2017 announcing that the licensees who had imported product approved prior to the regulation enforcement in 2012 must submit the inspection application to Thai FDA within 2020 (2). A large number of overseas pharmaceutical manufactures may be increasing considerably by 2020, therefore, desktop inspection system should be verified to ensure the high quality of inspection of GMP compliance status of overseas manufactures including production process and product quality assurance. The assessment system should be proved to be reliable,

efficient and be able to screen only the qualified manufactures that meet standards for drug registration and importing pharmaceutical products into Thailand.

4.1.2.2 GMP desktop inspection situation categorized by type of manufacturer

It is widely accepted that the PIC/S GMP guideline of PIC/S organization is highly international standard and extensive implementation. Many GMP inspectorate units of drug regulatory authority in the world became a PIC/S member and implemented PIC/S GMP guideline in their own countries including Thailand whereas some were not. Type of overseas manufacturer could imply different levels of quality or reliability of GMP compliance, in other words, non-certified manufacturers may require more close monitoring and detailed inspection than the PIC/S-certified ones as inspected and approved by PIC/S participating authorities before. Here, the manufacturers were categorized into three types:

1) The overseas manufacturers located on a site within jurisdiction of a PIC/S participating authority e.g. those located in EU countries, UK or USA.

2) The overseas manufacturers located outside jurisdiction of a PIC/S authority but certified by PIC/S authority (certified by PIC/S) e.g. those located in India or China and inspected by PIC/S member. This type in Table 8 was categorized in PIC/S manufacturer when analyzed in Table 10.

3) The overseas manufacturers located outside jurisdiction of a PIC/S authority and not certified by PIC/S authority (non-PIC/S) e.g. those located in India or China and never inspected by PIC/S member.

Results of the number of overseas manufacturers categorized by type of manufacturer are provided in Table 8.

Table 8 Number of overseas manufacturers under GMP desktop inspection categorized by type of manufacturer

Manufacturer type	2016		2017		2018	
	Number (sites)	%	Number (sites)	%	Number (sites)	%
PIC/S manufacturer	93	70.5	136	78.2	352	69.2
Certified by PIC/S manufacturer	32	24.2	31	17.8	149	29.3
Non-PIC/S manufacturer	7	5.3	7	4.0	8	1.6
Total	132	100.0	174	100.0	509	100.0

According to the three years situation (Table 8), the majority of manufacturers (up to 95%) was PIC/S and certified by PIC/S and approximately 70% was PIC/S manufacturers. On the other hand, the number of non-PIC/S manufacturers was in a very small proportion and decreased steadily over the period of study. The number of PIC/S and certified by PIC/S manufacturer can imply a good quality of inspection system which is the same as standard used in local manufacturer. Such manufacturers will be enforced the PIC/S guidelines throughout the product life cycle that equivalent to domestic manufacturers. It suggests that the imported products from PIC/S and certified by PIC/S manufacturers potentially have proper quality and standardization. It is of note that, still, there have been a few of non-PIC/S manufacturer appeared in the inspection system. Implementing desktop inspection with this type of manufacturer should be taken into consideration due to the fact that these manufacturers may have deviated GMP standards based on their own quality system criteria and internal inspectors which were from different levels of authorized inspectorate units such as prefecture-level, provincial/state-level or central national authorized.

4.1.2.3 GMP desktop inspection situation categorized by dosage forms

Manufacturing sites can be categorized by the dosage forms produced, namely, non-sterile, sterile and biological products (Table 9). Production of these dosage forms have different critical points, for example; specific production process of vaccine, in-process control step of tableting process, clean room classification and environmental monitoring of sterile filling area, leading to different strictly regulating. In addition, sterile product and biological product are different in term of source of origin: sterile product is from chemical compound whereas biological product is from biological substance.

Table 9 Number of overseas manufacturers categorized by dosage forms

Manufacturer type	2016		2017		2018	
	Number (sites)	%	Number (sites)	%	Number (sites)	%
Non-sterile manufacturer	80	60.6	97	56.1	280	55.0
Sterile manufacturer	31	23.5	52	30.1	140	27.5
Biological manufacturer	21	15.9	24	13.9	89	17.5
Total	132	100.0	173	100.0	509	100.0

The same trend were found in 2016-2018. It is apparent that the number of non-sterile manufacturer had more than half proportion, and was three-fold of the biological manufacturers. This might be because non-sterile products are very common among treatments and have no complexation production process, thus no complicated regulation of manufacturing. In the meantime, sterile and biological manufacturers are minority in the inspection system but they have a complexity of manufacturing processes and are difficult to control the quality of product such as filter integrity validation in filling process of aseptic preparation of sterile product needs additional GMP requirement. More importantly, microbial contamination may cause by the noncompliance GMP manufacturer which then can be fatal as most products of the last two groups are delivered directly into the blood circulation. Therefore, the desktop inspection system shall ensure that the required documents

can cover a wide range of activities running for the production of these three different dosage forms.

4.1.3 Quality defect of import product analysis

The product quality defect can be directly reflected by the number of product complaints and product recalls that are monitored by the Bureau of Drug Control, Thai FDA. The analysis of complaints and recalls can be useful for supporting the risk analysis and risk evaluation steps in the aspect of ranking the occurrence and severity score rationally. The complaint is an important indicator that represents the quality defect of pharmaceutical products.

Regarding quality defect management of the Thai FDA, there are many pathways to receive complaints, for example, from consumers and healthcare unit (like the hospital, drug store, private clinic) including other departments under ministry of public health (such as Department of Medical Sciences, Department of Disease Control and provincial health office). Many serious complaints, reported as harmful and life-threatening to human or veterinary, may lead to recalling the product from the market. Consequently, recall is another important indicator of drug quality problem. The categorization of rapid alert and recall system in Thailand classifies to two class: voluntary recalls by licensee and mandatory recalls by the Thai FDA. The recall process of both import and local drug products is similar; however, only mandatory recalls is advertised on website (56). In addition, all of the complaint or recall reports have to be investigated in terms of causes, corrections, corrective actions and preventive actions by manufacturers and licensees.

The results of complaints and recalls analysis were presented in the topic of the number of reports, dosage forms, classification and cause.

4.1.3.1 Overview of complaints and recalls situations

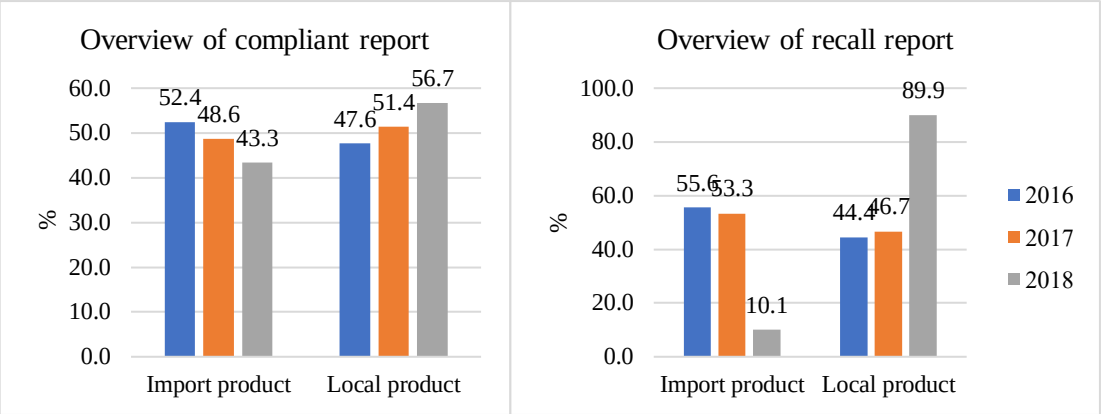


Figure 11 Overview of number of complaint report and recalls report

Figure 11 showed the overview of complaint and recall situations in 2016-2018 as the percentage, calculated by the total number of the imported and local products each year. Local product was compared with import product that produced by overseas manufacturer. The number of complaints and recalls can reflect the quality system of pharmaceutical manufacturers including the regulatory inspection system. Interestingly, in 2016-2017, imported products were reported to have more recalls than local product which was inspected by on-site inspection (55.6% (in 2016) and 53.3% (in 2017) of the total recalls from imported products), reflecting that higher defects of product quality in imported products. The limitation of data collection here is the total number of both products inspected cannot be clearly identified, therefore, the quality and reliability of both inspection system cannot be confirmed. Nevertheless, the highest percentage of 89.9% of total reports (equal to 80 recall reports of local products) were found in 2018 because Thai FDA commanded a withdrawal all marketing authorization of the generic drug name “Serratiopeptidase” from the market due to lack of scientific information for treatment as mandatory recalls as 57 of 80 recall reports (64.04% of total reports), so the data collection in this year was not a good representative for the general situation of the country.

4.1.3.2 Categorization of complaints and recalls by type of manufacturer

Table 10 Number of complaint and recall reports categorized by type of manufacturer

Manufacturer type	Number of complaints (cases)			Number of recalls (case)		
	2016	2017	2018	2016	2017	2018
PIC/S certified manufacturer	11 (50.0%)	12 (66.7%)	8 (61.5%)	5 (33.3%)	3 (37.5%)	5 (55.6%)
Non-PIC/S certified manufacturer	11 (50.0%)	6 (33.3%)	5 (38.5%)	10 (67.7%)	5 (62.5%)	4 (44.4%)
Total	22 (100%)	18 (100%)	13 (100%)	15 (100%)	8 (100%)	9 (100%)

Table 10 compared the number of complaints and recalls of import products under PIC/S and non-PIC/S certified manufacturers. A surprising correlation was found, the number of complaints from PIC/S certified manufacturers was much higher than that of non-PIC/S manufacturers in 2017-2018, this could be because the majority (>90%) of the overseas sites inspected was PIC/S certified manufacturers as shown in section 4.1.2.2. This also suggested that although manufacturers are inspected by PIC/S member that follows international standard as PIC/S GMP, complaints could still occur.

On the other hand, recalls reflect worse quality system than complaints. The majority of recalls was found from non-PIC/S manufacturers except in 2018. This highlighted that the desktop inspection of each type of overseas manufacturers should be highly taken into account especially non-PIC/S manufacturers type. However, until now, the ratio of inspected non-PIC/s manufacturers has been very low (Table 8: 2016: 5.3%, 2017: 4.0%, 2018: 1.6%). Therefore, careful inspection along with specific control system to this type of manufacturers should be taken action continuously.

4.1.3.3 Categorization of complaints and recalls by dosage forms

Table 11 Number of complaint and recall reports categorized by dosage form

Product type	Number of complaints (cases)			Number of recalls (cases)		
	2016	2017	2018	2016	2017	2018
Non-sterile	8 (36.4%)	6 (33.3%)	6 (46.2%)	2 (13.3%)	2 (25.0%)	4 (44.4%)
Sterile	9 (40.9%)	8 (44.4%)	4 (30.8%)	3 (20.0%)	4 (50.0%)	4 (44.4%)
Biological	5 (22.7%)	4 (22.2%)	3 (23.1%)	10 (66.7%)	2 (25.0%)	1 (11.1%)
Total	22 (100%)	18 (100%)	13 (100%)	15 (100%)	8 (100%)	9 (100%)

To understand the complaints and recalls clearly, data was analyzed by categorizing to three groups of dosage form (non-sterile, sterile and biological product) because each form has characteristic production lines, product characteristic and different critical points for site inspection. It can be seen that the number of complaints and recalls in each dosage form was relatively low, not more than 10 cases were found in each year. However, there are some limitations of this data collection, at present, it is not likely to know the total number of drug products that were approved and available on market for each product type in each year. Therefore, the reported cases were presented as the number of cases and were calculated as the percentage from the total cases of the three product types. The highest percentage of complaints was sterile products found in 2016 and 2017 (40.9% and 44.4% respectively) and non-sterile products (46.2%) as in 2018, however; the proportion of biological remains stable for three years. Besides, there were no clear trends of the number of recall reports, all product types could have been

recalled suggesting that the more complicated production processes used in sterile and biological products are possible to cause product recalls as the less complicated production processes ones as in non-sterile products. Surprisingly, there were 10 recall reports (or 66.7% of total reports) found from biological products in 2016, this is because the licensee has taken voluntary recalls of the 6 cases (out of 10) without quality defect problem for the trivalent OPV (t-OPV) vaccine, following the recommendation from WHO.

Overall, recalls number is less than complaint number in each product types, implying that serious cases of recalls have occurred less frequently and criteria of desktop inspection should be generalized to cover all product types. Although the higher percent of complaints and recalls in 2018 were non-sterile products, most defect problems of this dosage form have low harmful risk when compared to sterile products. Thus, it would be important to investigate causes of defect which are discussed in the following section.

4.1.3.4 Categorization of complaints and recalls by causes of defect

There are many causes of product complaints and recalls which have a direct or indirect impact to quality of product. All of the complaints and recalls analyze the root causes of problem, correction, corrective action and preventive action by overseas manufacturer. The reasons of product complaints and recalls were investigated and categorized to five main concerns including manufacturing process-related, transportation or distribution-related, storage procedure-related, source of API and other causes (e.g. incorrect use by patient or healthcare providers which are not related to GMP). However, there are some limitations of this data collection which are similar to the previous section (4.1.3.3). The number of causes of complaints and recalls was presented as number cases and percentage (Table 12). The results in this section can be useful to identify the weakness of product life cycle, to support risk analysis step and to structure general principles of documents review.

Table 12 Number of complaint and recall report categorized by causes of defect

Causes	Number of complaints (cases)			Number of recalls (cases)		
	2016	2017	2018	2016	2017	2018
Manufacturing process	12 (54.5%)	8 (44.4%)	7 (53.8%)	5 (33.3%)	3 (37.5%)	6 (66.7%)
Transportation	2 (9.1%)	1 (5.6%)	3 (23.1%)	0 (0.0%)	2 (25.0%)	0 (0.0%)
Storage	1 (4.5%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (11.1%)
Source of API	1 (4.5%)	3 (16.7%)	0 (0.0%)	2 (13.3%)	3 (37.5%)	1 (11.1%)
Other causes	6 (27.3%)	5 (27.8%)	3 (23.1%)	8 (53.3%)	0 (0.0%)	1 (11.1%)
Total	22 (100%)	18 (100%)	13 (100%)	15 (100%)	8 (100%)	9 (100%)

A majority of both complaints and recalls were caused by manufacturing process-related issues, for example; out of specification of finished products, impurities contamination in closed container, black spot contains in vial or ampoules of injectable product, dissolution problem during on-going stability study, mix-up contamination including the failure of utility support system as the HVAC system in a sterile cleanroom, which could be inspected by document inspection with batch processing record, stability study report or qualification and validation report. Interestingly, the number of recalls caused by manufacturing process-related increased sharply in 2018 (66.7% of total recall reports). Concerning API issues, although a minority of complaints and recalls was the source of API like impurity of

raw material, it still occurred and a high number of recalls was found in 2017 (37.5%). Another explanation for the high recalls number (53.3%) in 2016 was due to incorrect use by patient or healthcare providers that is not related with product quality problem. Therefore, it indicated that the desktop inspection of overseas manufacturers should be highly taken into account in terms of manufacturing process while the issues of API manufacturer, transportation and storage could not be ignored.

4.1.3.5 Categorization of recalls by type of recalls

The classification by using the criteria of law enforcement for recalls are voluntary and mandatory recalls. The voluntary recalls are called when the licensee or manufacturer finds the problem that does not meet in-house specification and regulation which may be associated with product quality, may be harmful to customers or may have some cosmetic defect related with company reputation, then the company reports to the Thai FDA voluntarily without compulsion. Contrastly, the mandatory recalls are applied when the medicinal products have quality problem, are found as non-complied with marketing authorization leading to significant risk and harm to patients, then are recalled by the Thai FDA.

Table 13 Number of recall reports categorized by type of recalls

Type of recalls	2016		2017		2018	
	Reports	%	Reports	%	Reports	%
Voluntary recall	11	73.3	6	75.0	6	66.7
Mandatory recall	4	26.7	2	25.0	3	33.3
Total	15	100	8	100	9	100

As shown in Table 13, the voluntary recalls had approximately three-fold as the mandatory recalls. This suggested that the overseas manufacturers and licensees had a proper mechanism of rapid alert system for control and monitoring the quality of products which then represented a good responsibility for consumers protection by the companies, themselves. By contrast, a minority of mandatory recalls were

steady. Thus, the monitoring system should be continuously maintained to ensure product quality.

Overall, the aforementioned data was collected and analyzed to understand background information of drug products, product quality and product defects which have a direct and indirect relationship with the inspection of production sites, thus could be applied to support the following steps of risk assessment: risk analysis and risk evaluation as discussed in section 4.3.

4.2 Risk identification

In this section, risk identification was demonstrated in two aspects, namely, analysis of regulation gap among six countries/organizations and workflow of desktop inspection in GMP Inspectorate Unit of Thai FDA and used as supportive data for identifying potential risk during team brainstorming. The differences in the regulation from the other five countries/organizations and the weak points of routine workflow were listed to discuss with the team to finalize the identified risks.

4.2.1 Risk identification by regulation gap analysis

GMP desktop inspection system were compared between Thailand and the five globally-selected countries/organizations in three points which were 1) objectives, principles and scope, 2) implementation and supervision and 3) regulatory contents (50). A list of selected countries/organizations was Singapore (51), Malaysia (52), Australia (53), WHO (5) and PIC/S (54). As shown in Table 14, the five countries/ organizations followed the four criteria set up in the method section (3.2.1). Furthermore, as of PIC/S accession and PIC/S GMP standard implementation, Australia firstly became a PIC/S member and in the top twenty from approximately fifty countries. Meanwhiles, Singapore and Malaysia's authorities became a PIC/S member approximately a decades before Thailand. This may imply that these three countries could be a good model to apply to Thailand and consult with their inspector due to the long experiences in the field, more stable, stricted and verified system may be learnt and implemented by those three countries.

Table 14 The comparison of general information of six selected countries/ organizations

Topics	Thailand	Singapore	Malaysia	Australia	WHO	PIC/S
1. Executing agency	Thai FDA	HSA*	NPRA*	TGA*	WHO	PIC/S
2. Supervising organization	Thai FDA	HSA	NPRA	TGA	By each NRA*	By each NRA
3. Accession to PIC/S	August 2016	January 2000	January 2002	November 1995	-	-
4. Assessor	Inspector	Inspector	Inspector	Inspector/ Assessor	Inspector	Inspector
5. Supervising to the site	Overseas site	Overseas site	Foreign site	Overseas site	Overseas site	Overseas site
6. Mode of execution	Compulsory	Compul-sory	Compulsory	Compulsory	Guideline	Guideline

*Remark;

HSA = Health Sciences Authority

NPRA = National Pharmaceutical Regulatory Agency

TGA = Therapeutic Goods Administration

NRA = National regulatory authority

4.2.1.1 Risk identification in the regulation principles, objectives and scope

This topic was analyzed in 5 sub-topics as summarized in Table 15. Regarding the regulation principle of desktop inspection from all selected organization, it was defined in the same way to ensure the quality of imported products from overseas pharmaceutical manufacturers having the same standard requirement as domestic manufacturers before approving the marketing authorization. Secondly, concerning the objective of inspection regulation, the content of Thailand system showed clear objectives and combined key content from the global aspects, covering two points which are to assess the manufacturers located outside country complies with own GMP standard and to ensure quality, efficacy and safety of the imported products as described by other five countries/organizations. Therefore, no clear gap was found in these two topics.

Table 15 The comparison of regulation principles, objective and scope of six selected countries/ organizations

Topics	Thailand	Singapore	Malaysia	Australia	WHO	PIC/S
1. Regulation principles	For consumers protection and to ensure that all imported products manufactured by overseas manufacturers comply with PIC/S GMP same as local manufacturers	Manufacturers importing medicinal products to Singapore are subjected to GMP conformity assessment, the overseas manufactures must be conformed to PIC/S GMP	To require the standard of manufacture and quality control of medicinal products manufactured outside Malaysia considered before the products are registered with the local authority	To enforce sponsors of a medicine or API that is manufactured overseas if there is acceptable evidence demonstrating that the overseas manufacturer complies with the principles of GMP for products registered	To verify and confirm GMP compliance of a manufacturer of products in foreign country based on the assessment of evidence of GMP compliance that includes recent inspection of the manufacturer by a competent regulatory authority	To confirm GMP compliance of overseas manufacturers by desktop inspection, if appropriate, the NRAs not require onsite inspection to avoid repetitive work, reduce regulatory burden and allow more efficient deployment of global inspection resources
2. Regulation objectives	To assess the manufacturers of medicinal products located outside of Thailand complying with PIC/S GMP and to ensure quality, efficacy and safety of the imported products	To assess the manufacturers of medicinal and/or therapeutic products located outside of Singapore by acceptable GMP evidence	To assess the conformance of foreign manufacturers to GMP requirements and ensure quality and safety of the imported products that are registered or in the process of registration/re-registration/change of manufacturing site with NPRA of Malaysia	To ensure the safety, quality, efficacy and timely supply of therapeutic goods of overseas manufacturer for Australian consumers	The guidance for NRAs to assess GMP confirmation using desk assessment, thus reducing repetitive work and frequency of inspections while relying on original and reliable documentary evidence from other regulatory authorities	The guidance for remote assessment of GMP compliance of overseas manufacturers where an acceptable level of GMP compliance can be confirmed and assured from the activities of another regulatory authority without onsite inspection

3. Scope of products	Finished products	Finished products	Finished products	- Active pharmaceutical ingredient (API) - Finished products - Contract testing laboratories or contract sterilizers	- Active pharmaceutical ingredient (API) - Finished products - Contract testing laboratories/contract sterilizers - Contract research organizations /clinical trial sites	Applied by National Competent Authority (NCA)
4. Type of products	Human and veterinary	Human	Human	Human	Human	Applied by NCA
5. Full name of regulation/ guideline	GMP clearance of overseas pharmaceutical manufacturer under The Drug Act	GMP conformity assessment of an overseas manufacturer under The Medicines Act and Health Products Act	Guidance document foreign GMP inspection under The Control of Drugs and Cosmetics Regulations (CDCR)	GMP clearance guidance under The Therapeutic Goods Act	Guidance on good practices for desk assessment of compliance with good manufacturing practices, good laboratory practices and good clinical practices for medical products regulatory decisions	Guidance: GMP Inspection Reliance

In terms of the products enforced by desktop inspection, all selected agency implemented the scope for finished products similarly; however, there was one main difference found. The scope of products inspection (Table 15), implemented in Thailand enforced only finished product, not covering all of the site activities like stated by Australia and WHO. Manufacturers should be categorized as the risk of the product including API (non-sterile and sterile), finished product (non-sterile and sterile) and contract testing laboratories or contract sterilizers that directly relate to the quality of product (e.g. API site or contract laboratory site). Narrow product scope may lead to some quality defect of product, for example, if API manufacturers fail the GMP compliance in the synthesis processing or quality control/quality assurance, it can cause a quality defect of final product such as toxic drug residues which can be harmful to patients. Therefore, this scope could be a significant gap of Thailand's regulation.

4.2.1.2 Risk identification in the implementation and supervision

Table 16 The comparison of implementation and supervision of six selected countries/ organizations

Topics	Thailand	Singapore	Malaysia	Australia	WHO	PIC/S
1. Renewal inspection	Only initial inspection	Re-inspection	Re-inspection	Renewal inspection	Renewal assessment	Maintain inspection

There could be another risk under the topic of renewal assessment due to single inspection at initial in Thailand desktop inspection system. This can directly affect product quality and reliability of Thailand's desktop inspection system. In the meantime, all other counties/organizations perform a re-inspection and maintain GMP compliance status throughout the remaining of the marketing authorization. Therefore, submitting applications for renewal of a GMP complying should be implemented prior to the invalid of the approval desktop inspection period in Thailand as on-site inspection of domestic manufacturers which is generally performed every one to three years depending on inspection results.

4.2.1.3 Risk identification in the regulation contents

Lists of documents for inspection were compared and discussed (Table 17) into four groups of overseas manufacturers. These four groups were divided as the criteria of the international mutual agreement and site location as the followings:

1) The “MRA manufacturers”, located in country under the international mutual recognition arrangement (MRA) (e.g. those located in ASEAN countries which under the ASEAN sectoral mutual recognition arrangement for GMP inspection of medicinal products or those located in EU countries, New Zealand or Singapore that had the mutual recognition arrangement with Australia).

2) The “PIC/S or WHO PQ manufacturer”, located in the jurisdiction of PIC/S member or certified by WHO prequalification (WHO PQ) team (e.g. those located in EU countries, UK, USA, Australia and other counties coming to PIC/S member from all over the world (Europe, Africa, America, Asia and Australasia) or those located wherever with certified by WHO prequalification team).

3) The “certified by PIC/S manufacturers”, outside of the jurisdiction of PIC/S member but inspected by PIC/S member (e.g. those located in India or China and inspected by PIC/S member).

4) The “non-PIC/S or non-WHO PQ certified manufacturers”, outside of the jurisdiction of PIC/S member and never inspected by PIC/S member or WHO prequalification team (e.g. those located in India or China and never inspected by PIC/S member or WHO PQ team).

Table 17 The comparison of regulation contents of six selected countries/ organizations

Item	Document requirement	Thailand	Singapore	Malaysia	Australia	WHO	PIC/S
1. MRA manufacturer	GMP Certificate	√	√	√	√	√	√
	GMP inspection report	√		√			√**
	CAPA report	√					
	GMP/Quality Agreement	√					
2. PIC/S or WHO PQ manufacturer	GMP Certificate	√	√	√	√	√	√
	GMP inspection report	√		√	√	√	√**
	CAPA report	√				√	
	GMP/Quality Agreement	√			√*	√*	
	Regulatory action details				√	√	
	Regulatory inspections list				√	√	
	List of products intended for supply / List of tests a laboratory				√	√*	
	Site Master File (SMF)/Quality Manual				√	√	
	Release procedure				√*	√	
	Validation master Plan (VMP)				√*	√*	
	Product Quality Review (PQR)				√*	√*	
	Manufacturing license					√	
	Market complaints register					√	
	Process validation report and Batch records					√*	

	List of reprocessed or reworked product batches in last year					√*	
	Out-of-specifications (OOS) procedure					√*	
3. The certified by PIC/S manufacturers	GMP Certificate	√	√	√	On-site inspection	On-site inspection	√
	GMP inspection report	√		√			√**
	CAPA report	√					Depend on each NRA
	GMP/Quality Agreement	√					
	Site Master File (SMF)	√					
4. The non-PIC/S or non-WHO PQ certified manufacturers	List of documentation	GMP assessment or on-site inspection	On-site inspection	On-site inspection	On-site inspection	On-site inspection	Depend on each NRA

Remark: * = Require by type of manufacturer, ** = And/or

Four points were discussed according to the individual groups of overseas manufacturers.

1) Risk identification in the regulation contents implemented for MRA manufacturers

Thailand requests four GMP documents from an overseas pharmaceutical manufacturer which are more than other countries and cover several aspects of production process and product quality. Interestingly, Singapore generally requires only GMP certificate but will require additional documents if questionable product quality and reliability occur. There should not be any risks occurring in desktop inspection of Thailand for MRA manufacturer system because more stricted and additional three documents are required for submission. At the same time, Thailand may reconsider to request less number of documents or only GMP certificate to save inspection resources as implemented in Singapore, Australia, WHO and PIC/S (Table 17). Moreover, the reduced documents lead to reduced inspection time and the best use of inspection resources.

2) Risk identification in the regulation contents implemented for PIC/S or WHO PQ manufacturer

Four documents are required in Thai's regulation, which are more number than required in Singapore and Malaysia but are less number than required in Australia and WHO, while equal to the document requirement set by PIC/S guideline in the case of the manufacturer having questionable product quality and reliability. These findings lead to a significant gap. As summarized in Table 18, Australia's regulation points out the criteria of required documents for submission by firstly dividing type of manufacturers into five groups due to different risks in each type.

Table 18 Required documents of Australia's regulation for desktop inspection

Type of manufacturers	Required document
1. API non-sterile manufacturer	1. GMP certificate 2. GMP inspection report 3. List of products intended for supply 4. Regulatory action details 5. Regulatory inspections list 6. Site master file/Quality manual.
2. API sterile manufacturer	Two additional documents from type 1 (above) 1. Validation master plan (VMP) 2. Product quality review (PQR)
3. Finished product of non-sterile manufacturer	Two additional documents from type 1 (above) 1. GMP agreement 2. Release product for supply procedure
4. Finished product of sterile manufacturer	Two additional documents from type 1 (above) 1. VMP 2. PQR 3. GMP agreement 4. Release product for supply procedure
5. Contract testing laboratories or contract sterilizers	1. GMP certificate 2. GMP inspection report 3. GMP agreement 4. Regulatory action details 5. Regulatory inspections list 6. SMF or equivalent 7. List of authority's tests

According to the document sets, it can be seen that the complicated manufacturing process like sterile site requires additional documents for evaluation e.g. API-sterile manufacturers require more documents than API non-sterile

manufacturers. More specific and detailed data could be provided and inspected from the wider range of documents required, subject to the risk of product types. These characteristic criteria may be developed from the lessons learnt in Australia as they have longer experienced in the desktop inspection than the other five countries as mentioned in the section of 4.2.1; therefore, identifying risks by comparing regulation content with Australia's could be beneficial to Thailand.

Table 19 Required documents of WHO's guideline for GMP desktop inspection

Type of manufacturers	**Required document**
1. API and finished products of non-sterile facilities	1. GMP certificate 2. Manufacturing license 3. Regulatory inspections list last three year with GMP inspection and CAPA report 4. List of market complaints register and one complaint report 5. Regulatory action details last three years 6. SMF/Quality manual (QM) 7. List of products intended for supply 8. PQR report 9. Process validation report 10. Batch records 11. List of reprocessed or reworked product batches in last year
2. API and finished products of sterile facilities	Two additional documents from type 1 (above) 1. VMP 2. Aseptic processing and filling validation reports for aseptic processing only
3. Outsourced testing laboratory and outsourced sterilization	1. GLP certificate or ISO/IEC certificate 2. QM or equivalent 3. Contract agreement 4. List of tests a laboratory was authorized to perform 5. Out-of-specifications procedure

In addition, WHO sets the required documents subject to the product types and their risk as in Australia. However, the difference is categorization as seen that WHO focuses mainly on non-sterile and sterile types with no separation between API and finished product (Table 19). Another difference is WHO requires more documents (such as market complaints report, out-of-specifications procedure, list of reprocessed product batches in last year), suggesting the stricted and tense inspection. From the criteria of required document under Australia' and WHO regulation, it can strengthen that categorizing the product types due to their risk before setting the required documents may be useful and raise the standard and reliability of desktop inspection.

To summarize, one potential risk can be caused by the same set of documents required by any product types produced by PIC/S and WHO PQ manufacturers. Categorization due to the product types and their risks should be done before setting the required documents as stated in Australia' and WHO regulations. More than four documents may be needed for the complicated production process like in aseptic technique used for sterile products while less than four documents may be applied to the products with low quality risk to save inspection resources.

3) Risk identification in the regulation contents implemented for certified by PIC/S manufacturers

In Table 17, Thailand's regulation requested five documents which are more items than the previous two types (MRA and PIC/S or WHO PQ manufacturers) and more than requested in Singapore and Malaysia. On the other hand, Australia and WHO perform an on-site inspection for this kind of manufacturers to visually observe manufacturing operations and GMP compliance practices and to closely ensure the quality of the inspection by claiming that desktop inspection is unable to verify GMP compliance status. While PIC/S does not specify any requirement for these types and leaves NRA to decide by themselves.

A gap was found in the aspects of conditional on-site inspection for the certified by PIC/S manufacturers in Thailand. This could be an important risk due to the fact that the certified by PIC/S manufacturers do not have a regular inspection, in other word, have an inspection by PIC/S team one time at initial without re-inspection like in the country of PIC/S members or WHO PQ team. Therefore, the quality standard throughout product life cycle cannot completely guaranteed.

4) Risk identification in the regulation contents implemented for non-PIC/S or non-WHO PQ certified manufacturers

The most surprising aspect of this type of manufacturer is that only Thailand mainly has the desktop inspection pathway for non-PIC/S manufacturer and non-WHO PQ certified manufacturer but will conduct an on-site inspection when 1) the inspection results are questionable in terms of quality and reliability or 2) non-equivalent with PIC/S standard, as implemented in domestic manufacturers, is spotted in submission documents. Although the regulation describes the criteria and pathway to on-site inspection, the additional required documents from the previous type of manufacturers (MRA, PIC/S or WHO PQ certified manufacture) are 8 items, namely,

(i) quality manual,

(ii) regulatory action details last five years,

(iii) list of products intended for supply and list of approved products from Thai FDA (if there is),

(iv) batch processing records and batch analysis record,

(v) standard operating procedure of release product for supply,

(vi) validation master plan and process validation report,

(vii) national/local GMP guideline and

(viii) list of documentation/picture of manufacturing process following the Thai FDA checklist.

On the contrary, the other 4 countries/organization perform only an on-site inspection with this type of manufacturers. This gap indicates that those agencies are not confident of GMP compliance of non-PIC/S or non-WHO PQ certified

manufacturers, assume that the GMP standard of this type of manufacturers is not equivalent to the one implemented in their own country and do not accepted desktop inspection pathway. The different inspection system is a very strong significant gap of Thailand's regulation. This pointed out the lack of on-site inspection throughout the product life cycle which may cause some quality issues inspected by internal inspectors. Deviated GMP standards and quality bias may probability occur in non-PIC/S GMP manufacturers since individual criteria of each authority and be inspected their own facilities by different levels of authorized inspectorate unit e.g. central inspectorate unit, state inspectorate unit, provincial or prefecture sub-unit, which may lack of inspection standardization when compare with the PIC/S member and WHO PQ team.

Overall, there are five gaps found in the regulation gap analysis. These could then be important risks which impact to the quality and reliability of the Thai FDA's desktop inspection system and effect on quality, efficacy and safety of the drug products as mentioned in the regulation objectives of Thailand. Nevertheless, all of the key findings from data analysis, here, would be brought to the team meeting to ensure that the gaps found in this section should be considered as the risks of desktop inspection in Thailand which would be further analyzed in the step of risk analysis and risk evaluation.

4.2.2 Risk identification by workflow analysis

Workflow for GMP desktop inspection is present in Figure 12. There are two main parties (licensee and Thai FDA staff) in desktop inspection network. Investigating the relationship between responsible persons, role and timeframe of the work was performed to understand the gap of the desktop inspection system. Three topics were discussed to identify the potential risks.

Responsible person	Work activity	Timeframe
Licensee/company	Step 1: Prepare the required documents	-
	↓	
Licensee/company	Step 2: Submit application form with required documents to Thai FDA	-
	↓	
Thai FDA officer	Step 3: Screen completeness of required documents (Accept/Reject)	30 minute/site
	↓	
GMP inspector	Step 4: Perform desktop inspection based on SOP and PIC/S GMP standard	23 - 83 days
	↓	
GMP inspector/ licensee	Step 5: Request additional document/declaration	7 - 14 days
	↓	
Lead GMP inspector or Quality system manager	Step 6: Verify inspection results	6 days
	↓	
Director	Step 7: Approve inspection results	1 days

Figure 12 Thai FDA workflow for GMP desktop inspection

4.2.2.1 An activity of entrepreneurs/licensees

Analysis of entrepreneurs' activities can be relating to the risk that indirectly impact the quality and reliability of desktop inspection system. If unstandardized or incorrect documents are submitted, it may impact the inspection results. Two potential risk are: 1) licensees misunderstand the required documents and 2) licensees submit uncomplete and/or incorrect document.

Firstly, licensees misunderstand the required documents in step 1 due to limited experiences of licensees, inadequate/incorrect data from overseas manufacturers and a large number of required documents. The licensees may unable to contact directly to the site manufacturers but they request the document from the globally-company, third-party company or its affiliates instead, resulting in miscommunication and received incomplete documents. Moreover, the foreign manufacturers (e.g. third-party manufacturers or original equipment manufacturer (OEM)) may hide some confidential data relating to some regulatory inspection deficiencies reported. Secondly, licensees submit uncomplete and/or incorrect documents in step 2 due to lack of understanding in the details of required documents and not having an example/template of each required document. Both potential risks from licensees may lead to rejected the application and delayed drug registration.

4.2.2.2 An activity of Thai FDA officer and inspectors

Several key findings were found from the routine activity analysis leading to the potential risk and impact to inspection process as followings (i) misunderstanding of required documents by officers, (ii) different background experience of GMP inspector, quality system manager and director, and (iii) inspector may not follow SOP.

It can be seen that involve four related persons (an officer, inspectors, lead inspector or QSM and director) involved in receiving and assessing the desktop inspection. Begin with the officer' responsibility, it is possible to receive incorrect or incomplete documents due to misunderstandings of the details of documents. One example of this weakness is that a large number of overseas manufacturers, approximately forty countries (29), intended to register and supply their own medicine products to Thailand, thus a GMP certificate issued by original regulatory authority can be various, not only the template but also important of information details e.g. validity of the certificate, scope of a dosage form which comply to GMP standard and specific remarks or term of conditions. A wide range of these details leads to confusion and accepting incorrect documents.

Meanwhiles, the work-related activities of the GMP inspectors who are responsible for the assessment of GMP compliance of overseas manufacturer potentially brought up two main risks. Firstly, the different background experiences in GMP desktop inspection contribute to the difference in inspection strictness and unstandardized inspection results. Although the inspector's qualification was assessed with the specific training before being authorized to inspection, there could be different perspectives and decisions being made. More experience person tends to have more strictness. Another two-related concerns may be caused by lead GMP inspector/quality system manager (QSM) and director in step 6 and step 7, respectively. The different background experiences of these two persons result in unstandardized inspection result verification and approving non-compliance GMP manufacturers. The second risk is that inspectors may not follow standard operating procedure of desktop inspection due to the fact that some inspectors overlook the procedure and periodic training are not compulsory. Therefore, work practices can be deviated from the SOP and the inspection process may be wrong.

4.2.2.3 The procedure of the inspection system

Inspection procedures can directly impact to quality of assessment results such as lack of stepwise approach to documents review and obsolete internal SOP.

Begin with the internal SOP of inspection process, the weakness was lack of stepwise approach to review the required documents. The SOP contains only process flow, responsible person and lead time as presented in Figure 12. Various practices could be performed for the document review, quality and reliability of inspection results could then be affected, in particular, when a large number of documents is required from the non-PIC/S certified or non-WHO PQ certified manufacturer (section 4.2.1.3: 4)). One example can be seen from the SOP release finished product for supply, the critical points to review should highly focus on the point of how the authorized person ensures each batch is manufactured and compliance with the product license (marketing authorization), and following by how the authorized person ensures how the finished product is released. It indicated that

the review procedure can be very detailed and can be individualized of each document.

The last finding was relating to the documentation control system. According to the PIC/S recommendation on quality system requirements for pharmaceutical inspectorate unit, the quality document should be periodically reviewed, annually updated and maintained a system especially for the documentation relating to inspection system. The SOP's desktop inspection might not be periodically reviewed due to a large number of SOPs (approximately forty SOPs in Post Marketing Control Division) and no alert system to monitor the due date SOP. Therefore, obsolete SOP can cause deviated inspection practices and errors of inspection results.

All in all, risk identification were primarily investigated by applying the analysis of regulation gap and workflow. The 14 potential risks, which tend to affect the quality and reliability of inspection system, were summarized in Table 20. However, to strengthen and identify the specific risks for further investigations, team brainstorming and interviewing international inspectors were performed in the following sections (4.2.3).

Table 20 Potential risks analyzed by regulation gaps and routine workflow of the Thai FDA

Risks
Potential risks analyzed by regulation gap analysis
1. Limited inspection to finished products only
2. Similar required document among non-sterile, sterile and biological manufacturers
3. Desktop inspection for certified by PIC/S member manufacturers
4. Desktop inspection for non-PIC/S or non-WHO PQ certified manufacturers
5. No regulation requirement for renewal/re-inspection of overseas manufacturers
Potential risks analyzed by workflow analysis
1. Licensees misunderstand the required documents
2. Licensees submit uncomplete and/or incorrect required document
3. Misunderstanding the required documents by screening officers

4. Different background experiences of GMP inspectors in performing inspection
5. Difference in background experiences of lead GMP inspector/QSM in verifying inspection results
6. Approved non-compliance GMP manufacturers by director
7. Inspectors may not follow SOP
8. Lack of stepwise approach to review the required document
9. Obsolete internal SOP

4.2.3 Risk identification by national and international GMP inspectors

Potential risks analyzed by regulation gaps and routine workflow of the Thai FDA were further investigated by interviewing by Thai inspector and representatives/ inspectors of selected countries/ organizations. The interview required respondents to comment on all the 14 potential risks, add additional risks, along with suggesting a risk reduction approach.

4.2.3.1 Risk identification by internal interview

All of the Thai GMP inspector interviewees agreed with all the 14 potential risks. However, interviewees suggested three additional potential risks of the workflow analysis. Firstly, the highly probable risk was an unlimited number of applications. The number of overseas pharmaceutical manufacturers increases continuously from 2016-2018 (132 sites in 2016, 174 sites in 2017 and 509 sites in 2018) indicated in pre-assessment data and the management policy allows unlimited number of applications, consequently, the time period required for document screening by Thai FDA officer (in step 3 of Figure 12) will be highly affected. High workload may cause errors such as received incomplete application for inspection. Secondly, the risk was the high workload of the inspector, caused by the increased desktop inspection applications. This may bring about an inspection error, missing critical points of assessment, and unable to finish inspection on time. In addition, the number of GMP inspectors is very limited, resulting in a delay of notifying inspection result to licensee and thus delay of drug registration.

The other risk, emerging from the workflow analysis, was credibility of translator and the translated documents from local language to English. All of the documents had to be translated to English before submission. The incorrect data and incomplete information both with intention or no intention could directly impact on decision of inspection approval. For example, mistranslation of the level and details of GMP deficiencies and the final conclusion in GMP inspection report were found irrelevant to the original language. This weakness may contribute to approval of the non-compliance GMP manufacturers.

4.2.3.2 Risk identification by representatives from selected countries/ organizations

All volunteers strongly agreed with the potential risks. The comments and suggestions including risk reduction approaches had been received from four representative inspectors/assessors in Philippines (ASEAN Listed Inspection Service under MRA), Australia (PIC/S member), Italy (PIC/S member since February 2000) and WHO. The full comments and suggestions from representatives can be found in Appendix 1.

Table 21 Selected risks and risk reduction approach from international views

Concern/Topic	Comments and risk reduction approach			
	Philippines	Australia	Italy	WHO
Regulation gap analysis				
1.Limited inspection to finished products only	Suggesting for further consideration	Additional API related document required	API supplier audit by FP manufacturer	Checking agreement between FP and API manufacturer
2.No regulation requirement for renewal/re-inspection	Re-inspection required	Re-inspection required	Site periodic audit by FP company	Specific period for re-inspection

3.Desktop inspection for non-PIC/S or non-WHO PQ manufacture	Agree with this risk, on-site inspection only	Agree with this risk, on-site inspection and/or evaluating internal inspectors	Agree with this risk, on-site inspection or documents support (SOP release for supply)	Agree with this risk, on-site inspection only
Workflow analysis				
1.Lack of stepwise to document review	Team meeting to generalize review procedures	Implement standardized work instruction and training	Training on PIC/S GMP guideline	Using standardized guideline and training in how to review documents
2.Different background experience of GMP inspectors in performing inspection	Harmonization on inspection process	Training and assigning the appropriate scope of inspection	Joint with PIC/S training program regularly	Training and use of different level for approval
3.Credibility of translator and the translated documents	Use accredited translator	Use the issuing authority	Use embassy qualified translator	Use the officially certified translation center

Remark: common suggestions were presented in grey boxes

The most common suggestions are an on-site inspection for non-PIC/S or non-WHO PQ certified manufacture and to use the credibility of the translator to translate the required documents. Those manufacturers types shall be implemented the on-site inspection. The desktop assessment is highly inadequate to verify the GMP compliance status. Italy proposed to focus on evaluating the procedure of release finished product for sale if Thailand's regulation is unable to perform an on-site inspection. On the other hand, translation of the required documents was suggested to use the credible translator not only the government institution but also private agency.

In addition, performing renewal/re-inspection was in a good agreement among Philippines, Australia and WHO whereas Italy proposed an option to continually audit by finished product company. Several risk reduction strategies were additionally recommended by Australian; (i) strengthening post-market reporting and compliance surveillance activities, (ii) strengthening requirements for marketing authorization holder (MAH)'s post-market responsibilities, (iii) sampling products available in market for test and (iv) increasing collaboration with other international regulators on GMP compliance signals.

Besides, inspector training strategy and standardized workflow procedure were suggested to reduce the two risks in terms of different background experience of GMP inspector and lack of stepwise to document review. To reduce and error of different background experience, assigning inspectors to the appropriate scope of the inspection with their background and trained, for example, dividing inspectors to two to perform an inspection of non-sterile manufacturer and sterile manufacturer after passing the specific training for each type of manufacturers can be done.

Interestingly, the risk of limited inspection to finished products, by not covering API site, should not be neglected and can be managed by various methods. Further requirement of specific documents (such as the procedure of approved vendor listed (AVL) of API and contract manufacturer agreement) and audit API supplier by FP manufacturer can be useful for risk reduction.

4.2.4 Risk identification by team brainstorming

Summary of the identified risks which was examined step by step, starting from regulation gap, workflow analysis, interview of Thai GMP inspectors and the representatives abroad, followed by risk assessment team were presented in Table 22. The final risk identification step concluded 17 risks for the following risk assessment steps (risk analysis and risk evaluation).

Table 22 The final risks obtained from risk identification step

Final risks
Regulation gap analysis
1. Limited inspection to finished products only
2. No regulation requirement for renewal/re-inspection
3. Similar required document among non-sterile, sterile and biological manufacturers
4. Desktop inspection for certified by PIC/S manufacturers
5. Desktop inspection for non-PIC/S GMP certified manufacturers
Workflow analysis
1. Licensees misunderstand the required documents
2. Licensee submit uncomplete and/or incorrect document
3. Misunderstanding the required documents by screening officers
4. Different background experience of GMP inspectors in performing inspection
5. Difference background experience of lead GMP inspector or quality system manager in verifying inspection results
6. Approved non-compliance GMP manufacturers by director
7. Inspectors may not follow SOP
8. Lack of stepwise approach in document review
9. Obsolete internal SOP
10. Unlimited number of applications *
11. High workload of the inspector *
12. Credibility of translator and the translated documents *

* Additional to the 14 potential risks stated in Table 20

4.3 Risk analysis and risk evaluation

Risk analysis and risk evaluation steps were investigated by using FMEA tool and presented together due to their mutual correlation. The use of FMEA should start from evaluation of potential failure mode for processes and their likely consequences on GMP desktop inspection system, which then affecting ranking risk priority number and risk level. These two steps were investigated by risk assessment team meeting via brainstorming and comprehensive discussion. The ranking scores were horizontally determined in the scale of 1-5 and were assessed in the order of occurrence (O), severity (S) and detectability (D) for each risk. Then, there were verified the ranked scale by vertically checked in the order of O among all identified risks for the first, S for the second and then D for the last to obtain the most appropriate values.

Team brainstorming is a reliable and well-known method, mostly used for risk analysis and risk evaluation and corresponding to a number of research publication (39, 40, 55). The strength of brainstorming is that interdisciplinary team represents the generalized inspection information. However, there are limitations found in these steps. The overall failure mode consequences of each risk could affect the desktop inspection system (in terms of quality and reliability) and products (in terms of quality, efficacy and safety) but the results were mainly reported based on the importance of such consequences (Table 23 and Table 24). The section was divided into two parts: 1) calculation of risk priority number and 2) results of risks level.

4.3.1 Calculation of risk priority number

Using FMEA tool, three main factors have to be defined for the calculation of risk priority number (equation 1). Ranking score of occurrence, severity and detectability was analyzed by the risk assessment team based on the potential failure modes and failure mode consequences of each identified risk, discussion and data analysis of regulation gap and workflow as presented from the highest to lowest RPN (Table 23 and Table 24).

4.3.1.1 Estimation of occurrence, severity and detectability for risks from regulation gap

The results of RPN were presented in the range of 18-100, depending on the value of occurrence, severity and detectability estimated as the followings.

The highest RPN value at 100 came from the desktop inspection pathway for non-PIC/S certified manufacturers or non-WHO PQ certified manufacturers. The estimation of occurrence ranking was five because, firstly, the majority of recalls was found from non-PIC/S manufacturers as analyzed in the data analysis section. Secondly, the ratio of the defect products of imported products was found more than half of the total comparing to those of local products. Next, the estimation of severity ranking was four. The deviated GMP standards from internal inspector which differ from the standardized inspection system of the PIC/S authorities may result in the inoperable system, product quality defect, and then product complaint and recall. The estimation of detectability ranking was five. It is possible that document assessment system fails to detect the potential cause of failure, particularly, when the manufacturer prepared good documentation without operation in practice. For example, supervisor has written clear procedures while operators do not follow the SOP, leading to the deviated practice.

Table 23 Summary of occurrence (O), severity (S), detectability (D) and RPN scores of the identified risks from regulation gap analysis

Inspection process	Potential failure mode	O	Failure mode consequences/effects	S	The ability of detection	D	RPN	Remark**
Scope of inspection								
1. Limited inspection to finished products only	Inspection of API-related manufacturing is missed	3*	Drug quality defect as a product complaints and product recalls may occur due to poor quality of the API	5	- Broaden scope of regulation for inspection API sites - Put more focus on the review of API supplier during finished products (FP) manufacturer inspection - FP company audits API supplier and conducts quality control test of API sampling - Collaborate with reputable regulatory authority to notify a quality-related issue of API - Periodic on-site inspection for API manufacturer	5	75	Debatable
Inspection implementation								
2. No regulation requirement for renewal/ re-inspection	No guarantee of GMP non-compliance throughout product life cycle	3	Non- GMP compliance manufacturer still occurred, may lead to poor drug quality	3	- Revise regulation for renewal throughout product lifecycle - Alert system notification of invalid inspection approval - Increase collaboration with other international regulators on non GMP compliance signals - Consider to add requirements of post-market responsibilities by licensee - Annual products sampling from market for QC testing	5	45	Debatable

Regulatory contents								
3. Similar required document among non-sterile, sterile and biological manufacturers	Critical control points of specific/important process can be missed	3	Approved non-compliance GMP standard which can directly cause drug quality defect	4	- Construct a list of required documents categorized by dosage forms (non-sterile, sterile and biological manufacturers) - Require more specific documents to ensure GMP compliance e.g. media fill validation or filter integrity validation report for aseptic sterile manufacturers	3	36	Agree
4. Desktop inspection for certified by PIC/S manufacturers	Questionable GMP standard as not fully implemented on-site inspections throughout product life cycle	2	Poor of drug quality, approved non-compliance GMP standard manufacturers or maybe deviated GMP standards from local inspectors	3	- Periodic on-site inspection alternating with desktop inspection e.g. perform desktop inspection every year along with an on-site inspection every two or three years depending on inspection results and risk assessment evaluation	3	18	Agree
5. Desktop inspection for non-PIC/S or non-WHO PQ certified manufacturers	Questionable GMP standard as not fully implemented on-site inspection, real conditions different from reported values in document, may non-systemic workflow in routine inspection of own authority	5*	Poor of drug quality, approved non-compliance GMP standard manufacturers or deviated GMP standards from local inspectors and community authorities	4	- On-site inspection/ Periodic on-site inspection - Joint inspection with overseas authority - Periodic on-site inspection alternating with desktop inspection - Desktop inspection with closed-circuit television - Evaluate non-PIC/S regulators in terms of GMP inspection system - Structure stepwise review of documents	5	100	Agree

* Rated from the frequency data shown in section 4.1 (data collection in 2016-2018), according to the definition of occurrence in Table 5 (section 3.3.1 of methodology)

** Agreed = RPN score was agreed by all team members, Debatable = RPN score was comprehensively debated before conclusion (the detail of score from each team member can be found in Appendix 2)

The second highest RPN value was at 75 relating to the limited inspection to finished products manufacturer only, not covering all of the site activities that relate to the quality of product such as API manufacturer or contract testing laboratories/contract sterilizers. In case some quality defect or non-GMP compliance problem is found from those sites, it may lead to significant risks with the finished product which can be harmful to patients. The correlation between occurrence and data analysis brought about the ranking of occurrence at three which is in the middle scale because of the combination of three facts; 1) complaints and recalls was showed the product defects caused by a source of API almost every year; however, 2) recall reports in 2017 with the cause of API source were one-third, while 3) no complaints related to API were reported in 2018 (data analysis section 4.1.3.4). The approximation of severity ranking was five. API manufactures generally deal with the starting material synthesis. Non-compliance to GMP, with inadequate control of the critical synthesis process, can contribute to API impurity and/or toxic residues contamination which then directly impacts the quality of product including the reliance of the inspection system. In addition, this risk has the highest severity because the failure is hazardous and can occur anytime without warning. The estimation of detectability ranking was as high as five. Currently, the API registration of overseas manufacturer is not required for inspection and the inspection of finished product manufacturer does not require the API related documents, thus unable to detect the potential cause of failure.

Regarding the third highest RPN, at present, the desktop guidance has no requirement for renewal/re-inspection, thus fails to maintain the GMP compliance status of an oversea manufacturer throughout product life cycle. Deviated practices from the GMP standard could have an influence to the quality assurance of the final products. The rank of occurrence was three as a medium scale, reflecting a regular incident. This correlated with the GMP desktop inspection situation in Thailand as the number of manufacturers increases significantly from 2016 to 2018, particularly in 2018, a large number of overseas manufacturers got approved without re-inspection. However, based on on-site inspection, the validity of an approval letter for a compliance manufacturer is generally in the range of one to three years depending

on inspection results, meaning that all the approved overseas manufacturers in 2016-2018 are about to be re-inspected now in 2020, if there is a rule in the guideline. At the same time, on-site inspection of these overseas manufacturers is considered to be inspected periodically by overseas regulatory authorities, especially a PIC/S manufacturer as being a majority of the situation in Thailand. Like the occurrence ranking, the ranking of severity was at the same level as three as estimated by the similar fact, failure and consequences. As mentioned previously, overseas manufacturers have been physically inspected by original regulatory authorities periodically. Contrastly, the detectability ranking was evaluated as high as five because the regulation has no renewal assessment pathway, hence it is not possible for the Thailand regulators to verify the maintenance of compliance status. In addition, there is no official channel to notify any serious GMP deficiencies or the failure of GMP compliance that inspected by local regulatory authority to the Thai regulator.

The risk of similar required document among non-sterile, sterile and biological manufacturers was listed as the fourth highest RPN value due to the fact that data of the specific manufacturing processes can reflect the quality of product nonspecific or insufficient/missing important data can lead to approved non-compliance manufacturer for registration. The occurrence was ranked as three. The possibility of failure is not high because more than half of overseas manufacturers is in the group of non-sterile compared with sterile and biological manufacturers and non-sterile types usually have uncomplicated manufacturing process which can be inspected by general required documents. The ranking of severity was four. The inspection may not cover all of the important activities such as the complicated process of sterile and biological products should require specific documents (e.g. the filter integrity validation or media fill validation) to ensure quality control and quality assurance of the process, presumably resulting in poor drug quality and/or harm to patients. The detectability ranking was three as the minimum required documents (site master file, GMP inspection report and CAPA report) seem to cover extensive manufacturing and quality activities which are general for all drug products and sufficient to detect the GMP compliance of those manufacturers.

The least RPN down to 18 was desktop inspection for certified by PIC/S manufacturers in Thailand which may be limitedly inspected by PIC/S authorities only at initial, for this reason, product quality throughout product life cycle cannot guaranteed. The rank of occurrence was two as a medium to low scale as the number of certified PIC/S manufacturers was minority, for example, 17% in 2017. The ranking of severity was three. Risk assessment team strongly believed that most of these manufacturers tend to have periodic inspection by PIC/S member, contributing to pharmaceutical quality system of the approved manufacturers. The detectability was three. Many of required documents can verify the consistency of PIC/S inspection (e.g. both GMP inspection report and site master file describe history of inspection) by PIC/S and/or local regulatory inspection or other the audits e.g. ISO team, globally-company audit.

4.3.1.2 Estimation of occurrence, severity and detectability for risks from workflow analysis

The RPN of all 12 identified risks from workflow analysis was calculated and ranked from highest to lowest (Table 24). The results of RPN were presented in the range of 10-80, depending on the value of occurrence, severity and detectability estimated as the followings. Of note, this estimation step was performed qualitatively, and mainly applied team discussion method rather than the facts analyzed in statistical data (pre-assessment section).

Begin with the highest RPN value at 80, lack of stepwise review or review based on inspector' experiences were agreed by the team to cause inconsistency of inspection results and thus less reliance of regulatory authority. The estimation of occurrence was ranked as four because each inspection has a large number of required documents with many critical points to review, it is difficult to review orderly without guideline. Additionally, all inspectors have the same basic of document review from the staff training. So, the occurrence was not high as five. Next factor, severity was scored as high as of five. Referring to the data analysis of product complaints and recalls over the last three years, the main cause of complaints and recalls was relating to manufacturing process e.g. dissolution time out of standard,

product leakage from the close container, mix-up contamination including the failure of utility support system which can be found in the specific documents like batch manufacturing and analytical record or process validation protocol and report. Failing in inspection of the specific points leads to system failure and occurs without warning as defined for five score. Meanwhiles, the detectability was ranked at four. It is highly possible that verified person (lead inspector and/or quality system manager), who do not have stepwise inspection procedure, cannot detect an error of the inspection results, leading to lower effectiveness of system control as scored to four.

Table 24 Evaluation of occurrence (O), severity (S) and detectability (D) score of each risk and calculation of RPN from workflow analysis step

Inspection process	Potential failure mode	O	Failure mode consequences/effects	S	The ability of detection	D	RPN	Remark**
Licensee								
Licensees misunderstand the required documents	Submit uncomplete and/or incorrect document	5	Rejected application form	3	- Provide manual for document preparation - Motivate regulatory association to organize annual meeting for licensees - Notify regulatory association to distribute updated regulation to licensees	2	30	Agree
Licensee submit uncomplete and/or incorrect document	Rejected application form	4	Cannot be registering and accessing to new medicines by patients	3	- Provide self-checklist for document preparation - Provide consultation center - Motivate regulatory association to organize annual meeting for licensees - Notify regulatory association to distribute updated regulation to licensees	2	24	Agree
Thai FDA officer/ GMP inspector								
Misunderstanding the required documents by screening officers	Receive uncomplete and/or incorrect document	3*	Inspectors reject application or request additional declaration	3	- Provide checklist for screening documents - Provide content of each document - Periodic technical training	3	27	Agree
Different background experience of GMP inspector in performing inspection	Unstandardized inspection	3	Difference in inspection strictness and results	4	- Assigning inspectors to the appropriate scope of inspection based on their experience - Verification by higher level inspectors before approval	3	36	Debatable

					- Group discussion by internal system - Shared inspection approval report to all internal inspectors - Periodic technical training - Use buddy system for coaching junior inspectors - Schedule monthly meeting to standardize inspection procedure - Joint PIC/S training program routinely			
Difference the background experience of lead GMP inspector or quality system manager in verifying inspection results	Unstandardized of verification inspection result	3	Difference in verification strictness and results	4	- Group discussion by internal system - Shared inspection approval report to all internal inspectors - Periodic technical training - Schedule monthly meeting to standardize inspection procedure - Joint PIC/S training program routinely	2	24	Agree
Approved non-compliance GMP manufacturers by director	Drug registered from non-compliance GMP manufacturers	2	Various/poor drug quality, harm to patient	5	- Verify inspection result by lead GMP inspector and quality system manager before approval	1	10	Debatable
Inspectors may not follow SOP	Work practice deviate from proper process	3	Inspection process may be wrong	4	- Verification by higher level inspectors before approval - Periodic technical training - Set up notification system for updated SOP	3	36	Agree

High workload of the inspector	Error/Missing critical points to review documents	3*	Inefficient of inspection result, Unable to finish inspection on time	4	- Increase number of inspectors - Manpower analysis - Establish electronic-submission and online inspection system - Set KPIs to enhance inspector's performance	3	36	Agree
Desktop inspection system								
Lack of stepwise approach in document review	Unstandardized inspection	4	Missing critical review point, Different inspection results, Bad reputation of authority	5	- Structure stepwise to review document and training inspectors - Harmonization on inspection procedure - Using personal aide memoire (shortly taken note) to review document (	4	80	Agree
Unlimited number of applications	Officer inadequate time to screening required document	4	Received the uncompleted application, Human error	3	- Limit appropriate number of applications per day - Online booking for submission	2	24	Agree
Obsolete internal SOP	Work practice deviate from current process	3	Inspection process may be wrong	3	- Perform periodic review routinely - Perform internal audit	2	18	Agree

Credibility of translator and the translated documents	Incorrect data, Missing critical point, Incomplete information	3*	Approved non-compliance GMP manufacturers	5	- Request certificate of translator/translation center - Request original document for cross-check - Confirm credibility of translated documents by cross-check with regulatory database - Collaborate with original regulators to cross-check the accuracy of translated documents - Blacklist questionable manufacturer/licensee for further consideration - Use only qualified embassy translator	4	60	Debatable

* Rated from the frequency data shown in section 4.1 (data collection in 2016-2018), according to the definition of occurrence in Table 5 (section 3.3.1 of methodology)

** Agreed = RPN score was agreed by all team members, Debatable = RPN score was comprehensively debated before conclusion (the detail of score from each team member can be found in Appendix 2)

Next, the second highest RPN value ranked to 60, credibility of translator and the translated documents was connected with incorrected/incomplete documents which then had an influence on inspection decision, the quality of production site and drug product. The estimation of occurrence was three because FDA manual indicated the requirement for document translation of translator authentication but the number of false applications was reported approximately 1 in 400 applications each year, corresponding to the definition of score at three. Turning now to the severity score, it was highest as of five because wrong decision and approval of non-compliance GMP manufacturers for registration can occur when mistranslation of quantity and details (like level of deficiency or inspection conclusion) of the critical documents such as GMP inspection report and approval of CAPA report. Consequently, this severity directly impacted the quality and reliability of desktop inspection. The estimation of detectability was four. It is laborious to be able to detect the translator authentication by checking documentary certificate only, together with limited screening time and consideration.

Lastly, the third highest RPN values showed an equal score at 36 among the three risks; (i) different background experience of GMP inspector in performing inspection, (ii) inspector may not follow SOP and (iii) high workload of the inspector. Firstly, different background experience of GMP inspectors is likely to cause difference in inspection strictness/decision and unstandardized inspection results by various inspectors. It was estimated as three in terms of occurrence because the inspector was qualified and appropriately assigned before performing inspection; however, there are too many inspectors and no periodic training frequently enough to generalize twenty individual background. On the other hand, the severity score was four because of the difference in inspection strictness which can directly impact inspection results, reliance and reputation of authority, for example, the same overseas manufacturer inspected by two Thailand's licensees (two importers and different trade name) got both approved and rejected, reflecting unstandardized inspection system and questionable inspection results. Next, the estimation of detectability was not high as the scale of three. The reason is that there is a verification of inspection system implemented, another person (lead inspector and/or

quality system manager) will double-check the result report before approving by the director as shown in the workflow diagram.

The second risk with 36 RPN, inspector may not follow SOP which the work practice deviate from proper process lead to the inspection process may be wrong, was estimated by the three factors in the same way with the previous risk (different background experience of GMP inspector). The occurrence was ranked to three as all inspectors have to attend SOP training program which allows them to reconsider the SOP. However, SOP was generally revised once every three years without refresh training, inattention to details during this period may occur. The severity ranking was four as inspectors deviate from standard work practice when facing complicated document review, causing an error of the inspection, unreliable system, and possibly, poor product quality. The detectability was ranked commonly as three as double check is always applied in the inspection system which could avoid the error. Lead inspector and quality system manager are in charge of verification of the inspection report before sending for director approval.

Next, the risk of high workload of the inspector caused a potential failure mode as an error or missing critical points to review the documents, resulting in inefficient inspection results and unable to finish inspection on time. The estimation of occurrence was ranked to three due to the fact that increasing number of manufacturers and limited human resource can give rise to the aforementioned potential failure. Nevertheless, there were a few reports regarding unable to finish inspection on time, so the occurrence was not more than three. The severity ranking was four because the quality of inspection results can be affected by high workload. The detectability was three because the failure and consequences from the risk can be detected by different level of inspectors before approval and by the monitoring system using to remind inspectors when approaching due date of inspection.

In addition, the risk of approved non-compliance GMP manufacturers by director was ranked as low risk. Although severity of poor drug quality was extremely high score, detectability score was ranked as lowest because the routine workflow has high ability to detect the failure mode consequence by the verification of

inspection result of lead GMP inspector and quality system manager before director approval.

4.3.2 Risk level

Results were shown in three level as the high, medium and low risk as defined in the quality risk matrix of methodology section 3.4.1. Two high risks, two medium risks and one low risk out of five total risks from the regulation gap while one high risk, nine medium risks and two low risks out of twelve total risks from workflow analysis were revealed (Table 25). Majority of identified risks were categorized as medium risk as shown in the yellow box.

Categorization of the risk level could help to prioritize the major risk for further risk management in terms of risk reduction and implementation. High risk level would urgently require the specific measures to avoid failure mode and failure consequences while maintain inspection standard and product quality, followed by taking action in the near future.

Table 25 The results of risks level from regulation gap and workflow analysis

Risk	RPN value	Risks level
Regulation gap analysis		
1. Desktop inspection for non-PIC/S or non-WHO PQ certified manufacturers	100	High risk
2. Limited inspection to finished products only	75	High risk
3. No regulation requirement for renewal/re-inspection	45	Medium risk
4. Similar required document among non-sterile, sterile and biological manufacturers	36	Medium risk
5. Desktop inspection for certified by PIC/S member manufacturers	18	Low risk
Workflow analysis		
1. Lack of stepwise approach in document review	80	High risk
2. Credibility of translator and the translated documents	60	Medium risk

3.Different background experience of GMP inspector in performing inspection	36	Medium risk
4. Inspector may not follow SOP	36	Medium risk
5. High workload of the inspector	36	Medium risk
6. Licensees misunderstand the required documents	30	Medium risk
7. Misunderstanding the required documents by screening officers	27	Medium risk
8.Difference the background experience of lead GMP inspector or quality system manager in verifying inspection results	24	Medium risk
9. Unlimited number of applications	24	Medium risk
10. Licensee submit uncomplete and/ or incorrect document	24	Medium risk
11. Obsolete internal SOP	18	Low risk
12. Approved non-compliance GMP manufacturers by director	10	Low risk

4.4 Risk reduction

Risk reduction step was reported as three divided sections; 1) risk reduction approaches, 2) implementation and 3) re-assessment. All 17 risks from the previous steps were analyzed by proposing risk mitigation strategies for current control processes and further recommendations. It can be very useful for the Thai FDA to minimize risks from both of regulation and work practice aspects for continual process improvement.

4.4.1 Risk reduction approaches

Risk reduction approaches were constructed based on team brainstorming including suggestions from interviewees in the perspectives of work practice and guideline regulation. Relating to the risk identification step, the results were separated into two sub-sections as the risk reduction of regulation gap and workflow analysis.

4.4.1.1 Risk reduction approach for the regulation of desktop inspection

Risk reduction approaches of the five identified risks were suggested by the risk assessment team, internal GMP inspectors and global inspectors. As shown in the order of highest to least RPN in Table 23, risk reduction was presented in the aspects of proposed strategy for future implementation.

Table 26 Risk reduction approaches of the five identified risks from regulation gap analysis

Risk	Risk reduction approaches
1. Desktop inspection for non-PIC/S or non-WHO PQ certified manufacturers	Proposed strategy: 1.1 Perform on-site inspection 1.2 Joint inspection with overseas regulatory authority to make the best use of human resource 1.3 Periodic on-site inspection alternating with desktop inspection 1.4 Desktop inspection with closed-circuit television (CCTV) to ensure correspondence of documents and in routine practice and to inspect critical areas 1.5 Evaluate GMP standard and inspection system of non-PIC/S regulators whether such regulators can be acceptable for desktop inspection 1.6 Structure a stepwise SOP to review the critical point of required documents such as focusing on QP release document 1.7 Sampling all imported products for quality control testing (as suggested by Italian interviewee)
2. Limited inspection to finished products only	Proposed strategy: 2.1 Broaden the scope of the regulation for desktop inspection of API manufacturers 2.2 Put more focus on the review of API supplier (document: approve vender list procedure) during finished product (FP) manufacturer inspection 2.3 FP company audits API supplier and conducts quality control test of API sampling (as suggested by Italian interviewee)

	2.4 Collaborate with reputable regulatory authority (e.g. EDQM) to notify a quality-related issue of API (as suggested by Australian interviewee) 2.5 Periodic on-site inspection for API manufacturer (if possible)
3. No regulation requirement for renewal/re-inspection	Proposed strategy: 3.1 Revise regulation requirement for renewal throughout product life cycle or establish a specific period based on the risk metric 3.2 Alert system notification of invalid inspection approval 3.3 Increase collaboration with other international regulators on non GMP compliance signals (as suggested by Australian interviewee) 3.4 Consider to add requirements of post-market responsibilities by licensee e.g. manufacturer audit by licensee (as suggested by Australian and Italian interviewee) 3.5 Annual products sampling from market for QC testing
4. Similar required document among non-sterile, sterile and biological manufacturers	Proposed strategy: 4.1 Construct a list of required documents categorized by dosage forms (non-sterile, sterile and biological manufacturers) 4.2 Require more specific documents to ensure GMP compliance e.g. media fill validation or filter integrity validation report for aseptic sterile manufacturers
5. Desktop inspection for certified by PIC/S manufacturers	Proposed strategy: 5.1 Periodic on-site inspection alternating with desktop inspection e.g. perform desktop inspection every year along with an on-site inspection every two or three years depending on inspection results and risk assessment evaluation

4.4.1.2 Risk reduction approach of workflow analysis

Risk mitigation strategies were examined as shown in the order of their importance from highest to least RPN values in Table 24. Risk reduction approaches were demonstrated as two groups; one is proposed strategy for future implementation and the other is implemented strategy which is implemented currently to the routine desktop inspection; however, there were many gaps that still caused some risks as identified above.

Table 27 Risk reduction approaches of the identified risks from workflow analysis

Risk	Risk reduction approaches
1. Lack of stepwise approach in document review	Proposed strategy; 1.1 Structure stepwise to review document and training inspectors (including routine periodic re-training) 1.2 Harmonization on inspection procedure (as suggested by Philippines interviewee) 1.3 Using personal aide memoire (shortly taken note) to review document (as suggested by WHO interviewee)
2. Credibility of translator and the translated documents	Implemented strategy; 2.1 Request certificate of translator/translation center to ensure the credibility of translated documents 2.2 Request original document for cross-check Proposed strategy; 2.3 Confirm credibility of translated documents by cross-check with regulatory database e.g. EUDRA GMP database of EU countries, COMSTATS GMP database of US FDA 2.4 Collaborate with original regulators to cross-check the accuracy of translated documents (as suggested by Australian interviewee) 2.5 Blacklist questionable manufacturer/licensee for further consideration 2.6 Use only qualified embassy translator (if possible)
3. Different background experience of GMP inspector in performing inspection	Implemented strategy; 3.1 Assigning inspectors to the appropriate scope of inspection based on their experience (higher level inspector responsible for sterile and biological manufacturer) 3.2 Verification by higher level inspectors before approval

	3.3 Group discussion by internal system when having a special quality issue 3.4 Shared inspection approval report to all internal inspectors for supporting inspection of the previously-inspected manufacturer Proposed strategy; 3.5 Periodic technical training or workshop, incorporating scenarios and quizzes for discussion 3.6 Use buddy system for coaching junior inspectors (as suggested by Australian interviewee) 3.7 Schedule monthly meeting to share critical issue and standardize inspection procedure 3.8 Joint PIC/S training program routinely
4. Inspector may not follow SOP	Implemented strategy; 4.1 Verification by higher level inspectors before approval Proposed strategy; 4.2 Periodic technical training or workshop, incorporating scenarios and quizzes for discussion 4.3 Set up notification system for updated SOP
5. High workload of the inspector	Implemented strategy; 5.1 Increase number of inspectors Proposed strategy; 5.2 Manpower analysis 5.3 Establish electronic-submission and online inspection system to reduce the time of internal document transfer and hence inspection time 5.4 Set KPIs to enhance inspector's performance (as suggested by WHO interviewee)

6. Licensees misunderstand the required documents	Implemented strategy; 6.1 Provide manual for document preparation Proposed strategy; 6.2 Motivate regulatory association to organize annual meeting for licensees 6.3 Notify regulatory association to distribute updated regulation to licensees
7. Misunderstanding the required documents by screening officers	Implemented strategy; 7.1 Provide checklist for screening the required documents Proposed strategy; 7.2 Provide content of each required document 7.3 Periodic technical training or workshop, incorporating scenarios and quizzes for discussion
8. Difference the background experience of lead GMP inspector or quality system manager in verifying inspection results	Implemented strategy; 8.1 Group discussion by internal system when having a special quality issue 8.2 Shared inspection approval report to all internal inspectors for supporting inspection of the previously-inspected manufacturer Proposed strategy; 8.3 Periodic technical training or workshop, incorporating scenarios and quizzes for discussion 8.4 Schedule monthly meeting to share critical issue and standardize inspection procedure 8.5 Joint PIC/S training program routinely
9. Unlimited number of applications	Proposed strategy; 9.1 Limit appropriate number of applications per day 9.2 Online booking for submission
10. Licensee submit	Implemented strategy; 10.1 Provide self-checklist for document preparation

uncomplete and/or incorrect document	10.2 Provide consultation center Proposed strategy; 10.3 Motivate regulatory association to organize annual meeting for licensees 10.4 Notify regulatory association to distribute updated regulation to licensees
11. Obsolete internal SOP	Implemented strategy; 11.1 Perform periodic review routinely 11.2 Perform internal audit

4.4.2 Implementation

To verify the feasibility of risk reduction, the selected solutions of highest RPN value were implemented as new practices in routine work before re-assessment. Notably, many risk reduction approaches were related to law and regulation which have some limitations for verification. Most people agreed that it would take long time to revise the regulation because it related to a number of parties and had many steps not only internal processes but also public hearing. Therefore, this risk reduction approach was unable to implement during the study period; however, further implementation by management team will be continuously performed for continual quality improvement. Until now, many risk reductions approaches (four topics: 1) perform on-site inspection for non-PIC/S or non-WHO PQ certified manufacturers, 2) evaluate GMP standard and inspection system of non-PIC/S regulators whether such regulators can be acceptable for desktop inspection, 3) revise regulation requirement for renewal throughout product life cycle, and 4) construct a list of required documents categorized by dosage forms (non-sterile, sterile and biological manufacturers)) were considered in a draft regulation.

Interestingly, having a stepwise document review is one of the applicable solutions to reduce the risks resulted from regulation gap and workflow analysis. This approach could directly impact quality of the inspection result and is possible to implement promptly in the workplace by revising internal procedure. Moreover, the revised procedure can be useful to evaluate all manufacturer types especially non-

PIC/S or non-WHO PQ certified manufacturer which have several required documents. Major critical points to review were clearly described in the desktop inspection SOP, and confirmed by users in the risk assessment team, as can be seen in Appendix 3 and Appendix 4. The harmonization and standardization of procedure were informed and trained to internal GMP inspectors. The responsible person was the author and the implementation period was one month.

4.4.3 Re-assessment

After implementing the risk mitigation of stepwise document review, risk assessment team performed risk analysis and evaluation again by ranking the three factors (O, S and D) and re-calculation of RPN values (equation 1). Interestingly, the stepwise procedures can be useful for improving the inspection of GMP compliance and ensure that the critical points of many required documents were verified before the inspection decision was made. Risk assessment team, particularly the GMP inspector, added that the stepwise review is very useful for both inspection of the important points of each document and standardization of the inspection results, leading to improvement of the quality and reliability of desktop inspection system.

For highest RPN of regulation gap analysis, re-assessment revealed that the occurrence decreased due to the reduced probability (5 to 3) of missing critical review point and different inspection results (potential failure mode). Besides, the detectability system can be enhanced by the use of a list of critical points to review, leading to a middle scale of detectability value (reduced from 5 to 3). Whiles the severity ranking remained the same (rated to 4) because the severity of potential consequences still has a high impact on the quality of inspection results and inspection system. Furthermore, unstandardized workflow to review many documents of non-PIC/S or non-WHO PQ certified manufacturer can be minimized by stepwise document review. The new RPN score reduced to 36 which was assigned as medium risk instead of 100 in high risk level. Regarding workflow analysis, the risk caused by lack of guideline for document review could be mitigated by the stepwise procedure. The new estimation of occurrence was reduced from 4 to 2, the severity was turned from 5 to 4 and the detectability was reduced from 4 to 3 and found

that the new RPN was reduced to 24 assigned as a medium risk. Both of the new RPN was changed to an acceptable level that can be found in Table 28.

Table 28 Re-assessment and calculation of RPN after implementing the risk mitigation of stepwise document review

Risks	O	S	D	RPN	Implementation	New O	New S	New D	New RPN
Desktop inspection for non-PIC/S or non-WHO PQ certified manufacturers	5	4	5	100	Structure stepwise to review document and training inspectors	3	4	3	36
Lack of stepwise approach in document review	4	5	4	80		2	4	3	24

However, it is unlikely to monitor the number of drug quality defect as complaints and recalls, resulted from stepwise implementation, because such approved manufacturers cannot import the drug product to Thailand until marketing authorization is granted which could further take approximately a year. The potential defect may occur after the imported products are available on market. Therefore, drug monitoring is continuously required in the following period. At the same time, after implementing risk mitigation process, the team re-evaluated this risk and other existing risks. The results were confirmed that no other new risks occurred.

Nevertheless, other remaining risks were performed risk mitigation action by expectation based on the risk assessment team experience and discussion, all of new RPN values were aimed at the lower values (Table 29). The summary of risk assessment of GMP inspection of an overseas pharmaceutical manufacturer based on desktop inspection system as required in Thailand including re-assessment was shown in Appendix 5.

In terms of the risk level of re-assessment, it was evident that all of the high risks were improved to medium risks while medium risks turned to low risks, corresponding to the lower score of RPN. To conclude, there were two medium risks and three low risks out of five total risks identified from the regulation gap while one medium risk and eleven low risks out of twelve total risks identified from the

workflow analysis (Table 29). The results showed that all of the new RPN changed to an acceptable level.

Table 29 The new risks level of the gap regulation and workflow analysis after re-assessment

Risk	O	S	D	RPN	Risks level	O*	S*	D*	RPN*	Risks* level
Regulation gap analysis										
1. Desktop inspection for non-PIC/S certified manufacturers or non-WHO PQ certified manufacturers	5	4	5	100	High	3	4	3	36	Medium
2. Limited inspection to finished products only	3	5	5	75	High	2	4	3	24	Medium
3. No regulation requirement for renewal/re-inspection	3	3	5	45	Medium	2	3	3	12	Low
4. Similar required document among non-sterile, sterile and biological manufacturers	3	4	3	36	Medium	2	3	2	12	Low
5. Desktop inspection for certified by PIC/S manufacturers	2	3	3	18	Low	2	3	2	12	Low
Workflow analysis										
1. Lack of stepwise approach in document review	4	5	4	80	High	2	4	3	24	Medium
2. Credibility of translator and the translated documents	3	5	4	60	Medium	2	4	2	16	Low
3. Different background experience of GMP inspector in performing inspection	3	4	3	36	Medium	2	4	2	16	Low
4. Inspector may not follow SOP	3	4	3	36	Medium	2	4	2	16	Low
5. High workload of the inspector	3	4	3	36	Medium	2	4	2	16	Low
6. Licensees misunderstand the required documents	5	3	2	30	Medium	3	2	2	12	Low
7. Misunderstanding the required documents by screening officers	3	3	3	27	Medium	2	2	2	8	Low
8. Difference the background experience of lead GMP inspector or QSM in verifying inspection results	3	4	2	24	Medium	2	3	2	12	Low
9. Unlimited number of applications	4	3	2	24	Medium	3	2	2	12	Low
10. Licensee submit uncomplete or incorrect document	4	3	2	24	Medium	3	2	2	12	Low

11. Obsolete internal SOP	3	3	2	18	Low	-	-	-	-	-
12. Approved non-compliance GMP manufacturers by director	2	5	1	10	Low	-	-	-	-	-

*Remark: Expected calculation

CHAPTER V
CONCLUSION AND RECOMMENDATIONS

The main objectives of this study were to study risk assessment of GMP inspection of overseas pharmaceutical manufacturers based on desktop inspection system as required in Thailand according to quality risk management (QRM) in ICH Q9 guideline and to evaluate potential failures of each risk, risk level and risk reduction measures. The study design was divided into five steps according to the quality risk management guideline of ICH organization. Firstly, pre-assessment step consisted of team set up and data analysis. To set up the risk assessment team, interdisciplinary background and work experience in GMP inspection and drug registration system of the Thai FDA were the main criterias which were important for brainstorming method used mainly to perform risk assessment. Meanwhiles, data analysis was performed by collecting the statistical data of the GMP desktop inspection situation and drug quality defect including imported product complaints and recalls over the last three years of 2016 – 2018 which were used as supportive data combining with team discussion. The number of overseas manufacturers in desktop inspection system increased continuously from 2016 to 2018. The majority was categorized in the PIC/S manufacturers and non-sterile manufacturers. Regarding the quality defect of imported product as reported in terms of complaints and recalls, the defect ratio of imported products was found to appear more often than those of local products in particularly in 2016 and 2017. The number of complaints and recalls of each dosage form was occurred every year without specific trend. The recalls that reflect worse quality system than complaints were found from non-PIC/S manufacturers. While the cause of complaint and recall reports were found mainly due to the manufacturing process. The results of data analysis were then used for consideration in risk analysis and risk evaluation step.

Next, risk identification step was conducted based on analysis of the regulation gap and routine workflow, together with team brainstorming and interview. Desktop inspection regulation implemented in Thailand was considered in three aspects as (i) objective, principles and scope, (ii) implementation and supervision and (iii) regulatory contents against five globally-selected countries/organizations (the HSA of Singapore, the NPRA of Malaysia, the TGA of Australia, WHO and PIC/S organization). While workflow analysis was examined based on current desktop inspection procedure used for licensees and Thai FDA. The potential risks were identified by brainstorming of the risk assessment team and interview of internal and international GMP inspectors. Five identified risks, namely, limitation of the inspection scope, renewal inspection, similar set of required documents for assessment and the inspection pathway for the certified by PIC/S manufacturer and the non-PIC/S or non-WHO PQ certified manufacturer, were found from regulation gap analysis. While twelve risks, related to licensees, inspectors including relevant persons and desktop inspection system, were found from workflow analysis. The examples of identified risks were lack of stepwise to review the required documents, credibility of translator and translated document and a set of risks, related to inspectors have different background experience in performing the desktop inspection, may not follow SOP and have high workload. The potential failure mode and failure mode consequences of each risk was identified and found that most risks tend to affect quality and reliability of inspection system. Total risks from risk identification step were further investigated for the intensity of risk which were prioritized for risk minimization.

Followed by risk analysis, FMEA tool of ICH guidance was applied to prioritize the identified risks by considering three main factors of occurrence (O), severity (S) and detectability (D). Then, risk evaluation step was evaluated as RPN values which is calculated by multiplying O, S and D values. Risk level were assigned as the high, medium and low risk level after calculation of RPN. All risks were investigated based on the results of the results from GMP desktop inspection situation and quality defects as summarized in pre-assessment section. The majority of risks level was revealed in a medium risk. Interestingly, the most potential negative effects on the quality and reliability of the desktop inspection system with the highest RPN values

were the desktop inspection pathway for non-PIC/S certified or non-WHO PQ certified manufacturers (RPN = 100, high-risk level) and the lack of stepwise approach in document review (RPN = 80, high-risk level) which resulted from regulation gap and workflow analysis, respectively. Such overseas manufacturers tend to have various GMP standards based on their own quality system criteria and be inspected by different levels of authorized inspectorate unit. In addition, due to the lack of stepwise approach for review required documents, unstandardized inspection contributes to the missing critical review point and the different of inspection results. The risks with highest RPN value have to be immediately taken for reducing the potential failure.

Finally, risk reduction step was examined by brainstorming of risk assessment team and interview of national and international GMP inspectors. All risks were described risk mitigating approaches and was verified the feasibility by implementing selected solutions in routine work before re-assessment. Re-assessment applied the same FMEA tools and RPN equation. The selected approach for the risk with the highest RPN value was implemented before re-assessment. Structure of a stepwise document review was the strengthening reduction strategy because it directly impacted quality of inspection results. The critical points to review in required documents were described and explained in desktop inspection standard operating procedure. The revised procedure can be very useful to guide all inspectors to work on the same platform for desktop inspection. Another risk reduction approach, related to regulation, was performed by drafting regulatory revision for further implementation (in terms of an on-site inspection for non-PIC/S or non-WHO PQ certified manufacturer, renewal inspection and construct a list of required documents by categorization of manufacturer type). After re-assessment, all high risks from regulation gap and workflow analysis were reduced to medium risk, corresponding to the lower score of RPN and were changed to an acceptable risk level.

The present study was noteworthy, contributing to the new practices and implementation of desktop inspection system especially the stepwise review of required documents. This work can be very useful for the Thai FDA to minimize the risks for continual quality improvement of the desktop inspection system for overseas pharmaceutical manufacturers.

The limitation of this study can be grouped as two topics; one is data collection and the other is timeframe for risk control and risk review. It is relatively difficult to compile data from various sources/departments without systematic documentation. To verify the feasibility of risk reduction approach in terms of law and regulation, a number of years is required to perform this process.

For future studies, it is recommended that the risk control of stepwise document review should be implement and re-assessed for more than a year. Secondly, implementation of all other risk reduction approaches should be implemented and re-assessed. Thirdly, validation of risk assessment can be conducted either by forming the new risk assessment team with the same scenario or using the same risk assessment team with the new scenario. Fourthly, systematic document should be established to prevent possible litigation and to bring about more effective risk assessment in the following cycle. Finally, the mechanism of risk review should be implemented and continued to monitor the identified risks if they impact the initial quality risk management decision.

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APPENDIX

Appendix 1

Comments and suggestions from four international representatives

Appendix 1A

Philippines's representatives (ASEAN Listed Inspection Service under MRA)

1. The risks from regulation gap analysis (Thai regulations against five globally-selected countries)

Risks of Thai FDA regulation	**Potential failure mode**	**Failure mode consequences/effects**	**Comment/ suggestion** (e.g. Agree?, Severity?, Other failure mode?)	**Propose risk reduction**
Limited inspection to finished products only	Inspection of API-related manufacturing is missed	Drug quality defect as a product complaints and product recalls may occur due to poor quality of the API	Agree	Implementation of API supplier's accreditation
No regulation requirement for renewal/re-inspection	No guarantee of GMP non-compliance throughout product life cycle	Poor drug quality, harm to patients	Agree	Perform re-inspection
Desktop inspection for non-PIC/S or non-WHO PQ certified manufacturers	Questionable GMP standard as not fully implemented on-site inspection, real conditions different from reported values in document, may non-systemic workflow in routine inspection of own authority	Poor of drug quality, approved non-compliance GMP standard manufacturers or deviated GMP standards from local inspectors and community authorities, no standardized workflow	Agree	Perform inspection

2. The risks from workflow analysis (Current workflow)

Risk	**Potential failure mode**	**Failure mode consequences/effects**	**Comment/ suggestion** (e.g. Agree?, Severity? , Other failure mode?)	**Propose risk reduction**
Lack of stepwise/critical point approach to review the required document	Unstandardized inspection	Missing critical review point, Different inspection results, Bad reputation of authority	Agree	Harmonization on inspection strategy or interpretation of the guide
Different background experience of GMP inspector in performing inspection	Unstandardized inspection	Difference in inspection strictness	Agree	Harmonization on inspection strategy or interpretation of the guide
Credibility of translator and the translated documents	Incorrect data, Missing critical point, Incomplete information	Approved non-compliance GMP manufacturers	Agree	Seek assistance for accredited translator

Appendix 1B

Australia's representatives (PIC/S member)

1. The risks from regulation gap analysis (Thai regulations against five globally-selected countries)

Risks of Thai FDA regulation	**Potential failure mode**	**Failure mode consequences/ effects**	**Comment/ suggestion** (e.g. Agree?, Severity?, Other failure mode?)	**Propose risk reduction**
Limited inspection to finished products only	Inspection of API-related manufacturing is missed	Drug quality defect as a product complaints and product recalls may occur due to poor quality of the API	Agree that this is a potential (high) risk, given that a large proportion of compliance concerns come from API manufacturers.	- Increase focus of the review of API supplier during finished product inspection - Introducing a desktop assessment framework for API manufacturers (in lieu of on-site inspection) - As a long-term goal, perhaps to do a compliance risk-based inspection of API manufacturers
No regulation requirement for renewal/re-inspection	No guarantee of GMP non-compliance throughout product life cycle	Poor drug quality, harm to patients	Agree that this is a risk (potentially high if there is no monitoring and regulation of post-market GMP compliance).	- Strengthening post-market reporting and compliance surveillance activities - Strengthen requirements for marketing authorization holder (MAH)'s post market responsibilities - Post-market testing - Increase collaboration with other international regulators on GMP compliance signals - Implement a risk-based re-inspection framework or renewal process for desk-top assessment

Desktop inspection for non-PIC/S or non-WHO PQ certified manufacturers	Questionable GMP standard as not fully implemented on-site inspection, real conditions different from reported values in document, may non-systemic workflow in routine inspection of own authority	Poor of drug quality, approved non-compliance GMP standard manufacturers or deviated GMP standards from local inspectors and community authorities, no standardized workflow	Agree that this is a risk. However, the extent would be unknown as it will depend on a number of factors, e.g. (as examples, but are not limited to) - Which country - What kind of medicines & risks associated with these medicines - How medicines in that country are regulated - How much is being imported to Thailand - Risk associated with post-market issues, etc.	Potential options: - Evaluation of which non-PIC/S regulators would be acceptable - Requirements for additional documentation to ensure GMP Compliance - Shorter validity period - Periodic on-site inspection to confirm the finding of the desk-top assessment

2. The risks from workflow analysis (Current workflow)

Risk	**Potential failure mode**	**Failure mode consequences/ effects**	**Comment/ suggestion** (e.g. Agree?, Severity? , Other failure mode?)	**Propose risk reduction**
Lack of stepwise/ critical point approach to review the required document	Unstandardized inspection	Missing critical review point, Different inspection results, Bad reputation of authority	Agree that this is a risk (potentially high if there are aspects not covered at the inspection).	- Training of inspectors (including routine periodic re-training) - Implement standardized inspection work plan and work instruction - Buddy system? e.g. have one lead inspector accompanying a more junior inspector - Periodic technical training or workshop, incorporating scenarios and quizzes for discussion

Different background experience of GMP inspector in performing inspection	Unstandardized inspection	Difference in inspection strictness	Agree, High risk	- Assigning inspectors to the appropriate scope of inspection appropriate to their background and training, e.g. non-sterile vs sterile - Implement a training framework to bridge the qualification gap (prior to assigning to that type of inspection)
Credibility of translator and the translated documents	Incorrect data, Missing critical point, Incomplete information	Approved non-compliance GMP manufacturers	Agree, Not sure about the severity or extend of this risk.	- Would it be possible to request for documents that have been certified or notarized by the issuing authority? - Where possible, confirm authenticity of the documents with the regulator or regulatory database, e.g. EUDRA, USFDA COMSTATS, - Collaborate with other recognized international regulators e.g. TGA, etc.

Appendix 1C

Italy's representatives (PIC/S member)

1. The risks from regulation gap analysis (Thai regulations against five globally-selected countries)

Risks of Thai FDA regulation	**Potential failure mode**	**Failure mode consequences/ effects**	**Comment/ suggestion** (e.g. Agree?, Severity?, Other failure mode?)	**Propose risk reduction**
Limited inspection to finished products only	Inspection of API-related manufacturing is missed	Drug quality defect as a product complaints and product recalls may occur due to poor quality of the API	Agree, Severity: High	- API sampling for test - Finished product manufacturer full testing on API - API supplier's audit by the FP Company
No regulation requirement for renewal/re-inspection	No guarantee of GMP non-compliance throughout product life cycle	Poor drug quality, harm to patients	Agree, Severity: High	- Marketing authorization holder (MAH) or importing company should perform an audit and a qualify person (QP) should declare the regular GMP conformity of the site
Desktop inspection for non-PIC/S or non-WHO PQ certified manufacturers	Questionable GMP standard as not fully implemented on-site inspection, real conditions different from reported values in document, may non-systemic workflow in routine inspection of own authority	Poor of drug quality, approved non-compliance GMP standard manufacturers or deviated GMP standards from local inspectors and community authorities, no standardized workflow	Agree, Severity: High	- QP release (for importer or MAH) according to a formal audit and/or QC full testing should be performed

2. The risks from workflow analysis (Current workflow)

Risk	**Potential failure mode**	**Failure mode consequences/ effects**	**Comment/ suggestion** (e.g. Agree?, Severity? , Other failure mode?)	**Propose risk reduction**
Lack of stepwise/critical point approach to review the required document	Unstandardized inspection	Missing critical review point, Different inspection results, Bad reputation of authority	Agree, Severity: High	- Training on PIC/S GMP
Different background experience of GMP inspector in performing inspection	Unstandardized inspection	Difference in inspection strictness	Agree, Severity: High	- Training on PIC/S GMP - Joint audit PIC/S Programme
Credibility of translator and the translated documents	Incorrect data, Missing critical point, Incomplete information	Approved non-compliance GMP manufacturers	Agree, Severity: High	- Use only “sworn translation” or use embassy qualified translator

Appendix 1D

WHO's representatives

1. The risks from regulation gap analysis (Thai regulations against five globally-selected countries)

Risks of Thai FDA regulation	**Potential failure mode**	**Failure mode consequences/ effects**	**Comment/ suggestion** (e.g. Agree?, Severity?, Other failure mode?)	**Propose risk reduction**
Limited inspection to finished products only	Inspection of API-related manufacturing is missed	Drug quality defect as a product complaints and product recalls may occur due to poor quality of the API	Agree	- Rely on GMP certificates for API manufacturers or may be obtained from a reputable authority (e.g. EDQM, EUDRAGMP). However, it is the responsibility of the FP manufacturer to ensure the quality of the API as part of the outsourcing activities agreement between FP & API manufacturers
No regulation requirement for renewal/re-inspection	No guarantee of GMP non-compliance throughout product life cycle	Poor drug quality, harm to patients	Agree	- Establish a specific period (e.g. five years) for reviewing the status of the registration and compliance beside reviewing post marketing surveillance (PMS) - However, this shall determine the need/ frequency of renewal/ re-inspection of manufacturing sites based on the risk metric.
Desktop inspection for non-PIC/S or non-WHO PQ certified manufacturers	Questionable GMP standard as not fully implemented on-site inspection, real conditions different from	Poor of drug quality, approved non-compliance GMP standard manufacturers or deviated GMP standards from local inspectors	Agree	- Desktop inspection is not applicable for manufacturers that is not located in country with stringent authority and onsite inspection is mandatory.

	reported values in document, may non-systemic workflow in routine inspection of own authority	and community authorities, no standardized workflow		

2. The risks from workflow analysis (Current workflow)

Risk	**Potential failure mode**	**Failure mode consequences/ effects**	**Comment/ suggestion** (e.g. Agree?, Severity? , Other failure mode?)	**Propose risk reduction**
Lack of stepwise/critical point approach to review the required document	Unstandardized inspection	Missing critical review point, Different inspection results, Bad reputation of authority	Agree	- Using standardized aide memoire and continuous training in how to review the documents as per SOP
Different background experience of GMP inspector in performing inspection	Unstandardized inspection	Difference in inspection strictness	Agree	- Continues training regarding major topics in GMP and use of different level of approvals
Credibility of translator and the translated documents	Incorrect data, Missing critical point, Incomplete information	Approved non-compliance GMP manufacturers	Agree	- Requesting the company to provide translated documents from officially certified translation centres

Appendix 2

Detail of occurrence (O), severity (S) and detectability (D) scores from each team member and calculation of risk priority number (RPN) values

Appendix 2A Detail of occurrence (O), severity (S) and detectability (D) scores from each team member and calculation of risk priority number (RPN) values of regulation gap analysis before implementing risk reduction

Risks	I*	II*	III*	IV*	V*	VI*	O	S	D	RPN	Conclusion and brainstorming
Scope of inspection											
การตรวจประเมินเฉพาะสถานที่ผลิตยาสำเร็จรูป (Limited inspection to finished products only)	O=3 S=5 D=5	O=3 S=5 D=5	O=3 S=5 D=5	O=3 S=5 D=4	O=3 S=5 D=4	O=3 S=5 D=5	3	5	5	75	- Debatable, in terms of D - O = 3 เนื่องจากมีจากข้อมูลปัญหาคุณภาพยามาจากโรงงานผลิต API ต่อเนื่องทุกปี ซึ่งมีจำนวนแตกต่างกันออกไป โดยจำนวนที่พบเข้าข่ายตามนิยามของการให้คะแนนนี้ - S = 5 เนื่องจากผลที่เกิดขึ้นจากโรงงาน API ที่ไม่ได้มาตรฐานหรือไม่มีคุณภาพ เช่น การปนเปื้อนของสารต่าง ๆ ระหว่างการสังเคราะห์ยา ส่งผลต่อคุณภาพของผลิตภัณฑ์โดยตรง - D = 5 แม้จะมีการยื่นเอกสาร GMP certificate ของสถานที่ผลิต API ก่อนการขึ้นทะเบียนแล้วก็ตาม แต่การไม่มีระบบหรือไม่ได้ตรวจสอบคุณภาพมาตรฐานการผลิตสถานที่ผลิต API ก่อนการขึ้นทะเบียนและให้อนุญาตนำเข้านั้น ทำให้ไม่สามารถมีระบบหรือช่องทางในการตรวจสอบได้ โดยเฉพาะโรงงานผลิต API โดยมากจะเป็นประเภท Non-PIC/S
Implementation											
การไม่มีข้อกำหนดให้มีการตรวจประเมิน GMP สถานที่ผลิตยาในต่างประเทศต่อเนื่องเป็นประจำ (No regulation requirement for renewal/ re-inspection)	O=3 S=3 D=5	O=3 S=3 D=5	O=3 S=3 D=5	O=3 S=3 D=5	O=3 S=4 D=5	O=3 S=4 D=5	3	3	5	45	- Debatable, in terms of S - O = 3 เนื่องจากจำนวนสถานที่ผลิตยาที่ผ่านการตรวจตั้งแต่ปี 2016-2018 จะหมดอายุในปี 2019-2021 ซึ่งมีจำนวนปานกลางตามนิยามของการให้คะแนนนี้ - S = 3 แม้ว่าสถานที่ผลิตยาเหล่านี้ได้รับการตรวจในครั้งแรกจาก อย.แล้ว แต่จากการพิจารณาข้อมูลเชิงสถิติที่เสนอมีสถานที่ผลิต

											ยาประเภท PIC/S จำนวนมากประมาณ 70% ในแต่ละปีซึ่งจะได้รับการตรวจจากหน่วยงาน PIC/S ของประเทศนั้น ๆ เป็นระยะ จึงมีความรุนแรงในระดับปานกลาง - D = 5 เนื่องจากการไม่ได้ตรวจสอบคุณภาพมาตรฐานการผลิตยาเป็นระยะตลอดอายุของทะเบียนตำรับยา ทำให้ไม่มีระบบที่สามารถตรวจสอบคุณภาพได้ และหากเกิดข้อบกพร่องร้ายแรงกับสถานที่ผลิตยาในต่างประเทศ ปัจจุบันยังไม่มีช่องทางอย่างเป็นทางการในการแจ้งให้ประเทศไทยทราบ
Regulatory content											
การกำหนดให้มีการพิจารณาเอกสารเหมือนกันทุกประเภทของสถานที่ผลิตยา (Similar required document among non-sterile, sterile and biological manufacturers)	O=3 S=4 D=3	O=3 S=4 D=3	O=3 S=4 D=3	O=3 S=4 D=3	O=3 S=4 D=3	O=3 S=4 D=3	3	4	3	36	- Agreed - O = 3 เนื่องจากข้อมูลเชิงสถิติพบจำนวนสถานที่ผลิตยามากกว่า 50% อยู่ในประเภท non-sterile ซึ่งมีขั้นตอนการผลิตที่ไม่ซับซ้อน รายการเอกสารที่กำหนดให้พิจารณาจึงส่งผลให้โอกาสในการเกิดข้อบกพร่องอยู่ในระดับปานกลาง - S = 4 เนื่องจากการที่ไม่ได้กำหนดเอกสารที่จำเพาะเจาะจงแต่ละประเภท จะส่งผลโดยตรงกับคุณภาพของการตรวจ เช่น การผลิตยาปราศจากเชื้อที่ผลิตโดยเทคนิคปราศจากเชื้อต้องทำ media fill ซึ่งเป็นขั้นตอนสำคัญ หากไม่มีการพิจารณาตรงนี้อาจจะมีความรุนแรงมากต่อคุณภาพของผลการตรวจได้ - D = 3 เพราะรายการเอกสารที่กำหนดในปัจจุบัน มีความสามารถเพียงพอในเบื้องต้นที่จะตรวจสอบขั้นตอนเฉพาะของแต่ละผลิตภัณฑ์ได้ เช่น SMF, inspection report and CAPA plan report เป็นต้น

การตรวจประเมินด้วยระบบการตรวจสอบเฉพาะเอกสารสำหรับสถานที่ผลิตยาประเภท Certified by PIC/S (Desktop inspection for certified by PIC/S manufacturers)	O=2 S=3 D=3	O=2 S=3 D=3	O=2 S=3 D=3	O=2 S=3 D=3	O=2 S=3 D=3	O=2 S=3 D=3	2	3	3	18	- Agreed - O = 2 จากข้อมูลเชิงสถิติจะเห็นได้ว่าสถานที่ผลิตยาประเภท Certified by PIC/S มีจำนวนไม่มาก เช่น ในปี 2016 อยู่ในช่วงประมาณ 17% ของสถานที่ผลิตยาทั้งหมด เป็นต้น ทำให้โอกาสในการเกิดจึงมีไม่มาก - S = 3 ความรุนแรงอาจมีไม่มากนักเนื่องจากว่าสถานที่ผลิตยาประเภทนี้เคยผ่านการตรวจประเมินจากสมาชิกองค์กร PIC/S ด้วย PIC/S GMP หรือ WHO prequalification team (WHO PQ) ด้วย WHO GMP แล้ว ความรุนแรงที่จะเกิดขึ้นต่อความน่าเชื่อถือของระบบการตรวจของประเทศไทยหรือความรุนแรงที่อาจเกิดขึ้นกับตัวผลิตภัณฑ์จากสถานที่ประเภทนี้จึงอยู่ในระดับปานกลาง - D = 3 ถึงแม้ว่าสถานที่แห่งนี้จะไม่ได้อยู่ในประเทศ PIC/S แต่ผ่านการตรวจประเมินจาก PIC/S หรือ WHO PQ team แล้ว ระบบการตรวจประเมิน Desktop inspection มีการขอเอกสาร GMP inspection report และ CAPA plan มาพิจารณาซึ่งเป็นกลไกที่จะตรวจสอบสถานการณ์ปฏิบัติตามหลักเกณฑ์ GMP และประวัติการตรวจประเมินของสถานที่ผลิตยาแห่งนี้ได้
การตรวจประเมินด้วยระบบการตรวจสอบเฉพาะเอกสารสำหรับสถานที่ผลิตยาประเภท non-PIC/S หรือ non-WHO PQ (Desktop inspection for non-PIC/S or non-WHO PQ certified manufacturers)	O=5 S=4 D=5	O=5 S=4 D=5	O=5 S=4 D=4	O=5 S=4 D=5	O=5 S=4 D=5	O=5 S=4 D=5	5	4	5	100	- Agreed - O = 5 จากข้อมูลเชิงสถิติจะเห็นได้ว่าสถานที่ผลิตยาประเภทนี้มีจำนวนน้อยที่สุด (1-5%) แต่พบปัญหาการเรียกเก็บยาคืนมาก (60 กว่า %) ทำให้โอกาสในการเกิดจึงมีมาก - S = 4 เนื่องด้วยระบบการตรวจที่แตกต่างกันของแต่ละหน่วยงานและหลายระดับ เช่น รัฐ มณฑล จังหวัด รวมถึงมาตรฐาน GMP ที่เป็นมาตรฐานภายใน หากตรวจเพียงแต่

											เอกสารเท่านั้น ความรุนแรงที่จะเกิดขึ้นต่อความน่าเชื่อถือของระบบการตรวจของประเทศไทยหรือความรุนแรงที่อาจเกิดขึ้นกับตัวผลิตภัณฑ์จากสถานที่ประเภทนี้จึงอยู่ในระดับสูง - D = 5 เนื่องจากมีระบบที่ตรวจสอบได้ยาก หากมีการเตรียมเอกสารจากผู้ผลิตที่ดี ตรงตามข้อกำหนด แต่พนักงานไม่ปฏิบัติตามอาจเกิด deviation ได้ และส่งผลต่อคุณภาพของผลิตภัณฑ์ ซึ่งยังไม่มีระบบการตรวจในจุดนี้

*Remark

I = Delegate from GMP inspection of overseas pharmaceutical manufacturers sub-committee

II = Delegate from drug quality defect working group

III = Lead GMP inspector

IV = Reviewer from the drug registration unit

V = Delegate from manufacturers licensing unit

VI = The author

Appendix 2B Detail of occurrence (O), severity (S) and detectability (D) scores from each team member and calculation of risk priority number (RPN) values from workflow analysis before implementing risk reduction

Risks	I*	II*	III*	IV*	V*	VI*	O	S	D	RPN	Conclusion and brainstorming
Licensee											
ความไม่เข้าใจในเอกสารที่ต้องยื่นพิจารณาของผู้ประกอบการ (Licensees misunderstand the required documents)	O=5 S=3 D=2	O=5 S=3 D=2	O=5 S=3 D=2	O=5 S=3 D=2	O=5 S=3 D=2	O=5 S=3 D=2	5	3	2	30	- Agreed - O = 5 เนื่องจากมีโอกาสในการเกิดสูงมาก โดยมีข้อมูลการยื่นคำขอให้ตรวจประเมินของผู้ประกอบการพบว่ามีคำขอที่ยื่นแล้วเอกสารไม่ถูกต้องอยู่ในระหว่างจำนวนตามนิยาม (1 ใน 5) - S = 3 เนื่องจากจำนวนของรายการเอกสารและรายละเอียดของเนื้อหาในแต่ละประเภทเอกสารที่ไม่ถูกต้องหรือไม่เข้าใจของผู้ประกอบการจะค่อยไม่กระทบกับคุณภาพและมาตรฐานของสถานที่ผลิตยา - D = 2 เพราะมีระบบการตรวจสอบความครบของเอกสารที่ศูนย์ One Stop Service Center (OSSC) และยังมีขั้นตอนของผู้ตรวจพิจารณาที่จะสามารถตรวจสอบและร้องขอเอกสารเพิ่มเติมได้อีกครั้งถ้าเห็นว่าไม่ครบถ้วน
ผู้ประกอบการยื่นเอกสารไม่ครบถ้วนหรือไม่ถูกต้อง (Licensee submit uncomplete and/or incorrect document)	O=4 S=3 D=2	O=4 S=3 D=2	O=4 S=3 D=2	O=4 S=3 D=2	O=4 S=3 D=2	O=4 S=3 D=2	4	3	2	24	- Agreed - O = 4 เนื่องจากมีโอกาสในการเกิดสูง โดยมีข้อมูลการยื่นคำขอให้ตรวจประเมินของผู้ประกอบการพบว่ามีคำขอที่ยื่นแล้วเอกสารไม่ถูกต้องอยู่ในระหว่างจำนวนตามนิยาม (1 ใน 25) - S = 3 เนื่องจากจำนวนของรายการเอกสารและรายละเอียดของเนื้อหาในแต่ละประเภทเอกสารที่ไม่ถูกต้องหรือไม่เข้าใจของผู้ประกอบการจะค่อยไม่กระทบกับคุณภาพและมาตรฐานของสถานที่ผลิตยา รวมถึงผู้ประกอบการสามารถยื่นคำขอมาได้อีกครั้ง โดยอาจจะทำให้การขึ้นทะเบียนล่าช้า แต่อยู่ในหลักเดือนซึ่งจะไม่รุนแรงมากนัก

											- D = 2 เพราะมีระบบการตรวจสอบความครบของเอกสารที่ศูนย์ One Stop Service Center (OSSC) และยังมีขั้นตอนของผู้ตรวจพิจารณาที่จะสามารถตรวจสอบและร้องขอเอกสารเพิ่มเติมได้อีกครั้งถ้าเห็นว่าไม่ครบถ้วน
Thai FDA officer/ GMP inspector											
ความเข้าใจผิดของเจ้าหน้าที่ที่ตรวจสอบความครบถ้วนของเอกสาร (Misunderstanding the required documents by screening officers)	O=3 S=3 D=3	O=3 S=3 D=3	O=3 S=3 D=3	O=3 S=3 D=3	O=3 S=3 D=3	O=3 S=3 D=3	3	3	3	27	- Agreed - O = 3 เนื่องจากข้อมูลที่ผู้ตรวจได้รับ หลังจากที่เจ้าหน้าที่ OSSC รับเอกสารเข้ามาอยู่ในระหว่างประมาณ 1 ใน 3-400 คำขอ ซึ่งอยู่ในระดับปานกลาง - S = 3 เนื่องจากมีผู้ตรวจและผู้ทวนสอบที่พิจารณาเอกสาร หากพบเอกสารไม่ถูกต้อง จะมีขั้นตอนการขอเอกสารเพิ่มเติมได้อีกครั้ง จึงทำให้ความรุนแรงอยู่ในปานกลาง - D = 3 แม้จะไม่มีระบบการตรวจสอบว่าเจ้าหน้าที่ OSSC รับเอกสารมาถูกหรือไม่ ก่อนที่จะรับคำขอเข้ามาในระบบหรือส่งให้ผู้ตรวจพิจารณา แต่ปัจจุบันมีขั้นตอนการตรวจจากผู้ตรวจและทวนสอบจาก Lead GMP inspector /QSM อีกขั้นตอน ทำให้ระบบการตรวจสอบตรงนี้มีคะแนนในระดับปานกลาง
ประสบการณ์ที่แตกต่างกันของผู้ตรวจประเมินในประเมินมาตรฐานสถานที่ผลิตยา (Different background experience of GMP inspector in performing inspection)	O=3 S=4 D=3	O=3 S=4 D=4	O=3 S=4 D=4	O=3 S=4 D=3	O=3 S=4 D=3	O=3 S=4 D=3	3	4	3	36	- Debatable, in terms of D - O = 3 เนื่องจากจำนวนผู้ตรวจมีมาก ประมาณ 20 คน ซึ่งมีประสบการณ์แตกต่างกัน แต่อย่างไรก็ตามปัจจุบันมีการใช้ระบบ Inspector Qualification จึงทำให้โอกาสในการเกิดอยู่ในระดับปานกลาง - S = 4 เนื่องจากว่าการที่ผู้ตรวจตรวจด้วยมาตรฐานแตกต่างกันจากการมีประสบการณ์ต่างกันส่งผลต่อคุณภาพของระบบโดยตรง เช่น สถานที่ผลิตยาเดียวกันผ่านการตรวจจากผู้ตรวจสองคน คนหนึ่งอนุมัติแต่อีก

											คนไม่อนุมัติ เป็นต้น - D = 3 แม้ว่าจะการเสนอคะแนนที่มากกว่า 3 แต่อย่างไรก็ตาม ตอนนี้มีระบบการทวนสอบผลการตรวจประเมินโดย lead GMP inspector และ quality system manager ซึ่งมีความสามารถที่จะตรวจสอบความเสี่ยงในจุดนี้ได้
ประสบการณ์ที่แตกต่างกันของหัวหน้าผู้ตรวจประเมินหรือผู้จัดการระบบคุณภาพในการทวนสอบข้อมูลผลการตรวจประเมิน (Difference the background experience of lead GMP inspector or quality system manager in verifying inspection results)	O=3 S=4 D=2	O=3 S=4 D=2	O=3 S=4 D=2	O=3 S=4 D=2	O=3 S=4 D=2	O=3 S=4 D=2	3	4	2	24	- Agreed - O = 3 เนื่องจากจำนวนผู้ทวนสอบแต่ละคนมีประสบการณ์แตกต่างกัน แต่อย่างไรก็ตามปัจจุบันมีการใช้ระบบ lead GMP inspector/QSM Qualification จึงทำให้โอกาสในการเกิดอยู่ในระดับปานกลาง - S = 4 เนื่องจากว่าการที่ผู้ทวนสอบที่ตรวจสอบด้วยมาตรฐานแตกต่างกันจากการมีประสบการณ์ต่างกันส่งผลต่อคุณภาพของระบบโดยตรง - D = 2 ปัจจุบันมีระบบการทวนสอบผลการตรวจประเมินโดยให้ทั้ง lead GMP inspector และ QSM รวมไปถึงหัวหน้ากลุ่มก่อนเสนอให้ผู้บริหารอนุมัติ
การอนุมัติสถานที่ผลิตยาที่ไม่ได้มาตรฐานตามข้อกำหนด GMP โดยผู้บริหาร (Approved non-compliance GMP manufacturers by director)	O=2 S=5 D=2	O=2 S=5 D=2	O=2 S=5 D=1	O=2 S=5 D=1	O=2 S=5 D=1	O=2 S=5 D=1	2	5	1	10	- Debatable, in terms of D - O = 2 เนื่องจากผู้บริหาร (director) มี 1 ท่าน รวมถึงจากข้อมูลเชิงสถิติพบว่าจำนวนสถานที่ผลิตยาที่อนุมัติโดยเฉพาะประเภท non-PIC/S ที่มีปัญหาคุณภาพยามีน้อย - S = 5 เนื่องจากผู้บริหารคือบุคคลที่มีอำนาจสุดท้ายในการอนุมัติให้โรงงานผ่านหรือไม่ผ่าน หากอนุมัติสถานที่ผลิตยาที่ไม่มีมาตรฐานตามข้อกำหนดจะส่งผลต่อคุณภาพของระบบโดยตรง - D = 1 เนื่องจากปัจจุบันมีระบบการตรวจสอบผลการตรวจประเมินของผู้ตรวจ โดยให้หัวหน้าในระดับ lead GMP inspector และ QSM เป็นผู้ทวนสอบรายงาน ทำให้ระบบการตรวจสอบสูง

ผู้ตรวจประเมินไม่ปฏิบัติตาม SOP (Inspectors may not follow SOP)	O=3 S=4 D=3	O=3 S=4 D=3	O=3 S=4 D=3	O=3 S=4 D=3	O=3 S=4 D=3	O=3 S=4 D=3	3	4	3	36	- Agreed - O = 3 เนื่องจากจำนวนผู้ตรวจมีมาก ประมาณ 20 คน แม้ว่าจะมีการอบรม SOP ในครั้งแรกที่มีการประกาศใช้แล้ว แต่ระหว่างที่มีการใช้งาน SOP เป็นระยะเวลา 3 ปี ยังไม่มีการอบรมซ้ำเป็นประจำทำให้มีโอกาสในการเกิดปานกลาง - S = 4 เนื่องจากผู้ตรวจที่ไม่ปฏิบัติตาม SOP ส่งผลต่อคุณภาพของระบบโดยตรง - D = 3 ปัจจุบันแม้จะมีระบบการตรวจสอบโดยบุคคลที่สอง แต่ใน SOP ไม่มีการระบุวิธีการหรือจุดสำคัญที่ต้องทวนสอบส่งผลให้ระบบการทวนสอบยังไม่ดีเท่าที่ควรนัก
ภาระงานที่สูงของผู้ตรวจประเมิน (High workload of the inspector)	O=3 S=4 D=3	O=3 S=4 D=3	O=3 S=4 D=3	O=3 S=4 D=3	O=3 S=4 D=3	O=3 S=4 D=3	3	4	3	36	- Agreed - O = 3 เนื่องจาก แม้ว่าจำนวนผู้ตรวจมีจำกัดกับจำนวนสถานที่ผลิตยามีจำนวนสูงมากตามข้อมูลเชิงสถิติ แต่จากการตรวจตรวจสอบข้อมูลภายในของหน่วยงานพบว่ามีจำนวนสถานที่ผลิตยาที่ดำเนินการไม่ทันตามกำหนดเวลาอยู่ในจำนวนปานกลางตามนิยาม - S = 4 หากผู้ตรวจที่มีภาระงานมาก การตรวจที่ไม่มีประสิทธิภาพมากนักส่งผลต่อคุณภาพของระบบโดยตรง - D = 3 เนื่องจากปัจจุบันมีระบบการอนุมัติรายงานโดยบุคคลที่สอง และมีหน่วยงานภายในในการติดตามการทำงานของผู้ตรวจซึ่งจะช่วยตรวจสอบในส่วนนี้ได้

Desktop inspection system											
การไม่กำหนดประเด็นสำคัญในการพิจารณาเอกสารแต่ละประเภท (Lack of stepwise approach to review the required document)	O=4 S=5 D=4	O=4 S=5 D=4	O=4 S=5 D=4	O=4 S=5 D=4	O=4 S=5 D=4	O=4 S=5 D=4	4	5	4	80	- Agreed - O = 4 เนื่องจากรายการเอกสารที่ต้องพิจารณาประเมินมีจำนวนมาก โดยเฉพาะสถานที่ผลิตยาประเภท non-PIC/S มีถึงประมาณ 20 รายการทำให้ดอกาสในการเกิดสูง - S = 5 เนื่องจาก SOP ไม่มีรายละเอียดจุดสำคัญที่ต้องพิจารณาเอกสารส่งผลต่อคุณภาพของระบบโดยตรง และจากข้อมูลปัญหาคุณภาพยามีมาจากการผลิตเป็นส่วนใหญ่ซึ่งจะตรวจได้จากเอกสารบันทึกการผลิตยาหรือรายงานการตรวจสอบความถูกต้องของกระบวนการ เป็นต้น - D = 4 ปัจจุบันมีระบบการทวนสอบผลการตรวจประเมินโดย lead GMP inspector และ QSM แต่ใน SOP ดังกล่าว ก็ไม่มีวิธีหรือจุดสำคัญที่ใช้ในการทวนสอบเช่นกันส่งผลให้การตรวจสอบในจุดนี้อาจจะยังไม่มีประสิทธิภาพมากนัก
การไม่จำกัดจำนวนคำขอให้ตรวจประเมิน (Unlimited number of applications)	O=4 S=3 D=2	O=4 S=3 D=2	O=4 S=3 D=2	O=4 S=3 D=2	O=4 S=3 D=2	O=4 S=3 D=2	4	3	2	24	- Agreed - O = 4 เนื่องจากจำนวนคำขอตรวจประเมินมีจำนวนสูงต่อวัน (ประมาณ 10-20 ต่อวัน) เจ้าหน้าที่ OSSC จึงมีโอกาสทำงานไม่ทันเวลาสูง - S = 3 เนื่องจากการรับเอกสารที่ไม่ครบส่งผลต่อคุณภาพการตรวจโดยตรง แต่อย่างไรก็ตามจะมีผู้ตรวจและผู้ทวนสอบที่พิจารณาเอกสารหากพบเอกสารไม่ถูกต้อง จะมีขั้นตอนการขอเอกสารเพิ่มเติมได้อีกครั้ง ความรุนแรงจึงปานกลาง

											- D = 2 แม้ว่าจะไม่มีระบบการตรวจสอบการตรวจรับเอกสารของเจ้าหน้าที่ OSSC ว่ารับเอกสารถูกหรือไม่ก่อนที่จะรับคำขอเข้ามาในระบบหรือส่งให้ผู้ตรวจพิจารณา แต่ปัจจุบันมีขั้นตอนการตรวจจากผู้ตรวจอีกครั้งก่อนการประเมิน และทวนสอบจาก Lead GMP inspector /QSM อีกหนึ่งขั้นตอนก่อนการเสนอเพื่ออนุมัติ
SOP ล้าสมัย (Obsolete internal SOP)	O=3 S=3 D=2	O=3 S=3 D=2	O=3 S=3 D=2	O=3 S=3 D=2	O=3 S=3 D=2	O=3 S=3 D=2	3	3	2	18	- Agreed - O = 3 เนื่องจากปัจจุบันมีข้อมูลจากหน่วยงานภายในว่าจำนวน SOP ที่หมดอายุไม่มากร่วมกับความถี่ในการทบทวนเอกสารที่ค่อนข้างนาน (3 ปี) โอกาสในการเกิดอยู่ในระดับปานกลาง - S = 3 เนื่องจากการทำงานตาม SOP ที่ไม่มีการปรับปรุงให้เป็นปัจจุบันส่งผลโดยตรงต่อคุณภาพการตรวจ แต่อย่างไรก็ตามในส่วนของ SOP มีระบุเฉพาะเรื่องของขั้นตอนการทำในภาพรวม เวลาที่จะต้องดำเนินการและผู้ดำเนินการ ยังไม่กำหนดจุดสำคัญที่ต้องพิจารณาเอกสารแต่ละประเภท ทำให้ความรุนแรงอยู่ในระดับปานกลาง - D = 2 เนื่องจากปัจจุบันมีระบบการติดตามการปรับปรุงแก้ไข SOP ตามกำหนดระยะเวลาของหน่วยงานกลาง ทำให้มีการระบบการตรวจสอบในจุดนี้
ความน่าเชื่อถือของผู้แปลหรือเอกสารที่แปล (Credibility of translator and the translated documents)	O=3 S=5 D=4	O=3 S=5 D=4	O=3 S=5 D=5	O=3 S=5 D=4	O=3 S=5 D=4	O=3 S=5 D=4	3	5	4	60	- Debatable, in terms of D - O = 3 เนื่องจากข้อมูลของเจ้าหน้าที่ OSSC ที่บันทึกมีจำนวนไม่มากประมาณ 1ครั้ง จาก 400 คำขอ สอดคล้องตามนิยาม - S = 5 เนื่องจากส่งผลความรุนแรงกับผลการตรวจประเมินโดยตรง เช่น การแปลจำนวน ระดับ หรือรายละเอียดข้อบกพร่องที่ผิดไปจากเอกสารต้นฉบับ เป็นต้น

											- D = 4 แม้ว่าปัจจุบันจะมีการกำหนดให้ยื่นเอกสาร certificate สถาบันการแปลหรือคนแปลมาด้วยแล้ว แต่การตรวจสอบเป็นเพียงการตรวจด้วยระบบ manual เท่านั้นซึ่งสามารถตรวจสอบได้ยาก รวมทั้งเจ้าหน้าที่ OSSC มีน้อยด้วย

*Remark

I = Delegate from GMP inspection of overseas pharmaceutical manufacturers sub-committee

II = Delegate from drug quality defect working group

III = Lead GMP inspector

IV = Reviewer from the drug registration unit

V = Delegate from manufacturers licensing unit

VI = The author

Appendix 2C Detail of occurrence (O), severity (S) and detectability (D) scores from each team member and calculation of risk priority number (RPN) values from regulation gap and workflow analysis after implementing risk reduction

Risks	I*	II*	III*	IV*	V*	VI*	New O	New S	New D	New RPN	Conclusion and brainstorming
Regulation gap risk											
การตรวจประเมินด้วยระบบการตรวจสอบเฉพาะเอกสารสำหรับสถานที่ผลิตยาประเภท non-PIC/S หรือ non-WHO PQ (Desktop inspection for non-PIC/S or non-WHO PQ certified manufacturers)	O=3 S=4 D=3	O=3 S=4 D=3	O=3 S=4 D=3	O=3 S=4 D=3	O=3 S=4 D=3	O=3 S=4 D=3	3	4	3	36	- Agreed - O = 3 เนื่องจากการมีแนวทางการตรวจประเมินจุดสำคัญสำหรับเอกสารแต่ละประเภทจะช่วยให้ผู้ตรวจทราบว่าจะต้องตรวจในประเด็นใดบ้าง ส่งผลให้โอกาสในการเกิดการตรวจประเมินที่ไม่ครบถ้วนลดลงมาอยู่ในระดับปานกลาง (จาก 5 เป็น 3) - S = 4 ให้คะแนนเท่าเดิม เนื่องจากความรุนแรงของการที่ผู้ตรวจตรวจเอกสารสำคัญไม่ครบถ้วนทุกประเด็นจะเกิดขึ้นต่อความน่าเชื่อถือของระบบการตรวจของประเทศไทยหรือความรุนแรงที่อาจเกิดขึ้นกับตัวผลิตภัณฑ์จากสถานที่ประเภทนี้จึงอยู่ในระดับสูง - D = 3 เนื่องจากการมีแนวทางการตรวจประเมินจุดสำคัญสำหรับเอกสารแต่ละประเภทจะช่วยให้ผู้ตรวจใช้เป็นเครื่องมือในการตรวจสอบตนเองว่าตรวจประเมินครบถ้วนประเด็นแล้ว คะแนนจึงลดลง (จาก 5 เป็น 3)
Workflow risk											
การไม่กำหนดประเด็นสำคัญในการพิจารณาเอกสารแต่ละประเภท (Lack of stepwise approach to review the required document)	O=2 S=4 D=3	O=2 S=4 D=3	O=2 S=4 D=3	O=2 S=4 D=3	O=2 S=4 D=3	O=2 S=4 D=3	2	4	3	24	- Agreed - O = 2 เนื่องจากรายการเอกสารที่ต้องพิจารณาประเมินมีจำนวนมากและแตกต่างในแต่ละประเภทสถานที่ผลิต การมีแนวทางการตรวจประเมินจุดสำคัญสำหรับเอกสารแต่ละประเภทสำหรับทุกสถานที่ผลิตยา จะช่วยให้ผู้ตรวจทราบว่าจะต้องตรวจในประเด็นใดบ้าง ส่งผลให้โอกาสในการเกิดการตรวจประเมินที่ไม่ครบถ้วนลดลงมาอยู่ในระดับ

											ปานกลาง (จาก 4 เป็น 2) - S = 4 ความรุนแรงของการที่ผู้ตรวจตรวจเอกสารสำคัญไม่ครบถ้วนทุกประเด็นจะเกิดขึ้นต่อความน่าเชื่อถือของระบบการตรวจของประเทศไทย แต่อย่างไรก็ตาม การมี SOP ที่กำหนดจุดสำคัญในการตรวจเอกสารสำหรับทุกประเภทสถานที่ผลิตนั้น ช่วยลดความรุนแรงลงได้ (จาก 5 เป็น 4) - D = 3 เนื่องจากการมีแนวทางการตรวจประเมินจุดสำคัญสำหรับเอกสารแต่ละประเภทจะช่วยให้ผู้ตรวจใช้เป็นเครื่องมือในการตรวจสอบตนเองว่าตรวจประเมินครบถ้วนประเด็นแล้ว คะแนนจึงลดลง (จาก 4 เป็น 3)

*****Remark

I = Delegate from GMP inspection of overseas pharmaceutical manufacturers sub-committee

II = Delegate from drug quality defect working group

III = Lead GMP inspector

IV = Reviewer from the drug registration unit

V = Delegate from manufacturers licensing unit

VI = The author

Appendix 3

GMP desktop inspection procedure of the Thai FDA

สำนักงานคณะกรรมการอาหารและยา
Food and Drug Administration

คู่มือขั้นตอนการปฏิบัติงาน

Procedure Manual (P)

ชื่อเอกสาร	การพิจารณามาตรฐานวิธีการในการผลิตยาของสถานที่ผลิตยาในต่างประเทศ	
รหัสเอกสาร	P-D3-17	
ครั้งที่แก้ไข	3	
วันที่ประกาศใช้	3 เมษายน 2563	
ผู้จัดทำ	นายวรานนท์ ชีวาจร	ตำแหน่ง เภสัชกรปฏิบัติการ
ผู้ตรวจสอบ	นางคัคนางค์ ปอแก้ว	ตำแหน่ง เภสัชกรชำนาญการ
	นายสมบัติ หิรัญศุภโชติ	ตำแหน่ง เภสัชกรชำนาญการพิเศษ
ผู้อนุมัติ	นายสุชาติ จองประเสริฐ	ตำแหน่ง ผู้อำนวยการกองยา

Appendix 4

Critical points to review the selected documents

Three selected documents were GMP inspection report, batch processing record and standard operating procedure of release product for supply.

The required documents	Example of critical points to review
GMP inspection report	- Most recent inspection report (e.g. not more than three years) - Report was issued by an overseas regulatory authority - Check correction of manufacturer's name and site address - Scope of report covers the scope of application (e.g. dosage form, steps of manufacture and buildings covered) - Inspection was performed according to equivalent PIC/S GMP standard - Time taken to inspect and size of inspection team was appropriation - Inspection finding and observation e.g. manufacturing processes, quality system, buildings and supporting systems - Number, level and details of GMP deficiencies e.g. critical, major and other deficiencies that found from on-site inspection - Require full report, not blind or brief report - Etc.

The required documents	Example of critical points to review
Batch processing record	- Formulation check - Weighting process (e.g. daily check of weight checker, logbook, cleaned record, weight tag) - Critical process parameter of production process e.g. mixing time, blending round, sieve size, speed of machine, filtration, temperature - Critical process parameter of packaging process e.g. coding, labelling, leaflet packing, temperature sealing - In process control e.g. appearance check, weight or volume check, disintegration time, pH - Quality control tested results and raw data checking e.g. assay, pH, psychical and microbiological test results - Reconciliation of starting and packaging material used record - Check percentage yield of each step (e.g. mixing, filling, packing) and finished product - Environmental control record (e.g. temperature, humidity, pressure differential) of each area - Line clearance record - List of operator/worker and signature - Time and date record - Etc.

The required documents	Example of critical points to review
SOP release product for supply	- Details of how qualified a person for release - List and responsibilities of authorized person and delegated person - Listed of review documents before release product for supply e.g. - Batch production and analytical record - Quality control testing results, - Non-compliance or deviation report - Out-of-specification investigations - Change control report - Environmental monitoring - Complaint and recall investigation report - Stability study report - Other related matters throughout production from all manufacturing sites - Details of status identification tag e.g. quarantine, approved or rejected tag - Check legally valid signature for every batch released - Traceability and completed history of each batch released - Etc.

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Appendix 5

The summary of risk assessment of GMP inspection of overseas pharmaceutical manufacturers based on PIC/S desktop inspection

Risk	Potential failure mode	Failure mode consequences/effects	O	S	D	RPN	Mitigation	Expected O	Expected S	Expected D	Expected RPN
Regulation gap analysis											
1. Desktop inspection for non-PIC/S or non-WHO PQ certified manufacturers	Questionable GMP standard as not fully implemented on-site inspection, Real conditions different from reported values in document, May non-systemic workflow in routine inspection of own authority	Poor of drug quality, Approved non-compliance GMP standard manufacturers or deviated GMP standards from local inspectors and community authorities	5	4	5	100	**<u>Proposed strategy:</u>** 1.1 Perform on-site inspection 1.2 Joint inspection with overseas regulatory authority to make the best use of human resource 1.3 Periodic on-site inspection alternating with desktop inspection 1.4 Desktop inspection with closed-circuit television (CCTV) to ensure correspondence of documents and in routine practice and to inspect critical areas 1.5 Evaluate GMP standard and inspection system of non-PIC/S regulators whether such regulators	3*	4*	3*	36*

							can be acceptable for desktop inspection 1.6 Structure a stepwise SOP to review the critical point of required documents such as focusing on QP release document 1.7 Sampling all imported products for quality control testing (as suggested by Italian interviewee)				
2. Limited inspection to finished products only	Inspection of API-related manufacturing is missed	Drug quality defect as a product complaints and product recalls may occur due to poor quality of the API	3	5	5	75	**<u>Proposed strategy:</u>** 2.1 Broaden the scope of the regulation for desktop inspection of API manufacturers 2.2 Put more focus on the review of API supplier (document: approve vender list procedure) during finished product (FP) manufacturer inspection	2	4	3	24

							2.3 FP company audits API supplier and conducts quality control test of API sampling (as suggested by Italian interviewee) 2.4 Collaborate with reputable regulatory authority (e.g. EDQM) to notify a quality-related issue of API (as suggested by Australian interviewee) 2.5 Periodic on-site inspection for API manufacturer (if possible)				
3. No regulation requirement for renewal/re-inspection	No guarantee of GMP non-compliance throughout product life cycle	Non- GMP compliance manufacturer still occurred, may lead to poor drug quality	3	3	5	45	**<u>Proposed strategy;</u>** 3.1 Revise regulation requirement for renewal throughout product life cycle or establish a specific period based on the risk metric 3.2 Alert system notification of invalid approval letter	2	3	3	18

							3.3 Increase collaboration with other international regulators on non GMP compliance signals (as suggested by Australian interviewee) 3.4 Consider to add requirements of post-market responsibilities by licensee e.g. manufacturer audit by licensee (as suggested by Australian and Italian interviewee) 3.5 Annual products sampling from market for QC testing				
4. Similar required document among non-sterile, sterile and biological manufacturers	Critical control points of specific/important process can be missed	Approved non-compliance GMP standard which can directly cause drug quality defect	3	4	3	36	**<u>Proposed strategy;</u>** 4.1 Construct a list of required documents categorized by dosage forms (non-sterile, sterile and biological manufacturers)	2	3	2	12

							4.2 Require more specific documents to ensure GMP compliance e.g. media fill validation or filter integrity validation report for aseptic sterile manufacturers				
5. Desktop inspection for certified by PIC/S manufacturers	Questionable GMP standard as not fully implemented on-site inspections throughout product life cycle	Poor of drug quality, Approved non-compliance GMP standard manufacturers or maybe deviated GMP standards from local inspectors	2	3	3	18	**<u>Proposed strategy:</u>** 5.1 Periodic on-site inspection alternating with desktop inspection e.g. perform desktop inspection every year along with an on-site inspection every two or three years depending on inspection results and risk assessment evaluation	2	3	2	12

Workflow analysis											
1. Lack of stepwise approach in document review	Unstandardized inspection	Missing critical review point, Different inspection results, Bad reputation of authority	4	5	4	80	<u>Proposed strategy;</u> 1.1 Structure stepwise to review document and training inspectors (including routine periodic re-training) 1.2 Harmonization on inspection procedure (as suggested by Philippines interviewee) 1.3 Using personal aide memoire (shortly taken note) to review document (as suggested by WHO interviewee)	2*	4*	3*	24*
2. Credibility of translator and the translated documents	Incorrect data, Missing critical point, Incomplete information	Approved non-compliance GMP manufacturers	3	5	4	60	<u>Implemented strategy;</u> 2.1 Request certificate of translator/translation center to ensure the credibility of translated documents 2.2 Request original document for cross-check	2	4	2	16

							<u>Proposed strategy:</u> 2.3 Confirm credibility of translated documents by cross-check with regulatory database e.g. EUDRA GMP database of EU countries, COMSTATS GMP database of US FDA 2.4 Collaborate with original regulators to cross-check the accuracy of translated documents (as suggested by Australian interviewee) 2.5 Blacklist questionable manufacturer/licensee for further consideration 2.6 Use only qualified embassy translator (if possible)				
3. Different background experience of GMP inspector in performing	Unstandardized inspection	Difference in inspection strictness and results	3	4	3	36	<u>Implemented strategy:</u> 3.1 Assigning inspectors to the appropriate scope of inspection based on their experience (higher	2	4	2	16

inspection							level inspector responsible for sterile and biological manufacturer) 3.2 Verification by higher level inspectors before approval 3.3 Group discussion by internal system when having a special quality issue 3.4 Shared inspection approval report to all internal inspectors for supporting inspection of the previously-inspected manufacturer <u>Proposed strategy:</u> 3.5 Periodic technical training or workshop, incorporating scenarios and quizzes for discussion 3.6 Use buddy system for coaching junior				

							inspectors (as suggested by Australian interviewee) 3.7 Schedule monthly meeting to share critical issue and standardize inspection procedure 3.8 Joint PIC/S training program routinely				
4. Inspectors may not follow SOP	Work practice deviate from proper process	Inspection process may be wrong	3	4	3	36	<u>Implemented strategy:</u> 4.1 Verification by higher level inspectors before approval <u>Proposed strategy:</u> 4.2 Periodic technical training or workshop, incorporating scenarios and quizzes for discussion 4.3 Set up notification system for updated SOP	2	4	2	16
5. High workload of the inspector	Error/Missing critical points to review documents	Inefficient of inspection result, Unable to finish inspection on time	3	4	3	36	<u>Implemented strategy:</u> 5.1 Increase number of inspectors	2	4	2	16

							<u>Proposed strategy;</u> 5.2 Manpower analysis 5.3 Establish electronic-submission and online inspection system to reduce the time of internal document transfer and hence inspection time 5.4 Set KPIs to enhance inspector's performance (as suggested by WHO interviewee)				
6. Licensees misunderstand the required documents	Submit uncomplete and/or incorrect document	Rejected application form	5	3	2	30	<u>Implemented strategy;</u> 6.1 Provide manual for document preparation <u>Proposed strategy;</u> 6.2 Motivate regulatory association to organize annual meeting for licensees 6.3 Notify regulatory association to distribute updated regulation to licensees	3	2	2	12

7. Misunderstanding the required documents by screening officers	Receive uncomplete and/or incorrect document	Inspectors reject application or request additional declaration	3	3	3	27	<u>Implemented strategy:</u> 7.1 Provide checklist for screening the required documents <u>Proposed strategy:</u> 7.2 Provide content of each required document 7.3 Periodic technical training or workshop, incorporating scenarios and quizzes for discussion	2	2	2	8
8. Difference the background experience of lead GMP inspector or quality system manager in verifying inspection results	Unstandardized of verification inspection result	Difference in verification strictness and results	3	4	2	24	<u>Implemented strategy:</u> 8.1 Group discussion by internal system when having a special quality issue 8.2 Shared inspection approval report to all internal inspectors for supporting inspection of the previously-inspected manufacturer	2	3	2	12

							<u>Proposed strategy:</u> 8.3 Periodic technical training or workshop, incorporating scenarios and quizzes for discussion 8.4 Schedule monthly meeting to share critical issue and standardize inspection procedure 8.5 Joint PIC/S training program routinely				
9. Unlimited number of applications	Officer inadequate time to screening required document	Received the uncompleted application, Human error	4	3	2	24	<u>Proposed strategy:</u> 9.1 Limit appropriate number of applications per day 9.2 Online booking for submission	3	2	2	12
10. Licensee submit uncomplete and/or incorrect document	Rejected application form	Cannot be registering and accessing to new medicines by patients	4	3	2	24	<u>Implemented strategy:</u> 10.1 Provide self-checklist for document preparation 10.2 Provide consultation center	3	2	2	12

							Proposed strategy: 10.3 Motivate regulatory association to organize annual meeting for licensees 10.4 Notify regulatory association to distribute updated regulation to licensees				
11. Obsolete internal SOP	Work practice deviate from current process	Inspection process may be wrong	3	3	2	18	Implemented strategy: 11.1 Perform periodic review routinely 11.2 Perform internal audit	-	-	-	-
12. Approved non-compliance GMP manufacturers by director	Drug registered from non-compliance GMP manufacturers	Various/poor drug quality, harm to patient	2	5	1	10	-	-	-	-	-

*New O, S, D and RPN (implemented risk reduction approach)

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